Official Journal of the
Malaysian Medical Association

The Medical Journal of Malaysia

Volume: 76

Issue No: 4

July 2021

ISSN 0300-5283 PP 2121/01/2013 (031329) MITA(P) 124/1/91

MJM

Official Journal of the Malaysian Medical Association

Volume 76 Number 4 July 2021

EDITORIAL BOARD

PP 2121/01/2013 (031329) MCI (P) 124/1/91 ISSN 0300-5283

The Medical Journal of Malaysia is published six times a year.
MJM is published bimonthly ie. January, March, May, July, September and November.

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Printed by: Digital Perspective Sdn. Bhd.
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Acknowledgements:
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Nuclear medicine in Malaysia – Strengths and challenges for physicians after more than half a century of experience

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ABSTRACT

Nuclear medicine (NM) has been established in Malaysia for almost 60 years. It is a specialty that utilizes radiopharmaceuticals for theranostics, by the assessment of bodily functions to diagnose certain diseases and conditions particularly in oncology, cardiology, and neurology as well as to provide therapeutic solutions in certain instances. The strengths of NM include the establishment of various nuclear medicine centres throughout the country, including in Sabah and Sarawak, particularly for general nuclear medicine, and the mushrooming of positron emission tomography computed tomography (PET/CT) centres along the states in the west coast of Malaysia, the institution of a formal national nuclear medicine physician training programme, and collaboration with international bodies to develop theranostic services. The challenges for NM ahead are namely regulatory and financial constraints for utilizing newer radiopharmaceuticals available in the international market, expansion of accredited training programmes to produce skilled healthcare workforce, optimization of resources at hand and multidisciplinary collaborations to reduce premature mortality of patients caused by non-communicable diseases, particularly cancer.

INTRODUCTION

Nuclear medicine (NM) is a medical specialty that utilizes radioactive tracers known as radiopharmaceuticals to enable the assessment of the functions of the body, especially at a cellular and molecular level, hence facilitating the diagnosis and treatment of diseases. NM has been established for almost 60 years in Malaysia; with doctors (mainly from radiology or internal medicine background training), physicists, nurses, and technologists who have had some training overseas or local parallel training related to the NM field, running the clinical services across various hospitals and centres in the country. At present, there are more than 10 government facilities in Malaysia providing NM services and almost an equal number of facilities in the private sector offering either positron emission tomography computed tomography (PET/CT) or general nuclear medicine services. The mushrooming of these centres, particularly with the utility of PET/CT, has strengthened the role of the NM discipline in the management of oncology cases in Malaysia. Furthermore, a giant step forward was taken in 2007 towards establishing a regular stream of well-trained nuclear medicine physicians, when a formal specialist training programme conferring the Master of Medicine (Nuclear Medicine) was offered by Universiti Sains Malaysia.

Likewise, the Ministry of Health, Malaysia too has been proactively involved in training non-physician personnel such as radio-pharmacists, medical physicists, and nuclear medicine technologists in order to meet the demands of this growing field.

Strengths and challenges in the new millennia

Despite a turf battle with other specialties to claim the 'ownership' of NM practices, many advancements have been made in establishing it as a unique specialty that deals with the diagnosis, staging and treatment of oncology cases, as well as a special role in the diagnosis of cardiology and neurology cases. The perception of this field in the medical community can be further strengthened with designing and initiating a training programme that is broad and comprehensive of complementary imaging and therapy options. A potential option is to adopt a national training programme such as the one started in the United Kingdom of Great Britain that has fortified knowledge on cross-sectional imaging by providing cross training in radiology and internal medicine into the pathway for specialization in NM. A sound understanding of what the specialty has to offer can promote better utility of the resources at hand. Furthermore, due to the COVID-19 pandemic, many continuous medical education programmes have been relegated to the virtual realm. Despite, the challenges wrought by the globally affecting movement control orders, NM physicians are still able to disseminate and share information worldwide through online webinars and conferences. This was stunningly evident in the recently held highly, successful meeting by the Society of Nuclear Medicine and Molecular Imaging (SNMMI) that was fully conducted on a virtual platform. It is believed that the upcoming national nuclear medicine conference by the Malaysian Society of Nuclear Medicine & Molecular Imaging (MSNMMI) in September 2021 will share a similar success.

Moreover, there are three key factors that help in consolidating NM services as having a critical role in disease management in Malaysia. These include the knowledge of the development, production, and validation of radioactive tracers (also known as radiopharmaceuticals), skills in acquisition and interpretation of nuclear diagnostics imaging, along with the formulation, administration, and management of targeted radionuclide therapy. [18F]Fluoro-deoxyglucose, or better known as [18F]FDG, is an example of a widely used radiopharmaceutical in the field of nuclear diagnostics. [18F]FDG has been the workhorse for PET/CT diagnostics since 1994. Although non-specific in activity, it is an indispensable radiopharmaceutical for the diagnosis,

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staging, assessment of treatment response, and detection of recurrence for certain oncological indications, including lymphoma, non-small cell lung cancers, and oesophageal cancers; to name a few.

Since then, many more radiopharmaceuticals have been approved by the Food and Drug Administration (FDA) in the United States of America once they comply with the national drug quality standards compendiums, such as the U.S. Pharmacopeia (USP).[1] Whereas, in Europe, recommendations by the European Pharmacopeia (EP) is enforced by the European Medicines Agency (EMA). To date, there are more than twenty approved radiopharmaceuticals in the market that are utilized for oncology, cardiology, or neurology indications. Recently, a novel radiopharmaceutical called [18F] fibroblast activation protein inhibitor ([18F]FAPI) has been developed, and this shows great promise to be a strong contender for mainstream oncology imaging agent compared to [18F]FDG. The advantage of [18F]FAPI is that it provides good sensitivity for the detection of malignancy, improved target-to-background radio for a wide range of cancers including brain tumours, and can be tagged with either [18F], [68Ga], and even [99mTc] radio-isotopes.[2] Apart from the high contrast resolution provided by this novel radiopharmaceutical due to its low uptake in normal tissues, it has also a potential to be used in theranostics applications for the treatment of certain cancers such as prostate cancer.[3] In neurology imaging, particularly for the management of Alzheimer's disease by quantifying the cerebral amyloid burden, novel amyloid-β imaging compounds have been utilized for PET/CT diagnostics,[4,5] but have yet to reach the shores of Malaysia. Despite, the regulatory and financial challenges, efforts have been taken to aid in the management of Alzheimer's disease and other neurological conditions such as epilepsy, at various centres in Malaysia, by utilizing [18F]FDG PET/CT diagnostics.[6]

The administration of targeted radionuclide therapy by NM physicians in Malaysia has also been gaining acceptance among the medical fraternity. Currently, target-specific somatostatin analogs i.e., DOTA-peptide molecules, and prostate-specific membrane antigen (PSMA) molecules, tagged with beta emitting radioisotopes, are being utilized as alternative therapies in patients with neuroendocrine tumours (NETs) and prostate cancers, respectively. At present, these therapeutic radiopharmaceuticals hold promise as a life-prolonging alternative treatment in patients with advanced NETs and prostate cancers, respectively who have previously undergone multiple lines of systemic chemotherapy. The NETTER clinical trial using [177Lu]DOTATE for metastatic neuroendocrine tumour patients, as well as the VISION and TheraP phase III clinical trials utilising [177Lu]PSMA for castrate resistant metastatic prostate carcinoma patients; have demonstrated significant improvements in the progression free survival of these patients.[7-9] The impressive results have enabled these treatment options to gain acceptance among clinicians in the oncology and surgery disciplines and have paved the way for certification by the FDA. The challenge for physicians now is on the timing for the institution of such therapies, which is usually decided in a multidisciplinary specialist setting.

Another challenge for NM physicians in Malaysia is the adequate optimization of resources at hand and multidisciplinary collaborations to reduce premature mortality caused by non-communicable diseases, particularly cancer. Currently, there are several installations of hybrid imaging technology in Malaysia such as PET/CT and single photon emission tomography computed tomography (SPECT/CT). The advantage of PET/CT is in its versatile ability to detect and quantify cancers at a molecular level, thus enabling the diagnosis, staging and follow-up of oncology cases. By using the value of radiopharmaceutical uptake in the liver as a background baseline uptake, NM physicians can quantify the tumour burden as well as assess the metabolic response of the tumour towards therapy.[10] Overall, SPECT/CT is relatively cheaper to maintain with lower costs of the radiopharmaceuticals and maintenance of the equipment, which may be an important consideration for installation in developing regions within the country.[11] Efforts are being taken to improve this modality in its ability to quantify tumour burden such as in the evaluation of bone metastasis.[12] Furthermore, in future if the production of [99mTc]-based radiopharmaceuticals are developed using FAPI, this would enable SPECT/CT to perform a wider range of diagnostics in cancer management.

Future considerations and the way forward

The Malaysian NM arena is rapidly changing since its inception, and we have come along way in recent decades. A proactive stance is needed among NM physicians in this country in order to build strong networks among clinicians from other disciplines. Incorporation of wider clinical skills prior to joining the specialty, enforcement of accredited structured training programmes, keeping abreast with international developments and promoting subspecialty interests in a system or disease-orientated division, as well as adoption of the know-how of artificial intelligence into the field are among the key approaches to ensure that the specialty remains viable in years to come.

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ORIGINAL ARTICLE

Understanding of Coronavirus Disease 2019 (COVID-19) and the practice of preventive measures among doctors and nurses in a university teaching hospital- A cross-sectional study

Boon Hau Ng, MMed[1], Hsueh Jing Low, MMed[2], Nik Nuratiqah Nik Abeed, MMed[1], Mohamed Faisal Abdul Hamid, MMed[1], Chun Ian Soo, MRCP[1], Petrick Periyasamy, MMed[3], Andrea Ban Yu-Lin, MMed[1]

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ABSTRACT

Introduction: Knowledge and adequate practice of preventive measures among health care workers (HCWs) are important to reduce the risk of COVID-19 transmission.

Methods: A cross-sectional study was conducted among doctors and nurses in the medical department in Pusat Perubatan Universiti Kebangsaan Malaysia between November 18, 2020 and December 18, 2020 during the third wave of COVID-19 epidemic in Malaysia. We studied the knowledge and practice of preventive measures of COVID-19 among doctors and nurses in the COVID-19 or sudden acute respiratory infection (SARI) wards and general medical wards. Data was collected using a validated self-designed google form online-questionnaire.

Results: A total of 407 subjects completed the study and 80.8% were females; 55.8% were aged between 30-39 years; 46.4% were medical doctors. The main source of COVID-19 knowledge was the Ministry of Health Malaysia (MOH) website (35.1%). Majority (97%) had sufficient knowledge and 82% practiced proper preventive measures. Doctors had a higher mean knowledge score compared to nurses ($p < 0.001$). HCWs working in COVID-19 or SARI wards scored higher in knowledge questions compared to those in the general medical wards ($p = 0.020$). Nurses practiced better preventive measures ($p < 0.001$). Good knowledge could not be predicted based on professions (OR: 0.222, 95% CI: 0.048 – 1.028, $p = 0.054$). Majority were unable to recall the proper steps of donning (85.8%) and doffing (98.5%).

Conclusions: Although majority had good knowledge and practiced proper preventive measures, there was a poor recall in donning and doffing steps regardless of place of practice. The MOH website is a useful platform for tailored continuous medical education and regular updates on COVID-19. Regular training and retraining on donning and doffing of PPE is needed to bridge this gap.

KEYWORDS:
COVID-19, novel coronavirus, knowledge, preventive measures, health care workers

INTRODUCTION

The COVID-19 pandemic started in December 2019, and has since caused multiple health related complications and death worldwide. The first COVID-19 outbreak in Malaysia was reported on the 25th of January 2020, originating from 3 tourists travelling from China arriving through Singapore. The second wave occurred in early March 2020, following an international religious assembly in Kuala Lumpur. This study was conducted in October 2020 during the third wave of COVID-19 in Malaysia.

Health care workers (HCWs) are frontliners of COVID- 19 pandemic and have a higher risk of contracting and transmitting the virus to colleagues, family members and patients. The risk of transmission can be caused by lack of proper isolation facilities, insufficient knowledge on COVID-19 and inadequate practice of preventive measures.[1-3]

The standard preventive measures are appropriate use of PPE, hand hygiene, implementation of mask policy and training and education on prevention of infection. Whilst these have been shown to be effective in reducing risk of cross-infection among HCWs, hospital-acquired COVID-19 infection has been reported.[4] Hospital acquired COVID-19 infection further increases the cost of treatment and delays discharges of cured patients. Exploring the extent of knowledge, compliance of HCWs to the steps of PPE and practice of preventive measures are important steps to address the potential missing link.

The advent of COVID-19 vaccination brings hope to the potential end to this pandemic. To date there are 3 main vaccines in the market with varying efficacy.[5-8] The vaccine confers immunity, reduces the severity of infection and potentially decreases transmission rates. There is no evidence that any of the current Covid-19 vaccines can completely stop people from being infected and this has implications for achieving herd immunity. The most effective way to curb this pandemic remains a good knowledge and practice of preventive measures against Covid-19.

This article was accepted: 29 April 2021
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MATERIALS AND METHODS

A cross-sectional survey study was conducted among 410 doctors and nurses between November 18th, 2020 to December 18th, 2020 in Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM) during the third wave of the COVID-19 epidemic in Malaysia in the medical department. This study explored the knowledge and routine practices of preventive measures and appropriate PPE steps in HCWs in the medical wards. This was a quantitative analysis investigating the knowledge and practice of preventive measures among doctors and nurses. A google form questionnaire link was sent out through WhatsApp messenger groups to HCWs in the medical department. The link was also shared personally to HCWs who were in the contact list of the investigators. This study included all 420 HCWs in the medical department. Only those who completed the questionnaire were recruited and data analysed. Subjects with incomplete answers in the questionnaire and who did not consent were excluded.

A self-administered questionnaire in the English language was developed based on existing published COVID-19 research and data from WHO websites and our clinical experience of treating COVID-19 patients in PPUKM.[5] The content and relevance of the questionnaire were checked and validated by the authors and two external infectious disease physicians. The questionnaire was subsequently validated in a pilot study involving 20 participants using an online platform.

There were 3 sections in the questionnaire which were demographic characteristics (gender, age, working experience, profession, location of practice and main source of knowledge on COVID-19), COVID-19 knowledge (which comprised 14 questions on general knowledge, symptoms, mode of transmission and treatment) and practice of preventive measures (which comprised 13 questions assessing practice of mask wearing, hand hygiene, adherence to safety practice and workplace protocols as well as knowledge of donning and doffing Personal Protection Equipment (PPE)). Questions were answered by either yes or no. The participants were asked to list the correct sequence of donning and doffing PPE in the theme of practice of donning and doffing. The options given were gown, gloves, eye protection, hand hygiene and mask. Only the correct sequence was given a score of 1. Each correct answer was given a score of 1 and an incorrect answer was given a score of zero. A high level of knowledge was defined by a score > 11 on the knowledge scale. Those who scored > 10 on the practice of preventive measure scale were considered to have an adequate adherence to COVID-19 prevention. A score of 75% and above was considered a good score.

All the researchers reviewed the interview materials, summarised and formulated the meaningful statements. Data was collected using google form online-questionnaire method. The subjects were informed about the study objectives and informed consent was obtained from each participant. The data were analysed using Statistical Package for Social Science (SPSS) software version 16. Demographic characteristics were analysed by descriptive statistics. Normally distributed continuous data were described as means and standard deviations (SD). The qualitative data was described in frequencies (n) and percentages (%) of total subjects. Chi-square-test was used to compare qualitative variables and association between doctors and nurses. Data were analysed using independent simple t-test and one-way analysis of variance (ANOVA) test. At 95% Confidence Interval, p value <0.05 was considered to be statistically significant.

RESULTS

Demographic characteristics

In all 410 HCWs participated and nearly all (n=407) completed the questionnaire (response rate=99.3%). Table I summarises the demographics of the subjects. Majority were females (n=329, 80.8%). Most subjects were aged below 40 years (n=335, 82.3%) and 310 (76.2%) had more than 5 years of work experience. A total of 189 (46.4%) subjects were medical doctors and one-third (n=132, 32.4%) of participants were directly involved in the management of COVID-19 or SARI patients.

Source of COVID-19 information

MOH website was the most common source 143 (35.1%), followed by social media (Facebook, WhatsApp messenger) 116 (28.5%). Continuous medical education accounted for only 77 (18.9%).

Knowledge about COVID-19

The least correct answers were related to vaccine development for COVID-19 where only 79 (19.4%) answered correctly (Table II). There was a difference detected between doctors and nurses in the following; COVID-19 is a viral disease ($p < 0.001$), COVID-19 is transmitted through close contact ($p = 0.005$), COVID-19 always causes death ($p < 0.001$) and antibiotics are effective in treating COVID-19 ($p < 0.001$).

Thirty-two participants (7.9%) scored 14, 207 (50.9%) scored 13, 129 (31.7%) scored 12, 27 (6.6%) scored 11 and 12 (2.9%) had a knowledge score of less than 11. A total of 393 (97%) subjects were considered to have sufficient knowledge (score > 11). The mean knowledge score was 12.52 (SD 1.00). Doctors had higher mean knowledge scores compared to nurses [12.77 (1.0) vs 12.29 (0.95), $p = 0.001$]. HCWs working in COVID-19/SARI wards scored higher than those in non-COVID-19/non-SARI wards [12.67 (0.79) vs 12.44 (1.08), p=0.020]. There was a significant association between knowledge scores and males ($p = 0.013$), doctors ($p < 0.001$) and practicing in COVID/SARI wards ($p = 0.020$).

Practice of preventive measures towards COVID-19

More than 75% of HCWs adhered strictly to the COVID-19 safety protocol, hand hygiene and proper PPE (Table III). In all 336(82%) subjects practiced adequate preventive measures (score > 10). Nurses practiced better preventive measures (OR 0.231, $p < 0.001$).

HCWs working in the COVID-19/SARI wards had lower mean practice scores [10.41 (SD 1.03)] compared to those working in the non-COVID-19/non-SARI wards [10.43 (SD 1.09)]; p=0. 886.There was a significant association between length of

Table I: Demographics, location of practice and main source of knowledge of study participants

Variables	Frequency (n = 407)	Percentage
Gender		
Male	78	19.2
Female	329	80.8
Age (years)		
20-29	108	26.5
30-39	227	55.8
40-49	68	16.7
>50	4	1
Working experience (years)		
<5	97	23.8
5-10	168	41.3
>10	142	34.9
Designation		
Nurses	218	53.6
Doctors	189	46.4
House officer	54	13.3
Medical officer	102	25
Specialist	8.1	33
Location of practice		
COVID-19/SARI ward	132	32.4
Non-COVID-19/Non-SARI ward	275	67.6
Main source of knowledge on COVID-19		
CME	77	18.9
MOH website	143	35.1
WHO website	24	6
Social media	116	28.5
Newspaper	3	0.7
Television	44	10.8

Table II: Knowledge of health care workers toward COVID-19 (n = 407)

Theme: Knowledge Questions	Correct Responses, n (%)			p value	95% CI
	Doctors (n=189)	Nurses (n=199)	Overall (n=407)		
1: General knowledge on COVID-19 disease					
COVID-19 is a viral disease.	188 (99.5)	204 (93.6)	392 (96.31)	<0.001	0.078 (0.010 - 0.595)
COVID-19 is transmitted through close contact.	170 (89.9)	211 (96.8)	381 (93.61)	0.005	3.369 (1.384 - 8.202)
COVID-19 is transmitted by respiratory droplets.	183 (96.8)	212 (97.2)	395 (97.05)	0.802	1.158 (0.367 - 3.654)
COVID-19 always causes death.	180 (95.2)	136 (63.4)	316 (77.64)	<0.001	0.083 (0.04 - 0.171)
The virus may be more dangerous for the elderly and patients with chronic diseases.	188 (99.5)	218 (100)	406 (99.75)	0.464	2.16 (1.945 - 2.398)
COVID-19 may lead to pneumonia and respiratory failure.	185 (97.9)	215 (98.6)	400 (98.28)	0.709	1.55 (0.342 - 7.013)
2: Symptoms of COVID-19					
Headache, fever, cough, sore throat, and flu are common symptoms of COVID-19.	187 (98.9)	214 (98.2)	401 (98.53)	0.690	0.572 (0.104 - 3.159)
The incubation period is from 2 to 14 days.	186 (98.4)	214 (98.2)	400 (98.28)	1.000	0.863 (0.191 - 3.905)
3: Mode of Transmission					
Asymptomatic patient can transmit COVID-19 to other people during the incubation period.	179 (94.7)	209 (95.9)	388 (95.33)	0.579	1.297 (0.516 - 3.263)
Wearing surgical or N95 masks can help prevent one from contracting COVID-19.	182 (96.3)	203 (93.1)	385 (94.59)	0.157	0.521 (0.208 - 1.305)
Social distancing of one-meter distance can help prevent one from contracting COVID-19.	188 (99.5)	217 (99.5)	405 (99.51)	1.000	1.154 (0.072 - 18.581)
Isolation of COVID-19 patient is effective in reducing the transmission of COVID-19	188 (99.5)	217 (99.5)	405 (99.51)	1.000	1.154 (0.072 - 18.581)
4: Treatment of COVID-19					
There is a vaccine for COVID-19 in development	34 (18)	45 (20.6)	79 (19.4)	0.531	1.186 (0.723 - 1.946)
Antibiotics are effective in treating COVID-19.	176 (93.1)	163 (74.8)	339 (83.29)	<0.001	0.219 (0.115 - 0.416)

Table III: Practice of preventive measure towards COVID-19 among HCWs

Statement	Yes, n(%)	No, n(%)
Theme 1: Wearing of surgical or N95 mask		
Do you use a surgical or N95 mask in the workplace?	365 (89.68)	42 (10.32)
Are you confident with the steps of wearing surgical or N95 masks the right way?	391 (96.07)	16 (3.93)
Theme 2: Hand hygiene		
Do you wash and disinfect your hands before contact with each patient?	400 (98.28)	7 (1.72)
Do you wash and disinfect your hands after contact with each patient?	405 (99.51)	2 (0.49)
Do you frequently clean and disinfect surfaces?	341 (83.78)	66 (16.22)
Do you carry a hand sanitiser?	318 (78.13)	89 (21.87)
Theme 3: Adherence to safety practice and workplace protocols		
Would you perform a COVID-19 screening test ordered before certain high risk procedure?	369 (90.66)	38 (9.34)
Do you adhere to your hospital COVID-19 safety protocol?	401 (98.53)	6 (1.47)
Do you keep yourself updated on the hospital COVID-19 safety protocol?	387 (95.09)	20 (4.91)
Do you wear proper personal protective equipment (PPE) when dealing with suspected or confirmed COVID-19 cases?	401 (98.53)	6 (1.47)
Would you report to your superior after attending a suspected or confirmed COVID-19 cases without wearing proper PPE?	394 (96.81)	13 (3.19)
Theme 4: Practice of donning and doffing		
Answered the donning sequence correctly.	58 (14.25)	349 (85.75)
Answered the doffing sequence correctly.	6 (1.47)	401 (98.53)

Table IV: Predictor of HCWs good knowledge on COVID-19

Variable	Good knowledge (score > 11)	Poor knowledge (score < 11)	OR (95% CI)	p value
Gender				0.35
Male	77 (19.5%)	1 (8.3%)	1	
Female	318 (80.5%)	11 (91.7%)	0.375 (0.048 - 2.952)	
Age (years)				0.644
20-29	106 (26.8%)	2 (16.7%)	1	
30-39	218 (55.2%)	9 (75%)	0.457 (0.097 - 2.153)	
40-49	67 (17%)	1 (8.3%)	1.264 (0.112 - 14.215)	
>50	4 (1%)	0 (0%)	INFINITE	
Designation				0.054
Doctor	187 (47.3%)	2 (16.7%)	1	
Nurse	208 (52.7%)	10 (83.3%)	0.222 (0.048 - 1.028)	
Length of years in service				0.211
< 5	96 (24.3%)	1 (8.3%)	1	
5-10	160 (40.5%)	8 (66.7%)	0.208 (0.026 - 1.691)	
> 10	139 (35.2%)	3 (25%)	0.483 (0.049 - 4.710)	
Location of practice				0.579
Non COVID-19/Non SARI ward	266 (67.3%)	9 (75%)	1	
COVID-19/SARI ward	129 (32.7%)	3 (25%)	1.455 (0.387 - 5.465)	
Main source of knowledge on COVID-19				0.444
CME	73 (18.5%)	4 (33.3%)	1	
Social media	112 (28.4%)	4 (33.3%)	1.534 (0.372 - 6.328)	
WHO website	24 (6.1%)	0 (0%)	INFINITE	
Newspaper	3 (0.8%)	0 (0%)	INFINITE	
MOH website	141 (35.7%)	2 (16.7%)	3.863 (0.691 - 21.589)	
Television	42 (10.6%)	2 (16.7%)	1.151 (0.202 - 6.551)	

service > 10 years (p=0.037), nursing profession (p < 0.001) and female gender (p <0.01) and better preventive measures practice. The correct sequence of donning and doffing PPE was low; 58 (14.3%) donning and 6 (1.5%) doffing.

Predictors associated with good knowledge and adequate practice of preventive measures on COVID-19

Logistic regression was performed to determine the factors associated with good knowledge and adequate practice regarding COVID-19 (Tables IV-V). Good knowledge of COVID-19 could not be predicted based on profession (OR: 0.222, 95% CI: 0.048 – 1.028, p = 0.054). While predictors of adequate practices were being a nurse (OR: 0.231, 95% CI: 0.130 – 0.411, p < 0.001) and female gender (OR: 0.317, 95% CI 0.180 – 0.558, p < 0.001).

DISCUSSION

The COVID-19 pandemic is an on-going global health emergency which continues to impact our lives and world economy. To date more than 2 million people have succumbed to the disease.[9] HCWs have a reported higher risk of infection with outbreaks in hospitals in Germany and Malaysia.[10] Knowledge of COVID-19 and good preventive

Table V: Predictor of HCWs good practice on COVID-19

Variable	Good practice (score > 10)	Poor practice (score < 10)	OR (95% CI)	p value
Gender				< 0.001
Female	284 (84.5%)	45 (63.4%)	1	
Male	52 (15.5%)	26 (36.6%)	0.317 (0.180 - 0.558)	
Age (years)				0.592
20-29	88 (26.2%)	20 (28.2%)	1	
30-39	185 (55.1%)	42 (59.2%)	0.999 (0.554 - 1.802)	
40-49	60 (17.9%)	8 (113%)	0.587 (0.243 - 1.419)	
>50	3 (0.9%)	1 (1.4%)	1.467 (0.145 - 14.845)	
Designation				< 0.001
Doctor	136 (40.5%)	53 (74.6%)	1	
Nurse	200 (59.5%)	18 (25.4%)	0.231 (0.130 - 0.411)	
Length of years in service				0.127
< 5	75 (22.3%)	22 (31%)	1	
5-10	137 (40.8%)	31 (43.7%)	0.771 (0.417 - 1.426)	
> 10	124 (36.9%)	18 (25.4%)	0.495 (0.249 - 0.982)	
Location of practice				0.269
Non-COVID-19/Non- SARI ward	231 (68.8%)	44 (62%)	1	
COVID-19/SARI ward	105 (31.3%)	27 (38%)	1.350 (0.793 - 2.298)	
Main source of knowledge on COVID-19				< 0.001
CME	55 (16.4%)	22 (31%)	1	
Social media	92 (27.4%)	24 (33.8%)	0.652 (0.334 - 1.272)	
WHO website	16 (4.8%)	8 (11.3%)	1.250 (0.468 - 3.338)	
Newspaper	2 (0.6%)	1 (1.4%)	1.250 (0.108 - 14.498)	
MOH website	131 (39%)	12 (16.9%)	0.229 (0.106 - 0.495)	
Television	40 (11.9%)	4 (5.6%)	0.250 (0.08 - 0.782)	

practices by HCWs are both important to protect and prevent cross-infection in the hospital setting. There is limited published data on the knowledge and practice of preventive measures among HCWs about the COVID-19.[11]

There were more females than males (80% versus 19.2%) in this study. The majority of participants were nurses, and in Malaysia nurses are mainly females. This is similar to reports from two other Asian studies where females were nurses.[12,13] There was a higher percentage of subjects with working experience more than 5 years (76.2%) compared to 28% to 70% reported in other studies.[13-15] One third of the HCWs in this study were in charge of the COVID-19/SARI wards. This is comparable to a study done in China where 42.6% of subjects were directly involved in COVID-19 prevention and treatment.[15]

The MOH website was the primary source of information on COVID-19 in our cohort. This is similar to a study in Vietnam where MOH website was one of the main sources of COVID-19 information.[13] This underlines the importance of regular updates on COVID-19 related information on MOH website. In our study approximately one-third of the HCWs used social media as their main source of information. This is similar to studies in Vietnam, United Arab Emirates and Pakistan.[13,16,17] This highlights the role that technology plays in dissemination of COVID-19 information. The majority of our subjects were millennials and their age coincides with the peak usage of many social media platforms such as Facebook and Instagram. It is logical to assume that they turn to social media as their main source of information during the COVID-19 pandemic. It also shows the importance of evaluating and vetting the information available as the large amount of information flooding the internet may cause confusion amongst HCWs. Providing a link of various approved websites on the MOH website is a logical solution. Despite the fact that the continuous medical education is an obvious platform for dissemination and improvement of COVID-19 knowledge, it was not the main source of knowledge in the majority of our subjects. In PPUKM the CME sessions are pre-planned to cover a wide array of medical diseases. What could have been done was to use the CME platform to update the COVID-19 disease regularly.

There were essential elements of variation between doctors and nurses. Overall our study cohort showed a high level of COVID-19 knowledge. This may be explained by the fact that for all of participants this is the first pandemic that they have experienced. The devastating consequence of this pandemic ranges from a change in lifestyle of mask wearing and social distancing became the norm to the increasing number of COVID-19 deaths reported on a daily basis. This fear is likely the driving force to know more about the disease. This is similar to studies conducted among HCWs in Italy, China and Vietnam.[13,18,19] Other studies showed conflicting results with a lower percentage of HCWs with sufficient knowledge.[15,20] When asked to indicate whether the statement "COVID-19 always causes death" was true or false, 95.2% of doctors and 63.4% of nurses answered correctly. This difference in risk perception may contribute to behavioural responses in the workforce and affect the efficiency of HCWs in dealing with this COVID-19. The nurses scored lower for two statements; "COVID-19 is a viral disease" and "antibiotics are effective in treating COVID-19". One possible explanation is doctors were invited to participate in online webinars on COVID-19 updates regularly and this was not extended to the nursing staff.

Hesitancy to get vaccinated is a threat to the fight against the spread of COVID-19. Many studies have shown different ranges of willingness to vaccinate ranging from 28.7% to 93.3%.[21,22] Our study explored the awareness of HCWs to the development of the COVID-19 vaccine. Only 20% of subjects were aware of the vaccine development with both nurses and doctors showing equally poor awareness. This lack of awareness could indirectly affect the willingness to vaccinate. There is a lot of misinformation that circulates in the media on vaccination. It is important to stress that vaccines in general are effective in limiting the spread of COVID-19 by providing herd immunity.

Most subjects practiced good preventive measures and adhered to safety practice of the workplace protocols when dealing with COVID-19 or SARI cases as recommended by MOH Malaysia and WHO. Handwashing practice was good in our cohort. These findings were consistent with studies conducted in Saudi Arabia and Pakistan where the rate of adequate hand washing was reported at 95.4% and 85.7% respectively.[17,23,24] In PPUKM, alcohol sanitisers are placed strategically at the entrance of each ward and staff are instructed to perform hand sanitising before entering each ward. In addition, these alcohol sanitisers are available at the end of every hospital bed. There are also posters reminding the public to perform hand wash and wearing of face mask. This study found that the practice of cleaning and disinfecting surfaces and carrying personal hand sanitisers to be lower. While hand washing campaigns are widely promoted on radio and TV, details of cleaning of disinfecting surfaces as well as promotion of hand held sanitisers are less so. Contaminated surfaces have been known to play an important role in the spread of health care associated infections such as Clostridium difficile, methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococci.[25] However, the transmission of COVID-19 by fomites on inanimate surfaces or objects is debatable.[26]

At the start of the pandemic PPUKM had multiple sessions on the correct sequence of PPE donning and doffing training aimed at HCWs. Subsequently each ward was responsible for their own staff training. There was no fixed schedule for retraining. Due to the possible lack of regular retraining, only 14.3% and 1.5% of our subjects knew the correct sequence of donning and doffing respectively. This is similar to a study conducted in United States of America where up to 90% of cases had incorrect selection and/or the sequence of doffing PPE.[27] Subjects were less familiar with the doffing sequence. A study done in China also showed that there were more errors in doffing PPE compared to donning where donning and doffing videos were reviewed.[28] The above study postulated that the errors were related to fatigue after intensive duties.[28] Our study found poorer recall of doffing. It is possible that subjects view doffing as a less likely source of contamination. This incorrect sequence of practice could affect patient care in a negative way as it can be a potential source of cross infection and self-contamination.[29] Direct exposure is always immediately treated, however occupational exposure from incorrect doffing may be missed. Improvement of procedures in PPE should emphasise not just donning but also doffing to ensure safety of HCWs.

The limitation of this study is the small sample size and cohort limited to the medical department of PPUKM. The results may not be generalised to other hospital HCWs and to other HCWs in other departments.

CONCLUSION

Although majority our HCWs had good knowledge and practiced proper preventive measures, there was a poor recall in donning and doffing steps regardless of place of practice. Regular training and retraining of HCWs on donning and doffing of PPE is needed. The MOH website is a useful platform for dissemination of COVID-19 information and should be updated regularly.

AUTHOR CONTRIBUTIONS

(1) Concept or design: BHN, ABYL, HJL
(2) Acquisition of data: BHN, ABYL, MFAH, NNNA
(3) Analysis or interpretation of data: BHN, ABYL, HJL, PP
(4) Drafting of the article: BHN, ABYL
(5) Critical revision for important intellectual content: CIS, ABYL, PP, MFAH

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

CONFLICTS OF INTEREST

All authors have disclosed no conflicts of interest.

ACKNOWLEDGEMENT

The authors sincerely acknowledge the staffs at Department of Medicine, PPUKM for their participation in this study.

FUNDING/SUPPORT

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ETHICS APPROVAL

This research was approved by the Health Research Ethical Committee of the University Kebangsaan Malaysia Teaching Hospital with the approval project code JEP-2020-573. Informed consent was obtained from all patients.

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Severity of anxiety disorder and other factors associated with disease severity among COVID-19 patients in a hospital, Bali, Indonesia

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ABSTRACT

Introduction: COVID-19 pandemic has a substantial impact on human life including the tourism sector (TS). Bali as a tourism destinations and the TS as major incomes of its population is greatly impacted, causing many to be jobless among those involved in TS. This situation may give psychological impact causing anxiety disorder (AD).

Objective: To investigate the association between severe anxiety disorder and other factors with COVID-19 disease severity.

Methods: This was cross-sectional study during March - November 2020. The diagnosis of SARS-CoV-2 was done by using RT-PCR from throat swabs, based on WHO's interim guidelines. AD was measured using self-reporting Generalized Anxiety Disorder-7 (GAD-7). All participants underwent, history taking, physical examinations, blood routine examination and chest radiography. Association between severe AD and other factors with COVID-19 disease severity were analyzed. Chi-square test (bivariate) and Logistic regression (multivariate) with the precision value of 95% was done and p-value less than 5% was considered significant.

Results: Positive rate of Covid-19 patients was 43% (292 / 678). Among those 292 with Covid-19, 74 (25.3%) participants had severe disease. Multivariate analysis showed severe anxiety (OR 696.11; 95%CI: 78.54 to 6169.98; p<0.001), hypertension (OR 37.02; 95%CI: 4.49 to 305.39; p=0.001) and neutrophyl lymphocyte ratio (NLR) less than 2.89 (OR 0.15; 95%CI: 0.04 to 0.62; p=0.009).

Conclusion: Severe anxiety, hypertension and NLR less than 2.89 are potential independent risk factors for severe infection of SARS-CoV-2 (COVID-19).

KEYWORDS:
Covid-19, Disease severity, Severe anxiety, Positivity rate, Associated factors

INTRODUCTION

Coronavirus disease 2019 (COVID-19), of a RNA virus family infects the vertebrates. The '2019 novel coronavirus (2019 – n Cov)' that is now known as the COVID-19, occured in Wuhan, China and it was previously known as Novel Coronavirus Pneumonia (NCP).[1,2] According to the WHO that it spread rapidly to 25 other countries. The COVID-19 incubation period is about 2 to 14 days and based on a study in Wuhan, mostly 3-7 days. The main routes of transmission were considered via respiratory droplets and close individual to individual contact (within 6 feet). Any contacts of individuals on surface or an object that has the virus on it and then touches their own eyes, noses or mouths can mean a transmission can occur.[3-5]

Nowadays COVID-19 is considered as resulting in complex challenges for physic-psychosocial health problems due to some of drastic public health measures. COVID-19 has various clinical manifestations from mild to severe. The severe disease can be rapidly changing to fatal condition such as acute respiratory distress (ARDS), multiple organ damage and even death.[6-8] In Bali; 12,583 individuals were confirmed to have Coronavirus disease 2019 (COVID-19); 11,555 had recovered and 404 were dead. In Indonesia a total of 457,735 individuals were confirmed to have Coronavirus disease 2019 (COVID-19); 385,094 had recovered and 15,037 were dead.[9] The severe impact on tourism sectors and the economy of Bali that contribute to the psychological aspect as most people confirmed with COVID-19 show psychological disorders with the various levels of Generalized Anxiety Disorder (GAD).[10-12] Other frequent symptoms include fever, cough, shortness of breath, pneumonia, and severe respiratory syndrome.[2] In some comorbidities such as diabetes, hypertension, hypertensive heart disease (HHD), coronary heart disease (CHD), pulmonary tuberculosis (PTB), chronic kidney disease (CKD), dengue hemorrhagic fever (DHF) are also seen. We suggest that investigating the risk factors for the severity of COVID-19 is crucial to improve the outcome of the disease. COVID-19 patients with generalized anxiety disorder (AD) (moderate severe anxiety), older adults and comorbidities are more likely to be aggravated.[13-15]

This study was conducted to investigate the association between severe AD and other factors with disease severity of hospitalized COVID-19 patients at Wangaya Hospital (WH) in Denpasar, Bali, Indonesia.

This article was accepted: 08 May 2021
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MATERIALS AND METHODS

Study Design and Populations

A cross-sectional study single-center was conducted at Wangaya Hospital in Denpasar Bali Indonesia from March 2020 to November 2020. The diagnosis of SARS-CoV-2 using RT-PCR on samples from throat swabs, based on WHO's interim guidelines.[16] AD was measured using GAD-7. This questioner was used by self-reporting by participants to measure the severity of AD. It was reported that the sensitivity and specificity of this tool using optimal cut-off point were 89% and 82%, respectively.[11]

We collected throat swabs from 678 suspected of SARS-CoV-2 infection. Among those, 292 patients were reported as positive COVID-19, and hospitalized at WH were consecutively included. All of the participants underwent, history taking, physical examinations, blood routine examination and chest radiography. A written consent form was provided to the participants wherein the procedure of the study was explained.

Data collection

Data of GAD-7 and other factors such as demography, clinical manifestations, laboratory results, chest radiographic and comorbidities were collected. Severity of AD was classified into 2 groups: none, mild to moderate anxiety (score 9 or less) and severe anxiety (10 or more) disorder.[11] The clinical symptoms and signs, laboratory results and chest X-rays were extracted from WH medical records. The neutrophil-lymphocyte ratio (NLR) is an inflammatory marker that can be used as an indicator of systemic inflammation; the NLR is defined by the absolute number of blood neutrophils divided by the absolute number of lymphocytes. Hypertension is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure 90 mmHg.[17] Coronary arterial disease is defined as the inability of atherosclerosis coronary arteries to perfuse the heart due to partial or total occlusion of the coronary arteries. Typical angina (chest pain); substernal chest discomfort of specific quality and duration among the patients who are identified the atherosclerotic risk factors. This was also support by electrocardiogram and cardiac marker.[18,19] Renal insufficiency is defined as creatinine serum concentrations ≥ 1.2 mg/dL, irrespective of cause.[20] Diabetes mellitus is defined fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) or 2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test or A1C ≥ 6.5% (48 mmol/mol) or in a patient with classic symptoms of hyperglycemia or hyperglycemia crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).[21] Abnormal chest X ray is defined according to radiologist expert that include previous conditions such as lung tuberculosis, chronic obstructive lung disease or associated with COVID-19 infection such as pneumonia.[22] Severity of COVID-19 was classified into: severe cases which should meet at least one of the conditions: shortness of breath with respiratory rate ≥ 30 (breath/min) or oxygen saturation (SpO2) ≤ 93 % in resting state. It included critical cases that should meet one of the following manifestations: respiratory failure and required mechanical ventilation or shock occurred, or combined with other organs damage and nursed in intensive care unit. All the data such as demography, history of travelling to region with COVID-19, history of contact, clinical manifestation, vital signs, laboratory, and underlying comorbidities such as hypertension and diabetes mellitus were obtained.

Statistical analysis

To describe the participant characteristics descriptive statistical tests were performed. The data distribution was tested by Kolmogorov-Smirnov test for normality. Mean and standard deviation were displayed for variables with numerical or continuous scales and normally distributed. If the data is not normally distributed, it was displayed in median and range values. The variables with categorical scale were displayed in frequencies (numbers and percents). The clinical and laboratory data were compared between the mild-moderate and severe groups. Simple logistic regression and multiple logistic regression were applied for bivariate and multivariate analysis. Statistically, significant level was set on p-value equal 5%, and data precision was expressed as 95% confidence interval.

RESULTS

Characteristics of Patients

Among the 678 patients who admitted to WH were diagnosed as suspect SARS-CoV-2 infection and collected throat swabs. In all 292 patients were reported as COVID-19 (43% positive rate). All those COVID-19 patients were enrolled in this study. Table I shows the clinical characteristics (demography, signs and symptoms, and laboratory findings) of the patients who participated.

Among 292 COVID-19 patients, 74 (28.1%) with severe disease. We found there were high prevalence (> 25%) of those with at least one co-morbid, abnormal chest X-ray, NLR < 2.89 and age ≥ 50 years. However, the prevalence of creatinine serum ≥1.2 mg/dL, hypertension, diabetes mellitus and coronary arterial disease were less than 25%. Severe AD and other factors (at least one comorbid, abnormal chest X-ray, NLR < 2.89, creatinine serum ≥1.2 mg/dL, age ≥ 50 years, hypertension, diabetes mellitus and coronary arterial disease) were selected as potential risk factors. It was shown that all those factors were significantly associated with disease severity. Among those, all positive strongly (potentially associated with increase risk) correlated with disease severity, except NLR ratio < 2.89 (shown negatively correlation) with potentially protective against severe COVID-19 disease (Table II).

If all of significant associated factors are put into regression model (using backward LR multiple regression analysis), it was shown that when beginning (first step on the analysis) with those eight factors, finally (fifth step on the analysis) only three factors significantly (p-value less than 0.05) associated with disease severity as an independent factor, consisted of severe anxiety disorder, hypertension and NLR < 2.89 (Table III).

DISCUSSION

This study found that in multivariate analysis (logistic regression), statistically there are the significant association between the independent factors such as severe anxiety

Table I: Clinical characteristics of COVID-19 patients (n=292)

Characteristics	n (%)	Minimum-Maximum	Mean (SD)
Demography			
Age(years)		14-90	48 (14)
Gender			
Males	154 (52.7)		
Females	138 (47.3)		
Travelling history	22(7.5)		
Contact history	258(88.4)		
Signs and symtoms			
Fever	242(82.9)		
Cough	232(79.5)		
Shortness of breath	136(46.6)		
Anosmia	56(19.2)		
Blood pressure (BP)			
SBP (mm Hg)		100-170	120 (14)
DBP (mm Hg)		60-100	75(8)
Heart rate (beats/mnt)			92(6)
Respiration rate/mnt		18-38	25(4)
Body temperature (oC)		36-38	37(0.6)
Laboratory			
White blood cells (K/mm3)		1.4-21.4	9.1(3.3)
Neutrophils (K/mm3)		1.6-17.5	5.2(2.5)
Lymphocytes (K/mm3)		0.4-4.4	1.6(0.9)
NLR		0.54 - 26.30	4.48(3.72)
Hemoglobin (g/dL)		6.7-17.7	12.9(1.5)
Platelets (K/mm3)		108-615	241(95)
BUN (mg/dL)		10-171	32(20)
Creatinine Serum (mg/dL)		0.1-7.5	1.0(0.77)
Blood sugar (mg/dL)		76-582	169(78)
AST (u/L)		7-140	44(23)
ALT (u/L)		14-253	48(33)
Oxygen saturation (%)		89-98	94(2)

NLR = neutrophil-lymphocyte ratio; BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = Alanine Aminotransferase

Table II: Association some associated factors and severity of COVID-19 patients.

			Severe			CI 95%(PR)		
Associated factors	Prev. (%)	Category	Yes	No	PR	Lower limit	Upper limit	P-value
Severe anxiety	28.1	severe	70	12	44.8	16.9	118.8	<0.001
		non-severe	4	206				
Comorbidities (≥1)	35.6	≥1	64	40	11.6	6.2	21.5	<0.001
		none	10	178				
Abnormal chest X-ray	49.3	yes	68	76	1.8	1.5	2.1	<0.001
		no	6	142				
NLR<median (2.89)	50.0	yes	6	140	0.08	0.04	0.2	<0.001
		no	68	78				
Renal insufficiency SC ≥1.2 mg/dL	19.2	yes	26	30	2.3	1.6	3.3	<0.001
		no	48	188				
Age (≥ 50 years)	52.7	≥ 50	60	94	1.5	1.3	1.7	<0.001
	<50	14	124					
Hypertension	18.5	yes	32	22	3.4	2.36	4.7	<0.001
		no	42	196				
Diabetes								
Mellitus	20.9	yes	47	14	6.6	4.5	9.6	<0.001
		no	27	204				
Coronary Arterial								
Disease	6.2	yes	12	6	2.9	1.99	4.37	<0.001
		no	62	212				

PR, prevalence ratio; NLR, neuhtophyl lymphocyte ratio; SC, serum creatinine. Significant p < 0.05

Table III: Multivariate analysis of association between comorbidities and the severity of COVID-19 patients

Factors*	B	P-value	Odds ratio	95% CI(odds ratio)	
				Lower	Upper
Severe Anxiety Disorder	6.55	<0.001	696.11	78.54	6169.98
Hypertension	3.61	0.001	37.02	4.49	305.39
NLR (< 2.89)	-1.871	0.009	0.15	0.04	0.62

*Only significant (P-value<00.5) variable were included in final step of multiple logistic regression
NLR, Neutrophil-lymphocyte ratio

disorder, hypertension and NLR with disease severity among COVID-19 patients at WH. But others factors such as age (≥ 50 years old) statistically is not associated with disease severity.

Anxiety disorder and COVID-19

AD is an adaptive emotional and behavioral response to threaten stimuli and is essential for survive. Chronic and persistent worry are characterized for AD. The worry, may relate to health, finances (salary deduction due to job losses), family (separation from family members and colleagues), social isolation, school closure and the future, excessive and mostly difficult to control.[11,12,14] As well as particularly in Bali due to tourism lock down.

This study found that in multivariate analysis (logistic regression), statistically there are the significant association between severe anxiety AD and disease severity (p<0.001; CI: 95% (78.54-6169.98) (Table II). In India, AD was found in 39.5% of 152 participants. Other study was reported that the lower frequencies of AD 13.0% in Wuhan and 10.8% in Singapore.[15,23,24] The factors that explain the difference are particularly cultural patterns and psychosocial, environmental, and work influence.[15] Another study among Italian and Iranian populations found that fear of COVID-19 was significantly correlated with anxiety, as a measured by the hospital anxiety scale.[25,26] Moreover, 25.4% of the participants experienced that their mental health (anxiety) had deteriorated since the pandemic. This alarming situation suggests that the COVID-19 pandemic has substantially contributed the AD in Hong Kong.[11] Among the Pakistani Social Media Users during COVID-19 pandemic, found 31% (94 of 303 participants) were AD.[27] A significant higher percentage of individuals with anxiety vs without considerable anxiety among Bangladeshi during COVID-19 pandemic (96.1% vs 69.8%, p < 0.001).[14]

Hypertension and COVID-19

The cytokines imbalance is considered as an explanation for the association between hypertension and severe COVID-19, cytokine storms and deterioration of COVID-19 due to exaggerated of IL-6 and TNF-alfa.28

This study found that in multivariate analysis (logistic regression), statistically there is the significant association between hypertension and disease severity (p = 0.001; CI: 95%(4.49-305.39) (Table II).

Another recent study by Huang reported that COVID-19 patients with hypertension were more likely than patients without hypertension to have severe pneumonia, excessive inflammatory reactions, organ and tissue damage and deterioration of the disease.28 Pittito (2020), reported that the hypertension was moderately and respectively associated with severity and mortality for COVID-19 patients (OR 2.50; 95% CI: 1.74-3.59).[29]

Neutrophil Lymphocyte Ratio (NLR) and COVID-19

Neutrophils represent the nonspecific immune system that initiate the body responses to inflammation, whereas the lymphocytes represent the protective component against inflammation. The inflammatory condition will trigger hypersecretion of inflammatory cytokines; IL-6 and TNF-α, resulting in a permanently high neutrophil count, but on the other hand the increased proinflammatory mediators will bind to lymphocyte surface receptors and subsequently initiate apoptosis of the lymphocytes, thus causing lymphopenia.[30] Neutrophil Lymphocyte Ratio (NLR) shows the inflammatory status. It is used as a marker of prognosis of several conditions included the acute inflammatory disease.

In this study we found an association between severity anxiety and NLR < 2.89 (OR 0.15; 95%CI: 0.04 to 0.62; p=0.009), shown negatively correlation with potentially protective against severe COVID-19. Other studies revealed that NLR has been shown to be an independent risk factor for diseases severity of COVID-19.[31-34] Long L et al (2020) found that 75.8% of patients with disease progression had an NLR of 2.973 during hospitalization, which may imply the severity of COVID-19 infection.[34,35] High NLR was shown by binary logistic analysis; hazard risk (HR): 2.46, 95% confidence interval (CI): 1.98-4.57 as an independent factor for poor clinical outcome of COVID-19, confirmed by a meta-analysis that reported significant increases in NLR values in severe COVID-19 patients.[36,37]

LIMITATION OF THE STUDY

This study has several limitations, such as; the study population only recruited patients within at WH.

CONCLUSION

Our study found a statistically significant association between hypertension, NLR and the severity of COVID-19 patients. The assessment of severe AD, hypertension and NLR may help identify the severity of the disease.

ACKNOWLEDGMENTS

We would like to thank the Director of WH, all of the participants and their family, the Wangaya COVID-19 Team and all of our colleagues who supported data collecting in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

The authors declared that there is no conflict of interest related to this study.

FUNDING SOURCES

The author received no specific funding for this work.

ETHICAL APPROVAL

The study procedure was approved by Ethical Committee of WH in Denpasar, Bali, Indonesia with register number: 14/RSUDW/Litbang/2020. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the participants.

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ORIGINAL ARTICLE

Predictors of adverse pregnancy outcome in a cohort of women with systemic lupus erythematosus in Malaysia

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ABSTRACT

Introduction: Pregnancy in women with systemic lupus erythematosus (SLE) is known to be associated with adverse pregnancy outcomes (APO). We aimed to determine the frequency of APO, the associated variables and predictors.

Materials and Methods: This retrospective study included all pregnancies seen at the SLE Clinic, Kuala Lumpur Hospital from January 2008 to May 2020. Maternal outcomes included SLE flare during pregnancy, preeclampsia and eclampsia. Foetal outcomes included foetal loss, preterm birth and small-for-gestational age (SGA) neonates. Clinical and laboratory variables were examined. Variables from univariate analysis were entered into logistic regression model. Odds ratio and 95% confidence interval were reported.

Results: Of the 131 pregnancies, 106 (80.9%) were live births. Twenty-six (24.5%) babies were born preterm and 35 (33%) neonates were SGA. Twenty-four (18.3%) women had disease flare during pregnancy, with the majority (22/24) being mild to moderate flares. Four women experienced preeclampsia while none had eclampsia. Predictors of adverse maternal outcomes included high SLEDAI-2K score, proteinuria and hypocomplementemia within 6 months before conception and during pregnancy; history of lupus nephritis (LN), pre-existing hypertension, antiphospholipid syndrome (APS), antiphospholipid antibodies, anti-Ro antibody and anti-RNP antibody. Predictors of adverse foetal outcomes comprised APS, preeclampsia, anti-Sm antibody, history of neuropsychiatric systemic lupus erythematosus (NPSLE) and azathioprine use.

Conclusion: Pregnancy in SLE women is best deferred until disease activity is in remission for at least 6 months before conception. A history of LN is associated with a 3-fold risk of renal flare during pregnancy. Haematological abnormalities are rare in disease flare during pregnancy.

KEYWORDS:
Predictors, maternal, foetal, outcomes, systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease which involves multiple organ systems and occurs predominantly in women of reproductive age. Fertility is generally not affected.[1] However, cyclophosphamide therapy used in the treatment of SLE has been known to affect gonadal function.[2] Pregnancy and its complications remain a concern to women with SLE as well as physicians who treat them given the fact that SLE has been shown to have significant impact on maternal and foetal outcomes.[3] Women with SLE are at significantly higher risk for foetal loss, preterm birth, preeclampsia and caesarean section when compared to women without SLE.[3-5] With increased understanding of the pathogenesis of SLE and improved treatment, higher rates of live births have been observed in women with SLE.[6] Identification of clinical and laboratory parameters that predict adverse pregnancy outcomes (APO) is vital to facilitate preconception counselling and management of SLE to ensure a favourable outcome for both mother and foetus. Therefore, we conducted this study to examine the frequency of APO, the clinical and laboratory parameters that are associated with APO, and the predictors of APO.

MATERIALS AND METHODS

This retrospective study included all pregnancies that occurred in women who attended the SLE clinic of Kuala Lumpur Hospital between January 2008 to May 2020. All patients fulfilled the American College of Rheumatology (ACR) 1997 revised classification criteria for SLE.[7] Exclusion criteria were patients who had ectopic pregnancies, induced abortions; and patients who had incomplete medical records. Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia. This study was also registered with the National Medical Research Register (NMRR-19-1232-48342).

Medical records of patients were systematically reviewed and data obtained. The following variables were recorded: demographic data; duration of SLE; associated antiphospholipid syndrome (APS); SLE activity within 6 months before conception and during pregnancy; gravidity and parity; presence of preeclampsia; outcome of pregnancy; gestational age; mode of delivery; indication for caesarean section; birth weight; duration of stay in neonatal intensive care unit (NICU); congenital heart block (CHB); medications received during pregnancy; pre-existing hypertension; history of LN, NPSLE and haematological manifestations. Laboratory parameters documented were full blood count, complement 3 (C3), complement 4 (C4), proteinuria; autoantibodies which

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included antinuclear antibody (ANA), anti-double-stranded deoxyribonucleic acid (anti-dsDNA), anti-Sm antibody, anti-Ro antibody, anti-La antibody, anti-ribosomal P antibody, anti-ribonucleoprotein (anti-RNP) antibody, lupus anticoagulant (LAC), anticardiolipin antibody (ACL) and anti-beta2 glycoprotein I antibody (anti-b2GPI).

Maternal outcomes included (1) disease flare during pregnancy, (2) preeclampsia and (3) eclampsia. SLE Disease Activity Index 2000 (SLEDAI-2K)[8] was used to evaluate disease activity of patients with SLE within 6 months before conception and during pregnancy. SLEDAI-2K score of ≥4 was defined as active phase of SLE. Mild to moderate disease activity was defined as SLEDAI-2K score of between 4 to 12. A score of >12 was considered severe disease activity.

Hypertension was defined as systolic blood pressure of 140 mm Hg or greater, or diastolic blood pressure of 90 mm Hg or greater. Preeclampsia was defined as the presence of hypertension and proteinuria of 0.3 g or greater in a 24-hour urine sample in patients with normal blood pressure and no evidence of proteinuria prior to 20 weeks of gestation. Eclampsia was defined as new onset of grand mal seizure activity and/or unexplained coma during pregnancy or postpartum in a woman with signs or symptoms of preeclampsia.

Foetal outcomes included (1) foetal loss, (2) small-for-gestational age (SGA) neonates and (3) preterm birth. Foetal loss was defined as the loss of pregnancy as a result of spontaneous abortion or stillbirth. Spontaneous abortion refers to spontaneous loss of the foetus before 20 weeks of gestation. Stillbirth was defined as the death of the foetus in utero above 20 weeks of gestation. Therapeutic abortion was defined as termination of pregnancy for medical indications. SGA was defined as birth weight below the tenth percentile for the gestational age. Preterm birth was defined as birth of a baby before 37 weeks of gestation.

Statistical analysis

In terms of analysis, each pregnancy was considered as an individual observation. Categorical variables were described in frequencies and percentages; while continuous variables were reported in means and standard deviations (SD), or medians and interquartile ranges (IQR). Fisher's exact test was used to analyse the significance of association between each variable and adverse outcome. Two-sided $p<0.05$ was considered statistically significant. Variables with a p-value of <0.05 from the univariate analysis were entered into a logistic regression model. Odds ratio (OR) and 95% confidence interval (CI) were reported.

RESULTS

A total of 131 pregnancies in 93 women were identified. Sixty-eight (73.1%) women had 1 pregnancy, 17 (18.3%) two pregnancies, four (4.3%) three pregnancies, three (3.2%) four pregnancies and one (1.1%) five pregnancies. There were 79 Malays (85.0 %), 9 (9.7%) Chinese and 5 (5.3%) Indians. Fifteen (11.5%) women had concomitant APS; while 4 (4.3%) had overlap syndrome, of whom 3 had rheumatoid arthritis and one had systemic sclerosis. Mean age at disease onset was 24.0 (SD 5.3) years and mean age at conception was 29.6 (SD 4.5) years. With regard to disease activity, the majority (84.3%) of women had inactive disease within 6 months before conception. SLE was diagnosed during pregnancy in 4 (3.1%) women. A history of LN was observed in 17 (13.0%) women while 8 (6.1%) women had pre-existing hypertension. Table I summarizes the baseline clinical characteristics and laboratory features of our patient cohort.

Of the 131 pregnancies, prednisolone was used in 113 (86.3%) pregnancies and hydroxychloroquine in 116 (88.5%) (Table II). Majority (93.9%) of women received aspirin. Low-molecular-weight heparin (LMWH) was prescribed to 13 of the 15 women with secondary APS. The remaining two women suffered miscarriages very early into the first trimester of pregnancy before their appointment at the SLE clinic. Hence treatment with LMWH was not initiated.

Foetal outcomes

There were 106 (80.9%) live births. Twenty-one (16.0%) pregnancies ended in spontaneous abortions and 3 (2.3%) were stillbirths. One (0.8%) woman underwent therapeutic termination of pregnancy in view of proteinuria and deterioration in renal function (Table III). Majority (22/25, 88%) of the spontaneous abortions occurred in the first trimester and early second trimester.

With regards to the 106 live births, mean gestational age at birth was 37.3 (SD 3.5) weeks (range 30.1 to 41.1). Twenty-six (24.5%) babies were born preterm. Mean birth weight was 2.60 (SD 0.49) kg and 35 (33.0%) neonates were SGA.

Fifty-two (49.1%) babies were delivered via vaginal route while the remaining 54 (50.9%) by caesarean section. The leading cause for caesarean section was failed induction of labour, as observed in 12 (32.4%) cases. This was followed by foetal distress in 11 (29.7%) cases and poor progress of labour in 7 (18.9%) cases. Three (8.1%) women had preterm premature rupture of membranes and 2 (5.4%) had preeclampsia.

There were no cases of neonatal death, foetal congenital heart block (CHB) or neonatal lupus erythematosus. Thirty-seven neonates were admitted to NICU. The duration of NICU stay ranged from one to 60 days.

Maternal outcomes

Twenty-four (18.3%) women experienced disease flare during pregnancy, of whom 22 (16.8%) had mild to moderate flare while 2 (1.5%) had severe flare (Table II). The mean SLEDAI-2K score for the aforementioned 24 women was 6.0 (SD 3.3). Twelve (50%) women had malar rash and 11 (45.8%) had proteinuria. Five (45.4%) of the 11 women with proteinuria had a history of LN. Haematological abnormality occurred in one woman, who had thrombocytopenia. All the women with disease flare received escalation in prednisolone dosage. Azathioprine was introduced in 6 women, all of whom had renal flare. The median dosage of prednisolone was 15 (IQR 10) mg daily, and the highest dose received was 60 mg daily. Four women developed preeclampsia, while none had eclampsia (Table III).

Table I: Baseline clinical and laboratory features

CHARACTERISTICS	NUMBER (%) n=131	MEAN (SD)	MEDIAN (IQR)
Age at disease onset (years)		24.0 (5.3)	
Age at conception (years)		29.6 (4.5)	
Duration of SLE (months)			72.0 (77.0) Range 0 to 268
Antiphospholipid syndrome	15 (11.5)		
Concomitant connective tissue disease	4 (3.1)		
Pre-existing hypertension	8 (6.1)		
History of lupus nephritis	17 (13.0)		
History of NPSLE	7 (5.3)		
History of thrombocytopenia	33 (25.2)		
History of leukopenia	47 (35.9)		
History of autoimmune haemolytic anaemia	12 (9.2)		
Autoantibodies			
Anti-dsDNA positivity (n=128)	62 (48.4)		
Anti-Sm antibody positivity (n=129)	37 (28.7)		
Anti-Ro antibody positivity (n=129)	66 (51.6)		
Anti-La antibody positivity (n=129)	27 (20.9)		
Anti-RNP antibody positivity (n=129)	34 (26.4)		
Anti-ribosomal P antibody positivity (n=129)	25 (19.4)		
Lupus anticoagulant positivity (n=57)	17 (29.8)		
Anticardiolipin antibody positivity (n=121)	13 (10.7)		
Anti-beta2-glycoprotein I antibody positivity (n=61)	6 (9.8)		

Table II: Patient characteristics within 6 months before conception and during pregnancy

Characteristics	Within 6 months before conception n=115*(%)	During pregnancy n=131(%)
SLEDAI-2K		
SLEDAI-2K unknown	16	0
SLEDAI-2K <4	97 (84.3)	107 (81.7)
SLEDAI-2K ≥4	18 (15.7)	24 (18.3)
SLEDAI-2K 4 to 12	16 (13.9)	22 (16.8)
SLEDAI-2K >12	2 (1.7)	2 (1.5)
SLE clinical manifestations		
Malar rash	9 (7.8)	12 (9.2)
Oral ulcers	6 (5.2)	3 (2.3)
Arthritis	4 (3.5)	4 (3.1)
Low complement 3	24 (20.9)	22 (16.8)
Low complement 4	14 (12.2)	17 (13.0)
Proteinuria	6 (5.2)	11 (8.4)
NPSLE	0 (0)	0 (0)
Thrombocytopenia	4 (3.5)	1 (0.8)
Leukopenia	2 (1.7)	0 (0)
Autoimmune haemolytic anaemia	0 (0)	0 (0)
Medications		
Prednisolone		113 (86.3)
Hydroxychloroquine		116 (88.5)
Aspirin		123 (93.9)
Low-molecular-weight heparin		13 (9.9)
Azathioprine		22 (16.8)

*n=115 as the status of 16 women with SLE were unknown within 6 months before conception because they presented to the SLE clinic when they were already pregnant, or had new-onset SLE at pregnancy.

Predictors of adverse maternal outcome

Univariate analysis demonstrated the following factors to be associated with adverse maternal outcomes. High SLEDAI-2K score within 6 months before conception, history of LN, hypocomplementemia within 6 months before conception and during pregnancy, proteinuria within 6 months before conception and during pregnancy, and anti-Ro antibody positivity were predictors of disease flare during pregnancy. APS, pre-existing hypertension, anti-RNP antibody positivity, LAC positivity, ACL positivity and proteinuria within 6 months before conception were significantly predictive of preeclampsia. Table IV summarizes the results of the univariate analysis.

Table III: Adverse maternal and foetal outcomes

	Number (%)
Adverse maternal outcome	
Flare during pregnancy (n=131)	24 (18.3)
Preeclampsia (n=109)	4 (3.7)
Eclampsia (n=109)	0 (0)
Adverse foetal outcome	
Foetal loss (n=131)	25 (19.1)
- Spontaneous abortion	21 (16.0)
- Stillbirth	3 (2.3)
- Termination of pregnancy	1 (0.8)
Preterm birth (n=106)	26 (24.5)
SGA (n=106)	35 (33.0)

Table IV: Variables associated with adverse maternal outcomes

	Flare during pregnancy		Preeclampsia	
	p value	OR (95% CI)	p value	OR (95% CI)
APS	0.727	1.20 (0.31,4.65)	0.007*	10.67 (1.34, 85.01)
SLEDAI-2K ≥4 within 6 months before conception	0.000*	23.00 (6.31, 83.89)	0.507	1.81 (0.18, 18.67)
History of lupus nephritis	0.039*	3.11 (1.02, 9.54)	0.428	2.36 (0.23, 24.40)
Pre-existing hypertension	0.146	3.09 (0.68, 13.98)	0.020*	20.00 (2.33, 172.72)
History of NPSLE	0.353	0.82 (0.75, 0.89)	1.000	0.96 (0.93, 0.99)
Haematological abnormalities within 6 months before conception	0.070	0.41 (0.16, 1.07)	1.000	1.06 (0.14, 7.80)
Anti-dsDNA	0.364	0.63 (0.25, 1.58)	1.000	1.08 (0.15, 7.98)
Anti-Sm antibody	0.197	1.95 (0.75, 5.07)	1.000	1.04 (0.10, 10.45)
Anti-Ro antibody	0.037*	2.93 (1.06, 8.06)	1.000	1.02 (0.14, 7.52)
Anti-La antibody	0.404	0.52 (0.14, 1.90)	1.000	1.04 (0.10, 10.45)
Anti-Ribosomal P antibody	0.597	1.38 (0.51, 3.75)	0.573	0.95 (0.91, 0.99)
Anti-RNP antibody	0.684	1.50 (0.32, 7.14)	0.022*	1.30 (0.97, 1.75)
Lupus anticoagulant	1.000	1.00 (0.26, 3.84)	0.022*	8.00 (1.02, 62.63)
Anticardiolipin antibody	0.253	2.94 (0.46, 18.79)	0.023*	30.00 (2.08, 433.13)
Anti-beta2 glycoprotein I antibody	0.137	2.81 (0.82, 9.61)	1.000	0.95 (0.91, 0.99)
Low C3 within 6 months before conception	0.004*	5.58 (1.78, 17.46)	1.000	1.33 (0.13, 13.59)
Low C4 within 6 months before conception	0.003*	7.67 (2.17, 27.04)	1.000	0.95 (0.91, 0.99)
Haematological abnormality within 6 months before conception	1.000	0.87 (0.81, 0.93)	1.000	0.96 (0.92, 0.99)
Proteinuria within 6 months before conception	0.003*	17.82 (2.92, 108.68)	0.036*	9.67 (0.76, 122.45)
Low C3 during pregnancy	0.000*	10.69 (3.76, 30.41)	0.498	1.85 (0.18, 18.96)
Low C4 during pregnancy	0.000*	22.47 (6.67, 75.70)	1.000	0.96 (0.92, 0.99)
Haematological abnormality during pregnancy	1.000	0.96 (0.93, 0.99)	1.000	0.96 (0.93, 0.99)
Proteinuria during pregnancy	0.000*	82.31 (9.74, 695.88)	0.295	4.04 (0.38, 43.46)

*denotes significant p value of <0.05; APS – antiphospholipid syndrome; SLEDAI – systemic lupus erythematosus disease activity index; NPSLE – neuropsychiatric systemic lupus erythematosus; OR – odds ratio; CI – confidence interval

Predictors of adverse foetal outcomes

Table V depicts the results of adverse foetal outcomes. APS, preeclampsia and anti-Sm antibody positivity were associated with foetal loss. Azathioprine use was associated with SGA neonates, and a history of NPSLE was related to preterm birth.

DISCUSSION

In spite of multiple risk factors that have been shown to have impact on pregnancy outcomes in women with SLE, a large proportion of women essentially have favourable outcomes. Analysis of our data demonstrated that lupus flare within 6 months before conception was significantly associated with a 23-fold increased risk of disease flare during pregnancy. This observation is consistent with previous studies.[9-11] Of note, the majority (22/24, 91.7%) of disease flares during pregnancy were mild to moderate in activity, while 8.3% were severe flares. The organs more frequently affected in lupus flares were the skin, joints and kidneys, similar to the observation by Petri.[12] Only one woman in our cohort had haematological abnormality, that was, thrombocytopenia. Interestingly, we did not observe any lupus flare that manifested with leukopenia or haemolytic anaemia. Therefore, our study suggested that haematological abnormalities are rare during pregnancy flares. We found that hypocomplementemia and proteinuria within 6 months before conception were predictive of disease flare during pregnancy. C3 and C4 are useful biomarkers in monitoring disease activity in SLE, and they are also used to distinguish exacerbation of disease activity from preeclampsia during pregnancy.[13] Hypocomplementemia is well recognized as an indicator of active disease, in particular, LN.[14] Likewise, the presence of proteinuria is a sign that represents active LN.

Our data also identified hypocomplementemia during pregnancy as a predictor of lupus flare during pregnancy. In normal pregnancy, complement levels are known to rise,

Table V: Variables associated with adverse foetal outcomes

	Foetal loss		SGA		Preterm birth	
	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)
APS	0.040*	3.40 (1.08, 10.69)	0.715	0.55 (0.11, 2.82)	0.686	1.61 (0.37, 6.95)
SLEDAI-2K ≥4 within 6 months before conception	0.756	1.17 (0.35, 3.97)	1.000	0.85 (0.24, 2.96)	1.000	0.79 (0.20, 3.13)
Preeclampsia	0.006*	17.17 (1.20, 244.62)	0.209	1.45 (0.37,48.48)	0.148	6.58 (0.57, 75.79)
History of lupus nephritis	0.740	1.36 (0.40, 4.60)	0.755	1.31 (0.39, 4.35)	1.000	0.91 (0.23, 3.61)
Pre-existing hypertension	0.648	1.45 (0.28, 7.65)	0.661	0.39 (0.04, 3.46)	0.634	1.58 (0.27, 9.19)
History of NPSLE	1.000	0.694 (0.08, 6.04)	1.000	1.02 (0.18, 5.83)	0.031*	7.09 (1.22, 41.30)
Haematological abnormalities within 6 months before conception	0.385	0.67 (0.28, 1.62)	1.000	0.88 (0.35, 2.21)	1.000	1.00 (0.41, 2.42)
Anti-dsDNA	0.824	0.88 (0.36, 2.14)	0.535	1.37 (0.61, 3.11)	0.822	0.86 (0.35, 2.09)
Anti-Sm antibody	0.026*	2.92 (1.18, 7.21)	0.473	1.44 (0.57, 3.65)	1.000	0.93 (0.33, 2.66)
Anti-Ro antibody	0.191	1.85 (0.75, 4.56)	0.300	1.63 (0.72, 3.71)	0.653	1.29 (0.53, 3.15)
Anti-La antibody	0.280	0.43 (0.12, 1.56)	0.231	1.80 (0.72, 4.54)	0.428	1.59 (0.59, 4.30)
Anti-Ribosomal P antibody	0.127	2.22 (0.89, 5.58)	0.633	1.25 (0.48, 3.22)	1.000	1.00 (0.35, 2.87)
Anti-RNP antibody	0.738	1.44 (0.39, 5.16)	0.711	1.44 (0.34, 6.09)	1.000	1.05 (0.26, 4.33)
Lupus anticoagulant	1.000	1.00 (0.26, 3.84)	0.745	0.70 (0.17, 2.84)	0.136	2.88 (0.79, 10.41)
Anticardiolipin antibody	0.106	2.56 (0.46, 18.79)	1.000	0.50 (0.05, 5.19)	1.000	0.67 (0.06, 6.97)
Anti-beta2 glycoprotein I antibody	1.000	0.82 (0.17, 4.02)	0.515	1.58 (0.44, 5.63)	0.265	2.15 (0.56, 8.21)
Low C3 within 6 months before conception	0.268	1.79 (0.64, 5.02)	0.258	2.02 (0.70, 5.82)	0.767	1.19 (0.38, 3.82)
Low C4 within 6 months before conception	0.295	0.28 (0.03, 2.23)	0.539	1.43 (0.43, 4.83)	0.730	1.40 (0.39, 5.08)
Haematological abnormality within 6 months before conception	1.000	0.79 (0.73, 0.88)	1.000	0.79 (0.73, 0.88)	1.000	0.75 (0.66, 0.84)
Proteinuria within 6 months before conception	0.093	4.45 (0.84, 23.69)	1.000	1.09 (0.09, 12.52)	1.000	1.52 (0.13, 17.62)
SLEDAI-2K ≥4 during pregnancy	0.771	1.22 (0.41, 3.69)	0.796	0.85 (0.24, 2.97)	0.738	0.79 (0.20, 3.13)
Low C3 during pregnancy	0.370	1.78 (0.62, 5.13)	0.151	2.33 (0.79, 6.86)	0.214	2.10 (0.68, 6.49)
Low C4 during pregnancy	1.000	0.89 (0.24, 3.39)	0.221	2.29 (0.73, 7.13)	0.324	1.88 (0.57, 6.22)
Haematological abnormality during pregnancy	1.000	0.81 (0.74, 0.88)	1.000	1.02 (0.09, 11.59)	1.000	1.56 (0.14, 17.94)
Proteinuria during pregnancy	0.438	1.67 (0.41, 6.81)	0.435	2.16 (0.51, 9.21)	0.099	3.46 (0.79, 14.95)
Azathioprine use	0.284	1.78 (0.62, 5.13)	0.044*	3.17 (1.07, 9.39)	1.000	1.03 (0.30, 3.52)

*denotes significant p value of <0.05

likely due to increased hepatic synthesis from the influence of oestrogen. Falling levels of complements during pregnancy, albeit within the normal range, have been shown to be associated with increased lupus activity.[13] Davis-Porada et al[15] identified low C4 level to be predictive of flare during pregnancy from the PROMISSE (Predictors of pregnancy outcome: biomarker in antiphospholipid antibody syndrome and systemic lupus erythematosus) study.[16]

Our cohort revealed that a history of LN was significantly associated with lupus flare during pregnancy, with an OR of 3.1 (95% CI: 1.02, 9.54). Similar conclusions were noted from earlier studies.[10,17-19] Therefore, it is crucial to closely monitor women who had a previous history of LN and include mandatory urinalysis at every follow-up visit during the antenatal period in order to promptly recognise a renal flare and avoid serious complications.

Univariate analysis in our study showed that anti-Ro antibody positivity had a significant correlation with lupus flare during pregnancy. This association has not been reported in the literature, mainly because this aspect has not been examined. Anti-Ro antibodies are known to be associated with neonatal lupus and CHB. The prevalence of CHB in the offspring of an anti-Ro antibody positive woman was reported as 2%.[20] Of note, there were no cases of CHB in our cohort. A possible explanation is that a vast majority (88.5%) of our patients received hydroxychloroquine during pregnancy. Over the past couple of decades, hydroxychloroquine has emerged as the cornerstone of SLE therapy. Its widespread use among pregnant women with SLE was derived from studies that demonstrated the benefit of hydroxychloroquine in preventing lupus flares during pregnancy.[9,21,22] In addition, a study by Izmirly et al[23] which involved databases from 3 countries reported that hydroxychloroquine use during pregnancy was associated with a decreased risk of cardiac neonatal lupus, indicating a protective effect. Unfortunately, the exact mechanism of how hydroxychloroquine exerts this effect remains to be elucidated.

Our data showed that the predictors for preeclampsia were APS, lupus anticoagulant positivity, ACL positivity, pre-existing hypertension, proteinuria within 6 months before conception and anti-RNP antibody positivity. Previous studies[24-26] had demonstrated similar associations wherein APS and antiphospholipid antibodies were positively linked to preeclampsia. Our findings suggest that patients with APS, as well as patients without APS but positive for antiphospholipid antibodies should be closely monitored for detection of preeclampsia.

Pre-existing hypertension and proteinuria within 6 months before conception were demonstrated as predictive factors for

preeclampsia in our cohort. Likewise, these findings were consistent with results from a population-based case control study conducted by Davies et al[27] which confirmed that pre-existing hypertension predisposed a woman to preeclampsia, and women who developed preeclampsia had a higher prevalence of pre-existing renal disease.

Reports from multiple studies have shown that foetal loss among SLE women varied widely from 3.9%[10,16] to 38.5%.[17,28,29] Overall, the rate of foetal loss in the general population is approximately 10 to 20%. The frequency of foetal loss in our cohort was 19.1%, which comprised spontaneous abortion in the first trimester and early second trimester. The predictors for foetal loss that were identified were APS, preeclampsia and anti-Sm antibody positivity. Our findings concurred with several studies[10,28,30] which demonstrated APS to be a risk factor for foetal loss. Nonetheless, our study showed that antiphospholipid antibodies per se were not risk factors for foetal loss, unlike other reports.[21,31-34] Foetal loss was inevitable in some of our APS patients despite having received the recommended treatment with low-dose aspirin and LMWH from the first trimester of pregnancy. This suggests that placental thrombosis is not the main aetiology in the pathogenesis of foetal loss. The exact mechanism of foetal loss in APS remains unclear, highlighting the need for further investigation into its pathogenesis in order to prevent obstetric APS.

We identified preeclampsia as a significant predictor for foetal loss, similar to conclusions drawn from a study by Liu et al.[35] Therefore, careful monitoring during the antenatal period is crucial for early detection and appropriate management of pregnancy-induced hypertension and preeclampsia.

Among the autoantibodies tested in our patients, anti-Sm antibody emerged as a risk factor for foetal loss. Interestingly, this association has not been reported. From our observation, the majority of studies which evaluated autoantibodies as predictors of adverse pregnancy outcomes did not include anti-Sm antibody in their analysis, having applied more emphasis on other autoantibodies, in particular, antiphospholipid antibodies. Therefore, we suggest to consider evaluation of anti-Sm antibody as a predictive factor for APO in future research.

Another foetal complication of SLE pregnancy is SGA neonates. The frequency of SGA neonates in our cohort was 33.0%, and the predictive factor identified was azathioprine use. Azathioprine was administered to patients with organ-threatening disease and those who had inadequate symptom control with hydroxychloroquine and prednisolone. Of the 17 women who received azathioprine prior to conception, the indication for 12(70.6%) of them was LN. Studies by Imbiascati et al[18] and Lacerda et al[36] found that a history of LN and active proliferative LN during pregnancy respectively, were associated with SGA neonates. Nevertheless, azathioprine per se has not been associated with low-birth-weight neonates.[37]

Preterm birth is a recognised complication of lupus pregnancies. The frequency of preterm birth in the general population was reported to be approximately 13.3%,[29] while preterm birth among women with SLE varied between 21.3% and 43.6%.[9,17] Meta-analysis by Bundhun et al[3] showed a significantly higher rate of preterm birth among women with SLE compared with women who did not have SLE, with a relative risk of 3.05 (95% CI: 2.56–3.63; p<0.01). The frequency of preterm birth in our cohort was 24.5%. The majority (61.5%) of preterm births occurred between 35 to 37 weeks of gestation, and premature rupture of membranes was noted to be the leading cause, comprising 69.2% of cases. Our study revealed a history of NPSLE as predictor for preterm birth, as described by de Jesús et al.[38]

With regard to medication, 93.9% of our SLE patients received low-dose aspirin during pregnancy. Aspirin is recommended and frequently prescribed for SLE patients during pregnancy for prevention of preeclampsia[39] given the greater risk of preeclampsia in pregnant women with SLE as opposed to women without SLE. In patients with concomitant APS, they received a combination of aspirin and heparin. It is conceivable that the low rate of preeclampsia in our patients may be attributed to the high frequency of maternal exposure to aspirin, thus confirming its protective role.

As a comparison, we wish to highlight that the rates of preeclampsia and eclampsia in the East Malaysian cohort as reported by Teh et al[10] contrasted with ours (13.9% of cases with preeclampsia and 1.7% of cases with eclampsia vs. 3.7% of cases with preeclampsia and 0% of eclampsia). A striking observation and plausible contributing factor was the considerably lower rate of aspirin exposure (40.9% vs. 93.9%) among their patients.

We observed a high caesarean section rate of 50.9% in our cohort. Notably, the rate of caesarean section among women in Malaysia was reported as 23.2%.[40] This confirms that women with SLE encounter greater risk of complications during pregnancy, than women without SLE.

The limitations of our study are acknowledged. This research is retrospective in nature and involved a single site. Nevertheless, the strengths of our study include the relatively large sample size and evaluation of numerous clinical and laboratory variables. A positive point in this study as opposed to multi-centre trials is the uniformity and standardization of patient care and treatment, which accordingly impacts the provision of consistent statistics on patient management. Various risk factors have been identified as predictors of adverse pregnancy outcome in previous studies. Nonetheless, no common predictive factors have been consistently ascertained to date. This is probably attributed to the various study designs, case definitions, as well as management strategies in different centres. In addition, patient populations are diverse and studies have shown that SLE patients of various descent demonstrate differences in clinical manifestations and treatment response.

For the information of our readers, pre-pregnancy counselling is routinely conducted at our SLE clinic. Counselling on contraception and pregnancy is given to all newly-diagnosed SLE patients as well as follow-up patients who are in the reproductive age. Our patients are frequently

reminded that SLE activity has to be stable or quiescent prior to conception in order to ensure a successful pregnancy. It is clear that patient education and shared decision-making are crucial in ensuring a better control of disease and ultimately, a positive outcome.

In conclusion, pregnancies in SLE women are associated with an increased risk of maternal and foetal adverse outcomes. Women with SLE need to defer pregnancy until disease activity has been in remission for at least 6 months in order to minimise the risk of flare during pregnancy. A history of LN is associated with a 3-fold increased risk of renal flare during pregnancy. Haematological abnormalities rarely manifest during disease flare in pregnancy. Greater use of aspirin and hydroxychloroquine contributed to low rates of preeclampsia and CHB, respectively. In spite of numerous obstacles, favourable pregnancy outcomes can be achieved albeit with close monitoring during pregnancy, prompt intervention and multidisciplinary involvement.

ACKNOWLEDGMENTS

The authors would like to extend our appreciation and thanks to Puan Sumarni bt Mohd Ghazali from Pusat Sumber Khas, Institute for Medical Research for her assistance in statistical analysis. The authors would also like to thank the Director-General of Health Malaysia for permission to publish this manuscript.

DISCLOSURE

Funding - This research did not receive any funding from any agency.

Conflicts of interest/Competing interest - The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ORIGINAL ARTICLE

Factors associated with Scrub Typhus infection: A case-control study from Luhe, China

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ABSTRACT

Introduction:Scrub typhus (ST) is an acute febrile infection and remains a significant health problem globally. This study aimed to determine the factors associated with ST infection in Luhe District, China.

Material and Methods: The case-control study was conducted among 116 cases identified through passive surveillance systems over three years.The control subjects were 232 living in the same village for more than six months without any history of ST infection were selected by matching to the age (within 5-years) and identified through active surveillance. Statistical analyses were performed using SPSS v. 25.0 for Windows (IBM SPSS, Chicago, IL, USA).

Results: The mean age of confirmed persons was 58.1(SD=10.15) years, while control subjects were 56.14 (11.57).There is no significant difference in gender, age, education, and occupations between case and control. Farmers had the most significant number of cases among occupational groups. The three factors that were significantly associated with an increased odds of having ST infection are bundling or moving waste straw (OR: 1.94, 95%CI; 0.99,381), morning exercise in the park or field (OR: 4.74 95%CI; 1.19, 18.95), and working as labourer in the vegetable field (OR:1.02, 95%CI:1.02,3.19).

Conclusions:Our findings suggested establishing a prevention and control strategy for these groups to lower ST development risk.

KEYWORDS:
Scrub typhus, Orientia tsutsugamushi, Case-control study

INTRODUCTION

Scrub typhus (ST) is an acute febrile infectious disease caused by *Orientia tsutsugamushi*. Globally, ST remains a significant health problem, affecting millions of people every year, and evidence has shown that more than one billion people are at risk due to the non-availability of effective vaccines or vector control efforts.[1] The most prevalent transmission mode of *Orientia tsutsugamushi* to humans is through the bites of infected larval mites known as "chiggers" (belonging to the family Trombiculide).[2] Both rodents and mites are reported as the natural reservoir and hosts of the virus.[3] The incidence of ST mortality rates ranged from <1% to 50% depending upon proper antibiotic treatment, the status of a person infected, and the strain of *Orientia tsutsugamushi* encountered.[4]

The endemicity potency of ST has occurred within a 13,000,000 km^2 area of Asia, mainly in the Asia Pacific tsutsugamushi triangle, and remained a burden over a considerable long period of time.[5] These endemic areas extend from northern Japan to the East and North of Russia. It connects to the north of Australia in the South and Pakistan and Afghanistan in the West and the Western Pacific islands and East Asia, including China.[1] In China, ST remains one of the most severe public health concerns. Historically, southern China was known as ST endemic region, and subsequently, the disease expanded to other provinces in both rural and urban areas.[6]

The incidence of ST in China increased 1952-1989 and 2006-2016, where 133,623 cases and 174 deaths were reported.[6] There was tremendous widespread and re-emergence of ST cases identified in the past decade in many regions, including Qingdao city, China.[7] It was recently documented in high-incidence areas in the mainland of China,[8,9] with an emerging and increasing threat for many people in Guangdong province, China,[10] Zhejiang Province,[11] Anhui Province,[12] north China, Shandong province,[13,14] and recently in Jiangsu Province, China.[15] In 2006, ST was added to the national infectious disease surveillance system as a voluntarily reportable disease mainly prevalent in tropical and subtropical regions.[7,10,13] A published case-control study documented that the developing risk factors of ST occur through agricultural exposure, such as working in rice fields in Thailand, Japan, and South Korea. This also occurred among those working in oil palm and rubber plantations in Malaysia.[16]

Previous epidemiological studies have identified that those people engaged in fruit farming, gathering chestnuts, who took breaks in the areas adjacent to Korea's agriculture operations are at risk of ST infection,[17] and also the people living in rural areas. In particular, the risk is more among people age 40 and above, and people with nonfarming occupations are reported to be at higher risk of death in China.[6] Other factors associated with the increase inST infection are through outdoor activities, particularly in rural areas and among the people living at the village edge of Jiangsu Province, and bundling or moving waste straw.[18]

This article was accepted: 19 May 2021
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Also, the rapid urbanization of the populations and modifications in the ecological environment contribute to the increase of ST incidence.[19] In settings susceptible to ST, the risks are higher for people living close to grassland and cemented floor yards.[20] Furthermore,those engaged in agricultural activities like piling weeds working in hilly areas and fields are at increase risk of ST infection.[20] Similarly, there is substantial evidence that those working in a dry field farming and livestock industry are increasingly exposed to ST in South Korea.[21] Other community-based case-control studies established that the distribution, re-emergence, and associated factors of ST infection are due to increased outdoor activity of urban people, rapid urbanization, aging populations, and public surveillance systems.[22]

A recently study reported an increase of ST in China.[23] Many studies concerning ST in China have only focused on the serological diagnosis and treatment of ST patients. However, some studies of ST-associated factors have been done in the other ST endemic regions,[18,20,22] Little attention has been given to assess the risk factors in other areas. Thus, we conducted a case-control study to identify the factors associated with ST infection in Luhe District, Nanjing, that might provide information and evidence-based prevention and control.

MATERIALS AND METHODS

This study was a case-control study conducted in Luhe district (Fig I), with a population of more than 67.74 million (2019) in the Northern part of Nanjing an area of 1485.50 km^2. This region has been considered as the main endemic area of ST. The native population here are mainly employed in industries and agricultural sectors.

We used a case-control design and 116 cases (101 of patients were diagnosed positively by serological method, and 15 cases were diagnosed positively by polymerase chain reaction (PCR) were considered. To obtain cases, we sought ST records from a passive surveillance system of data retrospectively gathered from medical record obtained from the Nanjing network of the surveillance system of Nanjing Municipal Center for Disease Prevention and Control, Jiangsu province, China, during the seasonal outbreak spanning from October 2015 to December 2017. Conversely, active surveillance was involved through prospective steps in identifying ST cases, and trained interviewers visited patients in the study area and identified matched control who may develop ST infections.

A total of 232 controls matched with cases were recruited to participate in the study (1 : 2 pair matching). Eligible controls were defined as active cases living in the same village for more than six months and were matched for age (within five years) and lacked ST history. If matched control was not available in the nearest household, the health staff chose the next household.In addition, several ST associated factors were considered in the following areas: Demographic characteristics of respondents; living environment of ST cases and controls; and places of agricultural labor, outdoor agriculture activities, and human behaviors factors in ST cases and controls.

Ethical approval was obtained from the Institutional Review Board (IRB) of the ethics committee of Jiangsu Province and Nanjing Municipal Center for Disease Prevention and Control in charge of the Ethics Committee of Research School of Public Health. All aspects of the study comply with the Declaration of Helsinki. A verbal and written informed consent were also obtained from all research subjects before conducting the survey.

After consent eligible individuals, a face-to-face interview was used to collect data using a standardized questionnaire validated by the Chinese Center for Disease Control and Prevention based on the Guidelines of ST in China. The questionnaire comprised three main sections: socioeconomic demographic factors, living habits, and outdoor activities previously presented by Lyu et al., 2013.[24] This questionnaire was developed in Chinese. Two trained research enumerators were engaged from the district CDC of Nanjing administrative territory and were trained on the research intent, procedures, and data collection technicality. The data collection was by the staff from the Centre for Disease Control and Prevention (CDC) who were highly knowledgeable in disease surveillance.

Data were entered using Epidata 3.1 (Jens M. Lauritsen, Odense, Denmark), and analysis was done using SPSS version 25.0 for Windows (IBM SPSS, Chicago, IL, USA). Continuous data were expressed as the mean (SD). Descriptive data were presented as frequency and percentage (n (%)) for categorical data, while Chi-square or Fisher's exact test (when appropriate) was used for categorical data to find a potential association between study variables.The goodness-of-fit of the model was evaluated using Hosmer_lemeshow $\chi 2$ statistics. All variables with a p-value of < 0.25 were considered for possible inclusion in a multivariate conditional logistic regression model.The adjusted Odd Ratios and the confidence interval set 95% CI were reported to predict the dimension of factors associated with ST. An alpha value of 0.05 was considered statistically significant.

RESULTS

Among all the 116 cases and 232 controls, 55 (47.4%) were males, and 61(52.6%) were females. The mean age was 58.1(10.15) years in cases and 56.14 (11.57) in control groups. The age group, 41-60, had the predominant number of cases proportion at 61 (52.6%) in the case and 118 (50.9%) in the control group. Occupation-wise, 90 (77.6%) cases and 187 (80.6%) controls were farmers. Out of the total, 73 (62.9 %) of cases and 145 (62.5%) of control were in primary school (Table I).

The living environment of the case and controls are summarized in (Table II). The findings showed that most of the cases and control groups 67 (57.8%) and 170 (73.3%), respectively, were living at the center of the village and town, and 96 (82.8%) and 142 (61.2%) were living in houses near grassland vegetable field or ditch (P=0.001), 44 (37.9%) and 14 (6.0) piling weed in the yard, and 66 (56.9%) and 196 (45.7%) lived in a house environment where the presence of mouse activities were observed. Thus, residential location, living in houses near grassland, vegetable field or ditch,

Table I: Demographic characteristics of respondents (N = 116 case, and 232 controls)

Characteristics	Characteristics		p-value*
	Case (n=116)	Controls (n=232)	
Gender			0.762
Males	55 (47.4)	114 (49.1)	
Females	61 (52.6)	118 (50.9)	
Age Mean (SD)	58.1(10.15)	56.14 (11.57)	0.123
Age group, year			0.359
20~40	5 (4.3)	19 (8.2)	
41~60	61 (52.6)	123 (53.0)	
>61	50 (43.1)	90 (38.8)	
Education level, years			0.517
≤ 6 years	73 (62.9	145 (62.5)	
> 6 years	43 (37.1	87 (37.5)	
Occupations			0.510
Farmer-related	90 (77.6)	187 (80.6)	
Non-farming activities	26 (22.4)	45 (19.4)	

*Computed using Chi-square or Fisher's exact test

Table II: Living environment of ST cases and controls

Characteristics	Characteristics		p-value*	Odds Ratio	95% CI
	Case (n=116)	Controls (n=232)			
Residential location			0.005		
Edge of village	49 (42.2)	62 (26.7)		0.513	0.29,0.88
Center of village and town	67 (57.8)	170 (73.3)			
House type			0.519		
Independent house	83 (71.6)	174 (75.0)		1.069	0.59,1.93
Apartment /other	33 (28.5)	58 (25.0)			
House yard with cement floor			0.826		
Yes	29 (12.5)	203 (87.5)		0.73	0.31,1.72
No	13 (11.2)	103 (88.7)			
Living in houses near grassland, vegetable field or ditch			0.001		
Yes	96 (82.8)	142 (61.2)		0.35	0.19,0.66
No	20 (17.2)	90 (38.8)			
Piling weeds in the yard			0.001		
Yes	44 (37.9)	14 (6.0)		0.12	0.06,0.24
No	72 (62.1)	218 (94.0)			
House environment presence of mouse activities			0.054		
Yes	66 (56.9)	196 (45.7)		0.89	0.53,1.49
No	50 (43.1)	126 (54.3)			

*Computed using Chi-square or Fisher's exact test; Abbreviations: (Odds Ratio&95%CI, Confidence Interval) are computed using binary logistic regression.

piling weeds in the yard environments, and house environment the presence of mouse activities are significant factors associated with ST infection.

The potential exposure of place of work and outdoor activities where exposure within one month is presented in (Table III). From the data, there is a significant relationship between the case and controls working as labor in the vegetable field (p=0.003), and those raising animals (dogs, pigs, goats, sheep, and rabbits) (p=0.001), bundling waste straw (P=0.008), having morning exercise in the parks or fields (p=0.001) and fishing (p=0.017), respectively.

The multivariate analysis output found that three factors are significantly associated with ST infection.

The three factors that were significantly associated with an increased odds of having ST are bundling or moving waste straw (OR: 1.94, 95% CI; 0.99,3.81), morning exercise in the parks or fields(OR: 4.74, 95% CI; 1.19,18.95), and working as laborers in vegetable fields (OR: 1.80, 95% CI; 1.02,3.19).Good calibration was also observed in the validation set, with χ^2= 6.645 a non-significant P-value of 0.575 derived from the Hosmer-Lemeshow test between the observed and expected events (Table IV).

DISCUSSION

Scrub typhus is known to be an endemic disease in the world with an exponential increase in spread,[25] including China.[10,23,26-28] Over the years, there has been an increase in the reported case from many parts of China like Beijing,20 Tai'an, Northern China,[29] Jiangsu,[15] and southern China,and rapidly spreading provinces across rural and urban areas.6 This study confirms the potential risk of ST that has been articulated in the previous finding of a recent survey conducted in Jiangsu.[15] Also, the same risk factors of ST identified in Beijing,[15] Korea,[20] Taiwan,[25] Guangzhou,[30] Qingdao city, China.[7]

In the present study,we found that the population of Luhe District is more likely to be infected with ST infection with the

Table III:Places of agricultural labor, outdoor agriculture activities, and human behaviours factors in ST cases and controls

Exposure within one month	Characteristics		p-value*	Odds Ratio	95% CI
	Case (n=116)	Controls (n=232)			
Places of agricultural labor			0.510		
Farming –related	90 (77.6)	187 (80.6)		0.99	0.54,1.82
Non-farming	26 (22.4)	45 (19.4)			
Working as labour in rice field			0.551		
Yes	18 (15.5)	43 (18.5)		0.94	044,2.03
No	98 (84.5)	189 (81.5)			
Working as labour in sweet potatoes fields			0.872		
Yes	16 (13.79)	35 (15.09)		0.64	0.25,1.68
No	100 (86.21)	197 (84.91)			
Working as labour in vegetable field			0.003		
Yes	51 (44.0)	142 (61.2)		1.97	1.18,3.29
No	65 (56.0)	90 (38.8)			
Working as labour in yellow soybean fields			0.339		
Yes	16 (13.8)	27 (11.6)		0.40	0.41,1.14
No	100 (86.2)	205 (88.4)			
Working as labour in cotton field			0.110		
Yes	6 (5.2)	25 (10.8)		2.18	0.52,9.20
No	110 (94.8)	207 (89.2)			
Raising animals (dog, pig, goat, sheep and rabbit)			0.001		
Yes	85 (73.3)	96 (41.4)		0.16	0.02,0.99
No	31 (26.7)	136 (58.6)			
Bundling or moving waste straw			0.008		
Yes	22 (19.0)	76 (32.8)		1.42	0.77,2.63
No	94 (81.0)	156 (67.2)			
Outdoor related activities					
Morning exercise in the park or field			0.001		
Yes	4 (3.4)	36 (15.5)		8.03	1.33,48.62
No	112 (96.6)	196 (84.5)			
Risk behaviors					
Dry clothes in the grass			0.30		
Yes	5 (4.3)	27 (11.6)		1.66	0.30,9.01
No	111 (95.7)	205 (88.4)			
Fishing			0.017		
Yes	6(5.2)	32 (13.8)		1.98	0.57,6.89
No	110 (94.8)	200 (86.2)			
Having travel history			0.405		
Yes	3 (2.6)	3 (1.3)		0.46	0.07,2.73
No	113 (98.3)	229 (98.7)			

*Computed using Chi-square or Fisher's exact test; Abbreviations: (Odds Ratio& 95%CI, Confidence Interval) are computed using binary logistic regression.

Table IV: Multivariate logistic regression analysis model of studieda factors associated with ST infection a

Variable (s)	Adjusted OR	95% C.I.
Age	1.01	0.99, 1.04
Raising animals (dog, pig, goat, sheep and rabbit)	0.38	0.20, 0.71
Houses near grassland, vegetable field or ditch)	0.39	0.19, 0.79
Piling weeds in the yard	0.15	0.07,0.32
Bundling or moving waste straw	1.94	0.99, 3.81
Moring exercise in park or field	4.74	1.19,18.95
Dry clothes in the grass	2.08	0.42, 10.25
labour in vegetable field	1.80	1.02,3.19
Working as labour in yellow soybean fields	0.29	0.10,0.82
Having travel history	0.28	0.05,1.63
Constant	1.14	

[a]Overalldata of the model results based on Hosmer and Lemeshow Test: Chi-square= 6.645; P=0.575; df=8. Abbreviations: OR = Odds ratio; CI = confidence interval.

evidence that 90 (77.6%) of the ST cases group and 187 (80.6%) of the control groups practiced farming activities. Thus, the factors associated with ST infection include living environments, workplace, outdoor agriculture activities, and human behavior. Comparatively, female patients were highly associated with ST infection compared with male subjects.[15] Farmers were exposed to chigger mites mainly because they were involved in agricultural activities.[31]

As evidenced in the living environment, other environmental consequences attributed some of the factors associated with ST to a residential location, living in houses near grassland, vegetable field or ditch, occupation, piling weeds in the yard, and house environment presence of mouse activities.This evidence is consistent with other studies conducted in Vientiane city, where living in neighborhoods with high buildings and close to markets were at greater risk of ST infection.[32] Also, this current research findings support the findings from previous study conducted in Bejing city.[24]

Furthermore, the results showed that places of agricultural labour, outdoor agriculture activities, and human behavior factors were similar to those reported in Korea,[17] Guangzhou,[20] and Beijing.[15] In this study, farmers are high-risk groups of ST infection. In China, outbreaks of ST are typically high among farmers and those living in rural areas.[20] The findings also reported exposure during the last month for the case and control in work, outdoor-related activities, and behaviors.

This study identified that the daily morning exercise in the parks, fishing in the rivers, raising animals (dogs, pigs, goats, sheep, and rabbits), bundling or moving waste straw, working as labourers, especially in the vegetable field, are the main factors that have been significantly associated with the risk of ST exposure. Since the vectors (mites) have high mobility and are widely spread in different vegetation types, grasses, and scrubland, this result is similar to the study conducted in Guangzhou and Beijing, which showed that morning exercise in a park or field or walking in the grassland was also associated factors with ST infection.[20] The current research findings are consistent with other previous studies that reported that cases tend to increase when people are exposed to ST infection during outdoor activities.[15,17,20] This result agrees with the study demonstrating that outdoor agriculture activities were also reported significant findings among cases compared with the control group in Korea.[17] The frequency of having outdoor agriculture activities have increases the factors associated with ST infection among humans[17] and showed protective associations to ST infection.[22]

The case-control method was applied to identify several factors associated with ST infection, and it was observed that there were twice as many reported cases among the farmer-related activities, such as bundling or moving waste straw, working as labour in vegetable fields. Each of these factors isan indicator of the ST risks.

Although this is the first case-control study that was conducted in Luhe District to assess ST infection risk, it is not without limitations. Firstly, data collection was based on a passive surveillance system only, and we used a relatively small sample size for analysis. Second, there was some potential for recall bias due to the methodology approach and the need for respondents to report infection experiences with ST in 2015-2017, which involved are call from a long time for the disease onset to be investigated. Nevertheless, these findings help to establish the screening of high-risk patients with ST infection in the district,which will be further used to improve the health planning and health care policies in the community. It will also facilitate the implementation of adequate health care services to establish for the future in establishing an evidence-based intervention strategy to reduce factors associated with ST infection.

ACKNOWLEDGEMENT

The authors would like to thank the health staff in Luhe District, Nanjing Municipal Center for Disease Prevention and Control for their participation in this work. The authors would also like to acknowledge all the multidisciplinary members and classmates who highly contributed to data collection and support in completing this study.

FUNDING

This study was funded by Jiangsu Provincial Social Science Foundation, grant number 13TYA001.

DISCLOSURE

None

CONFLICTS OF INTEREST

None

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ORIGINAL ARTICLE

Effectiveness of an independent physical activity programme in improving physical activity amongst breast and colorectal cancer survivors: Study protocol for a randomized controlled trial

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ABSTRACT

Background: Previous research has documented the benefits of physical activity (PA) for cancer survivors which include improved quality of life, physical, physiological, emotional and social functioning, reduced relapse of cancer and the mitigation of cancer mortality. This study aims to evaluate the effects of an independent PA programme based on PA level, quality of life, self-efficacy, outcome expectations, reinforcement, behavioural capability and observational learning amongst registered National Cancer Society Malaysia's (NCSM) cancer survivors.

Methods: A two-armed, parallel, double-blinded, randomized, controlled trial, intervention and wait-list control groups will be conducted amongst 106 NCSM's cancer survivors. The programme is developed based on a Social Cognitive Theory that combines both psychoeducation and social media approaches to behavioural intervention. The duration of intervention will be 2 months, in which data will be collected at baseline, 2-month (immediately post-intervention) and 4-month. The primary outcome of the study is to determine the PA level of the participant which will be measured as MET-minutes/week of PA using the International Physical Activity Questionnaire (IPAQ). There are four measurements of PA that are measured which are moderate and vigorous PA (MVPA) MET-minutes/week, light PA MET-minutes/week, moderate PA MET-minutes/week and vigorous PA MET-minutes/week. A Generalised Estimating Equation (GEE) analysis will be used to evaluate the effectiveness of the intervention, adjusted for baseline covariates on both continuous and categorical outcomes. This study will utilize a significance level of 0.05 with a confidence interval of 95% for means estimation in rejecting null hypothesis. The trial registered to the Australian New Zealand Clinical Trials (ANZCTR) with the Registration Number, ACTRN12620000039987.

Conclusion: The programme will be useful as a supplementary prescription to assist policy makers to strengthen non-pharmacological cancer management options and to empower cancer survivors to be self-reliant and self-sufficient to include PA as part of their recovery process.

KEYWORDS:
Independent physical activity, Cancer survivor, Social Cognitive Theory

INTRODUCTION

Cancer is a growing public health concern worldwide. According to a World Health Organization (WHO) report in 2018, cancer is the second most leading cause of mortality globally, which accounted for 9.6 million deaths.[1] In Malaysia, previous studies have documented the escalating cases of cancer incidence.[2,3] Compared to 2006, the incidence of cancer nearly doubled from 21,773 to 41,236 new cancer cases in 2016.[2,3] Despite the increase in new cancer cases over the years in Malaysia, the 5-year cancer survival rate is improving.[3] The 5-year survival rate for breast cancer survivors from 2000 until 2005 was 49.0%.[4] According to the MyScan 2018 report, an improving trend was observed whereby the 5-year survival rate from the data collected from 2007 until 2011 was 66.8%.[3] With the increase of incidence of cancer and the 5-year survival rate improvement, the chances of cancer survivors living longer is getting higher. Therefore, survivorship in cancer has become an important discussion in recent literature.

Meta-analysis and systematic reviews reported that any mode of physical activity (PA) intervention was proven to improve health-related quality of life, sleep quality, emotional well-being, self-esteem, cancer-related fatigue, social functioning, anxiety, aerobic fitness and functional capacity, reduced the risk of cancer relapses and mitigated cancer mortality for both breast and colorectal cancer patients.[5-7] Despite the many benefits of PA for cancer survivors, the level of PA performed by cancer survivors is expected to decline and many did not meet the recommended level of PA.[8-11] In Malaysia, there is a lack of PA national surveillance amongst the local cancer population. A case control study that was conducted on 51 breast cancer survivors who were diagnosed between 2005 to

This article was accepted: 25 May 2021
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2010 reported that only 23.5% engaged in the recommended level of PA.[12]

Various standalone methods to increase the uptake of PA participation amongst cancer survivors have been utilized, such as supervised training, non-tailored print materials, non-tailored internet sites, video-based aids or physician-directed approaches. However, a complex health awareness intervention module that is integrated with a solid theoretical framework has proven to be more superior than non-theory based intervention modules.[13] A theoretical framework, such as Social Cognitive Theory (SCT), considers a unique way for an individual to achieve a particular behaviour, in this case, a targeted PA level. In the intervention programme reported in this paper, the five constructs of SCT used are self-efficacy, behavioural capability, observational learning, reinforcements and outcome expectations. In conducting an intervention programme that involves behavioural change, a theory-based intervention has shown to have a positive impact in achieving the desired result.[14] The same applies to independent PA programs, which according to SCT, an important factor for encouraging a behaviour is by obtaining feedback and providing encouragement.[14,15]

The objective of this study is to implement and evaluate the effects of an independent exercise intervention programme based on PA level, quality of life, self-efficacy, behavioural capability, reinforcements, observational learning and outcome expectations amongst cancer survivors registered with the National Cancer Society Malaysia (NCSM).

MATERIALS AND METHODS

Study location

The NCSM (also referred as Persatuan Kebangsaan Kanser Malaysia) is a non-profit, tax exempt, charitable organization which was established in 1966 in terms of the laws of the Malaysian Societies Act and Registrar of Societies Malaysia.[16] NCSM is the first cancer organization in Malaysia which provides a holistic approach on education, care and support services for people affected by cancer and their caregivers. Currently NCSM has branches in six states (Johor, Negeri Sembilan, Melaka, Perak, Penang and Sarawak).[16]

Study design

This study trial is designed as randomized, controlled, patient and outcome assessor blinded with two parallel groups, intervention and wait-list control groups. Randomization will be 1:1 allocation ratio of intervention and control group using block randomization. It will be conducted amongst 106 NCSM's cancer survivors. The programme is developed based on a SCT that combines both psychoeducation and social media approaches to behavioural intervention. The duration of intervention will be 2 months, in which data will be collected at baseline, 2-month (immediately post-intervention) and 4- month. The primary outcome of the study is to determine the PA level of the participant and it is measured as MET-minutes/week of PA using the International Physical Activity Questionnaire (IPAQ). The secondary outcome of the study comprises two parts, quality of life and Social Cognitive Theory constructs. Quality of life (QoL) outcomes is measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) version 3.

Study duration

The study will be conducted from February 2020 to December 2021.

Study population and study setting

The sampling frame is both self-registered breast cancer and colorectal cancer patients attending or are active members of any of the two NCSM branches in Kuala Lumpur (KL) and Melaka. The recruitment process began in August 2019 until December 2020. The recruitment process to identify the eligible study population involves the distribution of flyers containing information regarding this study. The flyers shall be circulated internally within NCSM via Facebook, Instagram and WhatsApp groups. In addition, the study shall be promoted to its members in each NCSM event. Interested cancer survivors will be screened for eligibility by the researcher and randomly assigned to intervention or control groups. The inclusion criteria are as follows:

i. Malaysian citizen cancer patient between the age of 18 years old and 65 years old who are registered with NCSM and actively involved with NCSM KL and Melaka
ii. Stage I to III (or IIIA for breast cancer) who are not currently receiving (and do not plan to receive during the duration of study enrollment) chemotherapy or radiation therapy. The stagings are according to the American Joint Committee on Cancer Staging Manual 7th edition.
iii. More than 8 weeks post-surgical procedure
iv. Post-treatment three months
v. Obtained medical clearance from physician
vi. Grade 0 or 1 for Eastern Cooperative Oncology Group (ECOG) Performance Status

Exclusion criteria are as follows:

i. Participated, on average, 30 to 60 min per day (≥150 min per week) of moderate intensity for at least 5 days per week or 20 to 30 min per day (≥75min per week) of vigorous intensity for at least 5 days per week or an equivalent combination of the two 11
ii. Medical or psychological condition that would interfere with the ability to fully participate during the study enrollment (e.g., psychosis, schizophrenia, etc.)
iii. Recurrent disease,
iv. Elective surgery planned during the duration of the intervention that would interfere with intervention participation (e.g., breast reconstructive surgery) and
v. Planned travel that interferes with the scheduled study sessions (i.e., no travel in the first 4 weeks and no travel in the last week of the intervention).

Sample size

The sample size calculation is based on the detection of mean differences of total PA MET- min/week within an intervention group at 12 weeks (immediately after intervention) using the standard formula for trials using individual randomization.[17] At 95% level of significance, 80% power and 10% of non-participation among eligible participants, the number of participants for each intervention and control group is determined to be 53. Therefore, the total number of participants in this study, which includes both the intervention and the control groups shall be 106.

Table I: A summary of HoPS programme to improve physical activity among cancer survivors

Week	Components	#, Method	SCT constructs	What and How
1	Group education: -Health education -Group discussion	1x 2-hour and 30 minutes face-to-face meeting session	Behavioural capability Outcome expectations Reinforcements	The first 30 minutes is health education on physical activity knowledge, benefits of PA, goal setting, barriers of physical activity and motivation through a role model
	Practical session on exercise		Self-efficacy Behavioural capability	The next two hours are a coached exercise session
2	Structured direct remote contact feedback strategy	1x individual WhatsApp	Self-efficacy Behavioural capability	Online IPAQ survey and weekly feedback on physical activity progress
3	Structured direct remote contact feedback strategy	1x individual WhatsApp	Self-efficacy Behavioural capability	Online IPAQ survey and weekly feedback on physical activity progress
4	Structured direct remote contact feedback strategy	1x individual WhatsApp	Self-efficacy Behavioural capability	Online IPAQ survey and weekly feedback on physical activity progress
5	Structured direct remote contact feedback strategy	1x individual WhatsApp	Self-efficacy Behavioural capability Outcome expectations	Reminder on physical activity knowledge. Online IPAQ and feedback on journaling
6	Structured direct remote contact feedback strategy	1x individual WhatsApp	Self-efficacy Behavioural capability Reinforcements	Reminder on goal setting. Online IPAQ and feedback on journaling
7	Structured direct remote contact feedback strategy	1x individual WhatsApp	Self-efficacy Behavioural capability Reinforcements	Reminder on barriers of physical activity. Online IPAQ and feedback on journaling
8	Structured direct remote contact feedback strategy	1x individual WhatsApp	Self-efficacy Behavioural capability Observational learning	Reminder on motivation. Online IPAQ and feedback on journaling
	Practical session on exercise + video supplementation	1x 2-hour face-to-face meeting session	Self-efficacy Behavioural capability	The next two hours are a coached exercise session

#=Frequency, +=and, IPAQ= International Physical Activity Questionnaire

Randomization, allocation concealment and blinding

The method used to generate the sequence in which subjects will be randomized is the block randomization by computer generated random sequence method. A double-blinded technique was employed in which the participating cancer survivors and the outcome assessor are unaware of the group allocation. Third-party assignment is to be used, in which each eligible participant is number-coded by the researcher. Only the researcher will have access to the cancer survivor names and codes to ensure safe keeping and confidentiality of all records. The allocation process shall involve contacting the holder of the allocation schedule who is "off-site" using the code list. Participants will be contacted centrally by telephone once the allocation is assigned. Independent assessors shall be those who assess the outcomes, blinded and will not have involved with participants. For each outcome, the assessor is defined as the person who primarily records the outcomes. They shall be two independent assessors of whom each assessor is to be responsible at different study locality (first assessor is person in-charge for NCSM's KL branch and second for NCSM's Melaka branch).

Intervention

The name of the intervention programme is called Home-based Physical Activity for Survivors (HoPS) which is an independent programme that aims to improve PA level participation amongst cancer survivors, in particular breast and colorectal cancer survivors by applying SCT in the development of the program. Both psychoeducation and social media approaches shall be combined to implement behavioural intervention. Each participant in the HoPS programme shall be provided with a non-tailored printed booklet, videos and a gradual tapering down of face-to-face group meetings to improve knowledge and skills relevant to PA. WhatsApp media is to be used as a structured direct remote feedback communication method to enable supervised home-based PA. The independent PA programme is a 2-month intervention programme. The study flow has two phases; a training phase (2-month) and follow-up phase at 2-month (immediately post-intervention) and at 4-month (Table I).

Face-to-face group meetings

There will be 2 meet up sessions for all participants in the HoPS group. The sessions will provide a standard lecture delivered by the researcher using Microsoft Powerpoint slides followed by a coached exercise session. The first session will include a lecture on health education that explains the HoPS program, PA knowledge, barriers to PA and goal setting. The lecture will then be followed by a sharing session by a role model (a cancer survivor) who shall share their experiences in engaging in PA. In each of the session, a coached exercise session will then conducted by a certified exercise instructor with at least 3 years of experience. The focus will be to train the participants on how to perform the exercise routine correctly for cancer survivors. This shall involve both aerobic and resistance exercises.

Table II: Assessment tools used in the study

Domain	Items	Assessment Tools	Respondent	B[1]	2[2]	4[2]
Sociodemographic	Age, marital status, ethnicity, education, household income, BMI	Developed within study	Participant	x		
Medical Information	Tumor site, stage/grade, treatment plan, co-morbidities	Alberta Cancer Exercise physical activity screening form[21]	Physician	x		
Physical activity	- Moderate and vigorous PA MET-minutes/week, - Light PA MET-minutes/week, - Moderate PA MET-minutes/week and - Vigorous PA MET-minutes/week.	International Physical Activity Questionnaire (IPAQ)	Participant	x	x	x
Quality of Life	Functional scales, symptom scales and a global health status / QoL scale	EORTC QLQ-C30 version 3	Participant	x	x	x
Social support	Family and friends support	Validated 26-item from the Social Support and Exercise (Modified Sallis)[22]	Participant	x		
Social Cognitive Theory constructs	Self-efficacy	Validated 4-item scale developed for patients with chronic diseases[23]	Participant	x	x	x
	Behavioural Capability	6-item assessing specific components of physical activity knowledge and skill that are adopted from the Move More for Life study[24]	Participant	x	x	x
	Reinforcements	Validated 4-item that have been previously tested for reliability and validity[25]	Participant	x	x	x
	Outcome Expectations	Validated 5-item from the Exercise Pro Subscale[26]	Participant			
	Observational Learning	3-item assessing observational learning of cancer patients that are adopted from the Move More for Life study[24]	Participant	x	x	x

PA=physical activity, MET= metabolic equivalent, BMI=body mass index, EORTC QLQ= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, 1=baseline, 2=months

Booklet

A non-tailored or standardized printed booklet will be given to each HoPS participant which will serve as a handout for the lectures given in the face-to-face group meetings and include a personal PA dairy. As this booklet has been designed specifically for this study, it is written in the Malay language. It is a standardized booklet and participants are taught on how to set goals as well as schedule and track their PA.

WhatsApp messages

A structured direct remote contact feedback strategy using WhatsApp media will be used to channel supervised feedback to the HoPS participants. From week 2 to week 8, participants are to be requested to complete a short weekly International Physical Activity Questionnaire (IPAQ) in order to assess their PA level. The results will be analyzed to determine their daily and weekly activity patterns in relation to physical activities of moderate intensity. Participants will receive WhatsApp messages each week containing graphical presentation of individual progress of PA.

Video supplementation

A series of video-based aid will be given to the participants as supplementation for independent PA. The content of this video is a series of exercises which shall be one taught during coached exercise session. This video is hoped to serves as aid to guide on right technique exercises for cancer survivors.

The HoPS programme is a two-month intervention program. In the training phase, the face-to-face group meetings are to be held on week 1 and 8, while the structured remote feedback strategy will be delivered weekly during the training phase starting from week 2. From week 5 to 8, weekly standardized WhatsApp messages shall be sent to the participants which reiterates the salient points of the lectures covered during the face-to-face group meetings.

Participants in the control group will continue receiving standard care provided by their physician during the intervention period. They will receive the HoPS programme once the final data collection has been completed or wait-list control.

Outcomes

The primary outcome of the study is to determine the PA level of the participant. It will be measured as MET-minutes/week of PA using the IPAQ. There are four measurements of PA that are measured which are moderate and vigorous PA (MVPA) MET-minutes/week, light PA MET-minutes/week, moderate PA MET-minutes/week and vigorous PA MET-minutes/week. The study will only include moderate and

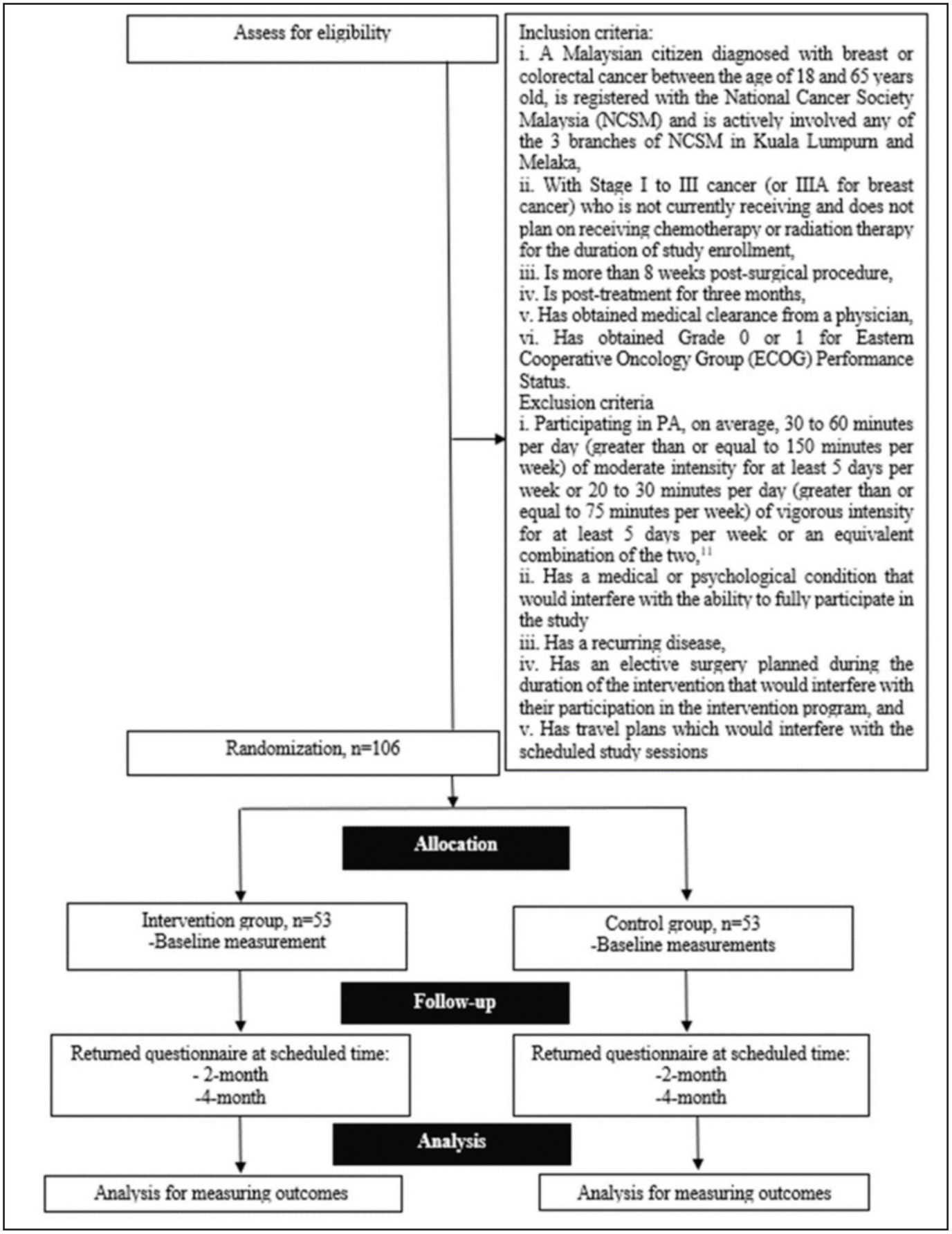

Fig. 1: Study design and process of the independent physical activity program.

vigorous PA for the first PA level measurement (MVPA MET-minutes/week), complying with the international guidelines recommendation of health or fitness benefits gained from these two PA levels for cancer survivors 11.

The secondary outcome of the study comprises will be of two parts, namely quality of life and SCT constructs. QoL outcomes is measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) version 3 which is composed of three measurements which are functional scales, symptom scales and a global health status / QoL scale. The scales range in score from 0 to 100. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems 18. SCT construct covers four measurements included in the study which are self-efficacy, behavioural capability, reinforcements, outcome expectations and observational learning. The covariates of the study include age, marital status, ethnicity, education, household income, Body Mass Index (BMI), tumor site, stage/grade, treatment plan, co-morbidities and social support. The assessment tools used are described in Table II.

Data Collection and Data Entry
There will be three stages of data collection which are at baseline, 2-month and 4- month. The baseline data will be collected via a self-reported questionnaire and to optimize validity of responses, a face-to-face meeting will be held to ensure clarity of the questions. This is important as the other two stages of data collection will be carried out utilizing an online survey. To minimize loss in follow-ups, and if the online questionnaire is not feasible, a telephone interview will be conducted. All the details of the respondents and the information will be kept confidential and used only for the research purposes.

Quality control
Questionnaire validation and reliability testing
There will be two types of validation conducted for the questionnaire which are content validity and face validity. The content of the questionnaires will be assessed and checked by Public Health Specialists, Public Health Specialists in Cancer Management, exercise specialist and psychometrics. All feedback and comments by the experts will be taken into consideration for further improvement of the questionnaires. The questions will be prepared in English and follow translational process according to the WHO guidelines (https://www.who.int/substance_abuse/research_tools/translation/en/) to maintain the meaning of the questions when it is translated to Malay. The face validity of questionnaire will be conducted among a group cancer survivor in NCSM's KL and these will not be included.

The reliability testing of the questionnaire will be conducted among 30 eligible individuals from KL branch of NCSM. Internal consistency reliability (using Cronbach's alpha for an item with Likert scale answer) and test-retest reliability (Intraclass correlation) will be used. The questionnaires will be administered twice to all the participants with an interval of two weeks for the test-retest reliability. The IPAQ questionnaire that contains continuous data will be assessed using test-retest reliability while the EORTC-QLQ and SCT constructs questionnaires that have Likert scale answers will be assessed using internal consistency reliability.

Intervention module validation
Content validity and pre-testing as well as cognitive interviewing with cancer survivors will be conducted for the intervention module. The content of the intervention module from booklet, video, structured messages in WA and slides presented in face-to-face group meeting will be vetted by public health specialists, public health specialist in cancer management, clinical psychologist and exercise specialists. The intervention module will then pre-tested with five cancer survivors from NCSM. During this session, cognitive interviewing will be also conducted to assess the understanding of the whole module with the participants. Further constructive comments and cues that may indicate an issue, including hesitation or information provided that seems to conflict will be discussed and improved prior to the commencing of this study.

Statistical analyses
Statistical Package of Social Sciences System (SPSS) version 25 will be used to analyze the data for this study. The data will be collected and analyzed using intention-to-treat analysis. Before the data analyse, screening will be conducted to detect any error. Any out of range data or any error will be checked with the respective respondents' questionnaire and correction is done accordingly. For inferential statistic, t-test / Mann Whitney U test and Chi square test/Fisher exact tests are conducted for continuous and categorical measurements respectively. These tests are formulated at baseline to look for homogeneity as well as at post-intervention to determine the differences between the intervention group and the control group. Generalised Estimating Equation (GEE) analysis will be used to evaluate the effectiveness of the intervention, adjusted for baseline covariates on both continuous and categorical outcomes. This study uses a significance level of 0.05 with a confidence interval of 95% for means estimation to reject the null hypothesis.

DISCUSSION

The independent PA programme proposed here will introduce a Malaysian tailored approach in two branches of NCSM. The work will contribute to the current knowledge in the area of implementation and the effectiveness of PA programme for cancer survivors. Until now there is minimal evidence from randomized community trials that proves the effectiveness of a PA programme on PA level improvement amongst cancer patients. This evidence is necessary to substantiate the urgency to invest in a comprehensive community (inter)national PA program. The presented intervention covers the different needs of prospective cancer survivors by providing both health education and remote feedback strategy related to PA. This supports the view that most prospective cancer survivors will benefit from evidence-based information to prepare themselves for cancer survivorship.

Whilst not every cancer survivor has access to resources and time to exercise, providing them with an independent PA programme would overcome the low uptake of PA. Cancer survivors appreciate the anonymity of PA programs that have face-to-face supervision and feedback with an exercise instructor or a health professional. However, cancer survivors have difficulties in complying with frequent physical meetings. The structure of this HoPS programme is developed to reduce the number of physical meetings, from a meeting for a group discussion to home-based PA. This is supported by previous publications relating to the preference of cancer survivors as reported in a systematic review where they preferred the intervention to be conducted at home with self-paced activity.19 However, according to SCT, positive reinforcement is substantial in both creating and maintaining behavioural change.[14,15] In addition, healthcare or expert collaboration in health promotion can result in an effective outcome for those involved. The strength of this independent PA programme is the use of IR 4.0 which is culturally tailored to Malaysians by relying on feedback using WhatsApp, a communication media that is widely and trusted by Malaysia's multicultural population.[20] A structured direct remote contact feedback strategy is the continuous feedback of progress of PA through healthcare collaboration or even other professional experts. It is remote as there is no physical meeting to supervise the progress of PA. The development of this feedback strategy is structured in a way so as to enable all cancer survivors to receive a personal graphical presentation of their own PA progress and standardized messages delivered by healthcare professionals or exercise experts using Whatsapp. When effectively facilitated, healthcare collaborations can enable fundamental improvements in community development and supports health promotion.

CONCLUSION

The development of the independent PA programme is expected to improve Malaysian cancer survivors PA level and will be useful as a supplementary prescription in cancer management that will help to improve cancer survivors' QoL during their cancer survivorship.

AETHICS APPROVAL AND CONSENT TO PARTICIPATE

An ethics approval for the study was obtained from Universiti Putra Malaysia Ethics Committee for Human Research (JKEUPM-2019-323). Trial registered on 21st January 2020 at the Australian New Zealand Clinical Trials (ANZCTR), ACTRN1262000003998721 Eligible participants will require to submit written informed consent form prior to the commencement of the study. Participation in the study is voluntarily without the influence of the organization, treatment center or physician. All the data provided in the study is confidential and access to WhatsApp data is limited to participants only.

CONSENT FOR PUBLICATION

Not applicable

DATA AVAILABILITY STATEMENT

Not applicable, data will be published once the research is finish

CONFLICT OF INTEREST

The authors of this work have nothing to disclose.

FUNDING

This study is being conducted under a Memorandum of Understanding (MOU) between Universiti Putra Malaysia and National Cancer Society Malaysia. This research also received grant from the Selangor state government amounting RM5,000 (EFT-B01845151). The collaborator has approved the study design and requires regular updates. The collaborator plays no role in methodology, study design, data analysis or writing of this manuscript.

AUTHORS' CONTRIBUTIONS

MO developed the initial intervention protocol. NAMZ, NA, TKA and MM supervised the development of the study protocol. MO and NAMZ were applicants in applying for the MoU between Universiti Putra Malaysia and NCSM. MO wrote the manuscript and all authors reviewed the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

The author would like to convey their utmost gratitude to the National Cancer Society Malaysia staff members for their invaluable support, assistance and advice throughout the process of this research.

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ORIGINAL ARTICLE

A review of idiopathic inflammatory myopathy cases in Terengganu, Malaysia: A single centre experience

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ABSTRACT

Introduction: The purpose of this study was to analyse the clinical characteristics of patients with idiopathic inflammatory myopathy (IIM) in Hospital Sultanah Nurzahirah (HSNZ), Terengganu, Malaysia. It also aimed to describe the disease manifestations in association with malignancy and other CTD.

Methods: This was a retrospective descriptive study involving all IIM patients who were managed by the Rheumatology Unit HSNZ from January 2010 to December 2019.

Results: In this review we described 15 cases wherein malignancy was detected in 4 patients after the diagnosis of IIM was made and 4 patients with overlap syndrome. One third of patients with malignancy and overlap syndrome had poor treatment response and succumbed to complications of the disease. Almost all of patients received corticosteroid as the first line therapy and nearly two thirds of them responded well to either corticosteroid alone or with combination therapy.

Conclusion: Although this study did not represent the whole population in Malaysia, it does provide a better understanding of the disease manifestation, treatment and disease complications in our cohort of patients.

KEYWORDS:
Myositis, Idiopathic Inflammatory Myopathy, Malignancy, Connective Tissue Disease

INTRODUCTION

Idiopathic inflammatory myopathy (IIM), also known as myositis, is a rare heterogeneous autoimmune disorder that leads to proximal myopathy and extra muscular manifestations, and may be part of a paraneoplastic syndrome.[1,2] The 119th European Neuromuscular Centre (ENMC) international workshop divides IIM into polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), non-specific myositis and immune mediated necrotizing myopathy.[3] The disease prevalence is 5 to 22 per 100,000 population with approximately 1.2 to 19 million persons at risk per year.[4] Most of the epidemiological studies on IIM are from Northern Europe and data for the Asian population is still lacking.[5]

The association between IIM and malignancy or other connective tissue diseases (CTD), is well known. However, there is a paucity of data pertaining to this association in Asian countries.[5] The pathophysiology of malignancy-associated IIM is still unclear but is hypothesized to be due to the autoimmune response to internal malignancy.[6,7] The risk of malignancy in IIM is 2 to 7 times higher than in the general population, particularly with DM.[8] A few meta-analyses showed that the risk for malignancy in IIM was significantly higher within the first year of diagnosis and remains high up to 5 years after IIM onset.[6,9,10] Based on studies among Norwegian and Chinese cohorts, the most commonly encountered malignancies were lung, ovarian and breast cancer in DM, non-Hodgkin lymphomas, lung and bladder cancer in PM, and prostate, colorectal, and haematological malignancies in IBM.[11,12]

Even though multiple clinical and laboratory features have been associated with malignancy in IIM and various malignancy screening strategies have been proposed, they remain to be proven. Malignancy screening should be performed in all IIM patients based on risk stratification including age and sex. A comprehensive history and physical examination including rectal, breast, pelvic and testicular examination, and basic laboratory testing should be performed in all IIM patients.[13] Studies on the use of tumour markers in clinical practice showed that they have a high false-positive and poor sensitivity rate, thus their ability to diagnose malignancy is still controversial.[14,15] A large DM cohort with 400 patients showed a blind assessment with computed tomography (CT) imaging was able to reveal malignancy in 59% of patients and the majority of them were asymptomatic.[6]

As IIM is often considered to be a paraneoplastic syndrome, a recommendation for malignancy screening has been adapted from the European Federation of the Neurological Societies (EFNS) task force. EFNS recommends primary screening with CT of the chest/abdomen/pelvis, pelvic ultrasound and mammography in women, ultrasound of the testes in men, and colonoscopy in men and women over 50 years of age. The task force also recommends for a repeat screening annually for 3 years and to proceed with further screening if new symptoms or clinical findings emerge.[16] IIM patients with malignancy also showed significant complications that contribute to a higher mortality rate.[17]

This article was accepted: 02 June 2021
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Some of the myositis-specific antibodies (MSA), particularly anti-TIF1 gamma, anti-NXP-2, and anti- SAE1 had been identified to be highly specific for malignancy-related IIM but none of the MSA is associated with a specific type of malignancy. The risk of malignancy is low in patients positive for anti-Mi-2, anti-SRP, anti-MDA5, anti-PL-7, anti-EJ, or anti-OJ antibodies.[12] Whereas, myositis-associated antibody (MAA) is found in CTD-related IIM.[7]

In this study, we analysed the baseline characteristics and demographic data of IIM patients in Terengganu, Malaysia and described the disease manifestations in association with malignancy and other CTD.

MATERIALS AND METHODS

This was a retrospective descriptive study involving all IIM patients who were managed by the Rheumatology Unit Hospital Sultanah Nurzahirah (HSNZ), Terengganu, Malaysia from January 2010 to December 2019. The study proposal was reviewed and approved by the National Medical Research Register (NMRR) (research and ethics approval ID NMRR-19-3433-52063). All IIM patients from the Rheumatology Clinic HSNZ were recruited into this study. The inclusion criteria were patients: (i) diagnosed with IIM based on the ENMC Classification criteria[3]; and (ii) aged 18 years and older. The exclusion criteria were patients: (i) who were on lipid lowering agents or other medications that can induce myositis; (ii) with endocrine or metabolic disorders such as hypokalaemia, thyroid disorder and Cushing syndrome; and (iii) with muscle trauma.

Demographic data such as age and gender, data on disease manifestation and duration, investigations and medications were retrieved from the Hospital Information System (HIS) and recorded in the data collection sheet. The data were expressed as mean ± standard deviation (SD) unless otherwise stated.

RESULTS

Demographic and clinical features

A total of 15 patients were included in this study, the majority of whom were women (73.3%). The median age at diagnosis was 44 years and the median disease duration was 24 months. The median duration of symptoms prior to the diagnosis was 8 weeks. Nine patients (60%) were diagnosed with PM, 3 (20%) with dermato-polymyositis (DM/PM), 2 (13.3%) with necrotizing autoimmune myositis (NAM) and 1 (6.7%) with DM. Fourteen cases (93.3%) presented with proximal myopathy, all of whom had elevated serum creatinine kinase (CK). The highest CK level documented was 46,000 IU/L. Nearly half of the patients (46.6%) had extra-muscular manifestations; mainly dysphagia (26.7%), interstitial lung disease (20%) and arthritis (13.3%). Heliotrope rash (20%), shawl sign (20%) and periorbital oedema (20%) were the most common skin manifestations; Gottron papules and V sign were the other manifestations.

Investigations finding

All patients except one underwent electromyography (EMG) as part of the investigation and 12 (80%) had typical myopathic EMG findings such as increased membrane irritability and spontaneous fibrillations. The EMG reports of the remaining 2 patients (13.3%) were not available. Six patients underwent muscle biopsy but only 26.7% had features consistent with inflammatory myositis. Five (33.3%) patients had myositis antibody testing but only 2 had positive autoantibodies; a patient with necrotizing autoimmune myositis which was positive for anti-Ku, anti-Ro and anti-SRP and a patient with overlap polymyositis and scleroderma which was positive for anti-TIF1 gamma. Five (33.3%) patients underwent magnetic resonance imaging (MRI) of the muscle and the finding was consistent with active myositis. The investigations performed are shown in Figure 1 and Table I.

Association with malignancy

All patients were screened for malignancy except one, as this patient defaulted our follow up. The malignancy screening included upper and lower gastrointestinal (GI) scopes, tumour markers, computed tomography of the neck, thorax, abdomen and pelvis (CT NTAP), mammogram, gynaecology and ENT assessment. Four patients (26.7%) had underlying malignancy, which was detected after the diagnosis of IIM. The details are shown in Table I.

Case 12 was diagnosed to have recurrence of ovarian cancer two months after the diagnosis of PM/DM. The patient had previous ovarian cancer in complete remission for the preceding 20 years and presented with new onset of symmetrical proximal muscle weakness, skin lesions and dysphagia. The patient had significantly elevated CK and LDH levels with a positive skin biopsy. Unfortunately, the patient had poor treatment response and succumbed to advanced malignancy.

Case 13 was diagnosed with PM/DM, followed by left breast carcinoma 3 months later. The patient also had the typical clinical features of IIM, and the malignancy screening confirmed the diagnosis of left breast carcinoma. The patient did not respond to treatment and succumbed due to malignancy complications.

Case 15 presented only with a skin lesion without proximal myopathy and the diagnosis of colon adenocarcinoma was made after seven months. The patient had no GI or constitutional symptoms but colonoscopy showed a rectal mass and biopsy confirmed adenocarcinoma of the colon. The patient showed a good treatment response after the tumour removal and a course of cancer chemotherapy along with the CS to control the skin lesion.

Case 14 was diagnosed to have papillary thyroid cancer 3 months after the diagnosis of PM. The patient had typical clinical manifestations of PM, underwent thyroidectomy and responded well to CS therapy.

Association with other CTDs

There were four cases (26.7%) that overlapped with another CTD; three cases (Case 8, Case 9, and Case 10) had SSc and one case (Case 11) had SLE.

Treatment and treatment response

Table I: Retrospective chart review

Case	Age at diagnosis (years)	Manifestation	Investigation	Diagnosis	Malignancy	Time to diagnosis of malignancy	Treatment and treatment response
1	45	Symmetrical proximal myopathy, no extra-muscular involvement	Elevated CK (1052 IU/L) and LDH (233 IU/L), positive EMG and muscle biopsy	Polymyositis	Nil	Not applicable	CS and MTX Good response
2	41	Symmetrical proximal myopathy, no extra-muscular involvement	Elevated CK (5000 IU/L), positive EMG and muscle biopsy	Polymyositis	Nil	Not applicable	CS, AZA and MTX Good response
3	55	Symmetrical proximal myopathy and arthralgia	Elevated CK (3899 IU/L) and LDH (451 IU/L), others not available	Polymyositis	Nil	Not applicable	CS Died from severe infection
4	44	Symmetrical proximal myopathy and ILD	Elevated CK (4672 IU/L) and LDH (1100 IU/L), positive EMG and MRI thigh, muscle biopsy inconclusive, negative MSA/MMA	Polymyositis	Nil	Not applicable	CS, MTX, AZA, MMF, IVIg Good response
5	47	Symmetrical proximal myopathy, no extra-muscular involvement	Elevated CK (1405 IU/L) and LDH (402 IU/L), positive EMG and muscle biopsy, normal MRI thigh	Polymyositis	Nil	Not applicable	CS, AZA and MTX Good response
6	23	Symmetrical proximal myopathy, no extra-muscular involvement	Elevated CK (6758 IU/L) and LDH (837 IU/L), positive EMG (consistent with necrotizing autoimmune myositis), positive anti-SRP, anti-RO and anti-KU	Necrotizing autoimmune myositis	Nil	Not applicable	CS and MTX Good response
7	28	Symmetrical proximal myopathy, no extra-muscular involvement	Elevated CK (46000 IU/L) and LDH (843 IU/L), positive EMG (consistent with necrotizing autoimmune myositis), negative MSA/MAA	Necrotizing autoimmune myositis	Nil	Not applicable	CS and MTX Good response
8	22	Symmetrical proximal myopathy, skin tightening and dysphagia (consistent with scleroderma)	Elevated CK (8460 IU/L), positive MRI thigh, negative MSA/MAA	Overlap Polymyositis and Scleroderma	Nil	Not applicable	CS, MTX (ceased due to lung fibrosis), AZA Good response
9	38	Symmetrical proximal myopathy and dysphagia	Elevated CK (786 IU/L) and LDH (960 IU/L), positive EMG and skin biopsy, positive anti-TIF1 gamma	Overlap Dermato-polymyositis and Scleroderma	Nil	Not applicable	CS and MTX Good response
10	24	Symmetrical proximal myopathy, dysphagia, skin tightening	Elevated CK (3670 IU/L) and LDH (1080 IU/L), positive EMG, muscle biopsy and MRI thigh	Overlap polymyositis and scleroderma	Nil	Not applicable	CS, AZA, MTX, CYC, IVIg, MMF, Rituximab Died from severe pulmonary hypertension
11	33	Symmetrical proximal myopathy and arthritis	Elevated CK (9748 IU/L), others not available	Overlap Polymyositis and SLE	Nil	Not applicable	Unsure (defaulted follow up)
12	75	Skin lesion, facial swelling, symmetrical proximal myopathy and dysphagia	Elevated CK (426 IU/L) and LDH (487 IU/L), positive skin biopsy, normal EMG	Polymyositis and Dermatomyositis	Yes, Recurrence of ovarian cancer	2 months	CS Died from advanced malignancy
13	70	Symmetrical proximal myopathy, periorbital edema and rashes, no extra-muscular involvement	Elevated CK (3900 IU/L) and LDH (602 IU/L), positive MRI thigh, normal EMG, no evidence of DM on skin biopsy	Polymyositis and Dermatomyositis	Yes, left breast invasive carcinoma	3 months	CS, IVIg Died from severe infection
14	68	Symmetrical proximal myopathy, no extra-muscular involvement	Elevated CK (8130 IU/L) and LDH (1519 IU/L), positive EMG and muscle biopsy	Polymyositis	Yes, metastatic papillary thyroid cancer	3 months	CS Good response
15	70	Skin lesion, no proximal myopathy	Normal CK and LDH, positive skin biopsy	Dermatomyositis	Yes, adenocarcinoma of colon	7 months	CS Good response

CK = creatinine kinase, LDH = lactate dehydrogenase, EMG = electromyography, MRI = magnetic resonance imaging, ILD = interstitial lung disease, MSA = myositis-specific antibody, MAA = myositis-associated antibody, CS = corticosteroids, MTX = methotrexate, AZA = azathioprine, MMF = mycophenolate mofetil, IVIg = intravenous immunoglobulin, DM = dermatomyositis

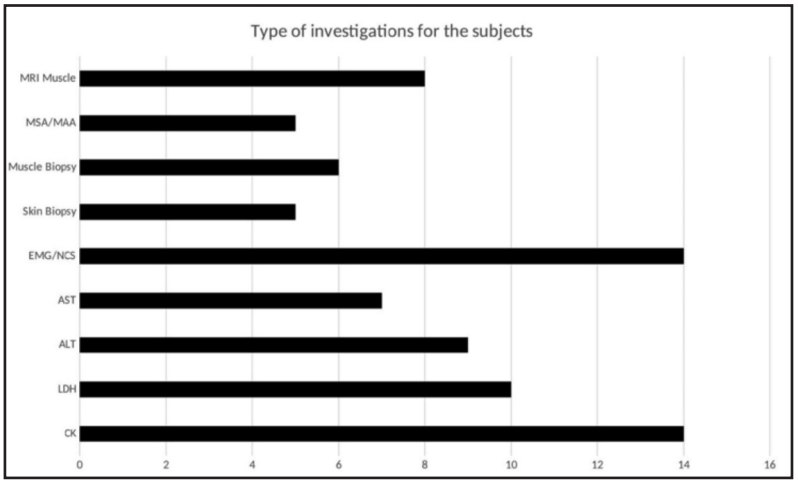

Fig. 1: Type of investigations done for the subjects.

All patients except one received corticosteroid (CS) as first line therapy and two patients (Case 14 and Case 15) responded well with corticosteroid alone. Patients who received a combination of corticosteroid and other immunosuppressive therapies (Case 1, Case 2, Case 5, Case 6, Case 7, Case 8 and Case 9) showed good treatment response and subsequently achieved disease remission.

The majority of the patients received either methotrexate (MTX) (60%) or azathioprine (AZA) (33.3%) as the second line agent. Other second line agents given to the patients included myophenolate mophetil (MMF), intravenous immunoglobulin (IVIg) and biologic therapy. IVIg was given as induction therapy for our refractory cases (Case 4 and Case 10) and when other immunosuppressive drugs were contraindicated (Case 13).

Nine patients (60%) responded well to their therapy and showed significant improvement of their symptoms and CK level. However, 4 patients (26.7%) (Case 3, Case 11, Case 12 and Case 13) had poor disease control despite a good dose of corticosteroid and immunosuppressant therapy, three of whom had secondary malignancy and SSc. The patients succumbed to disease complications such as infection, advanced malignancy and severe pulmonary hypertension.

DISCUSSION

The results of our case review are consistent with the previous Caucasian and Asian study that showed that IIM is a female predominant disease with a median age at diagnosis within the fourth decade of life.[5]

This review also demonstrated that more than half of the patients were diagnosed with malignancy or had overlap CTD. Four patients who were subsequently found to have cancer had IIM as the paraneoplastic manifestation. The patients with malignancy were detected within 2 to 7 months of their IIM diagnosis. Even though the number of patients in this study was small, our findings suggested that IIMs can be an early sign of malignancy. A study by Chow et al showed that the cancer risk was six-fold higher during the first year of the IIM diagnosis and lower during subsequent years of follow up.[10] Thus, monitoring of emerging malignancy related local/systemic symptoms during each clinic visit is very important for the first 5 years of diagnosis and this can be up to 20 years after the IIM diagnosis.[6]

Majority of our patients responded well with corticosteroid therapy with combination of second line treatment. Most of the existing studies recommended CS as the first line therapy. However, there was no specific recommendation for the dose and duration of the CS treatment regime.[18,19] Therefore, the decision for tapering of therapy was based on clinical and biochemical response.

Our patients who received a combination of corticosteroid and other immunosuppressive therapies showed good treatment response and subsequently achieved disease remission. This finding was similar to a previous study by Souza et al[18], who reported that individuals who received methotrexate or/and azathioprine showed an improvement in functional status and required lower maintenance CS doses. The survival rate of patients with malignancy or CTD related disease is known to be very poor.[17] Thus, all IIM patients should be evaluated for malignancies at diagnosis, followed by long-term surveillance for a better therapy and outcome.

Although muscle biopsy is the gold standard for the diagnosis of IIM[20], only 6 patients had muscle biopsy due to logistic limitations of the procedure, with only 26.7% demonstrating features consistent with inflammatory myositis. Bohan et al reported that 10-20% of patients with IIM may have normal muscle biopsy findings and the absence of inflammatory infiltrates does not exclude IIM.[21,22] The negative muscle biopsy results could be due to sampling error owing to skip lesions or treatment with CS prior to biopsy sampling.[22,23] The diagnostic yield can be improved with MRI guided muscle biopsy for a better interpretation. Having said that, we arranged for muscle biopsy in patients with recurrent relapses or poor treatment response before deciding on further treatment options.

As reported in previous studies, MSA assists in risk stratification for malignancy screening in IIM patients as certain MSA act as biomarkers for malignancy.[12,13] Only 33.3% of our patients had myositis antibody testing due to limited resources, mainly because it had to be done in a private laboratory. Anti-SRP autoantibodies have been

shown to be significantly associated with necrotizing autoimmune myositis[1] and it was positive in one of our patients. Although the patient had no extra-muscular involvement and responded well to immunosuppressive therapy at the time of this study period, the patient should continue to be monitored closely as anti-SRP positive patients are generally reported to have poor treatment response.[24] Another patient with overlap of polymyositis and scleroderma was positive for anti-TIF1 gamma but had no evidence of malignancy at the time of this study period. This patient required regular monitoring and screening for the possibility of malignancy in the future.

Most of our patients were diagnosed by their typical clinical manifestations, elevated muscle enzymes and EMG and/or antibody myositis panel. As proposed by David et al[20], patients with the classical clinical features of IIM, elevated serum CK and typical neurophysiological changes on EMG do not need a confirmatory muscle biopsy, unless management difficulties arise.

CONCLUSION

Although our study population was small and dominated by one ethnicity (Malays), it does illustrate the spectrum of manifestations and response to various treatment options of this potentially debilitating disease. The clinical manifestations of the IIM in our patient cohort as well as the treatment options and their responses appear to be similar to the other Asian and Western data, including the screening of malignancy and CTD in all IIM patients and the use of CS as first line therapy. Screening for malignancies is, therefore, an important part of the management.

ACKNOWLEDGEMENT

We would like to thank the Director General of Health Malaysia, the Director and the Head of Department of Medicine Hospital Sultanah Nurzahirah, Terengganu for allowing us to publish the paper.

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3D-SSP analysis for amyloid brain PET imaging using ^{18}F-florbetapir in patients with Alzheimer's dementia and mild cognitive impairment

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ABSTRACT

Introduction: The aim of this study is to use 3D-SSP and a population-comparable normal database to investigate the associations between amyloid deposition detected by ^{18}F-florbetapir PET and neurocognitive performance of participants with mild cognitive impairment (MCI) and Alzheimer's disease (AD).

Materials and Methods: ^{18}F-florbetapir PET and ^{18}F-FDG PET imaging was prospectively performed on 78 subjects (20 cognitively healthy controls [HC], 27 MCI patients, and 31 AD patients) within 6 weeks of their neurocognitive assessments. The PET datasets from 19 HCs were used to create an NBD. The 3D-SSP analysis and Z-score mapping of ^{18}F-florbetapir accumulations in the brain were further staged based on their accumulation patterns. Global and regional standard uptake value ratios (SUVRs) of ^{18}F-florbetapir were calculated using the cerebellar cortex as the normalised region. The relationships between the ^{18}F-florbetapir PET results, the clinical diagnoses and Thai Mini-Mental State Examination (TMSE) scores were determined.

Results: There was high agreement between the visual assessment results and the semiquantitative analysis (κ = 0.793 and 0.845). The stages of amyloid deposition were consistent with neurocognitive status across participants. Significantly higher SUVRs were found in AD than MCI and HC. Visual assessment and stage were not significantly correlated with TMSE scores. A significant negative correlation between the SUVRs and TMSE scores was partially demonstrated in MCI and AD, but not HC.

Conclusions: 3D-SSP analysis of ^{18}F-florbetapir PET provides special patterns and intensity of beta amyloid accumulation semi-quantitatively that are associated with the diagnosis and neurocognitive performances in MCI and AD patients.

KEYWORDS:
^{18}F-florbetapir; amyloid; brain PET; Alzheimer's disease; NEUROSTAT; 3D-SSP

INTRODUCTION

Alzheimer's disease (AD) creates a significantly negative impact on the quality of life of patients and their families and is a major socioeconomic burden. Conventional imaging modalities have a relatively limited ability to accurately differentiate the types of dementia. Glucose hypometabolism detected from ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) study provides characteristic patterns in AD, frontotemporal lobe dementia (FTD) and dementia with Lewy Bodies (DLB). However, there are overlapping of abnormalities. The accumulation of amyloid beta (Aβ) plaques in the brain is one of the important factors associated with the loss of synapses and neuronal degeneration during the preclinical phase of AD,[1] and it is required for a pathological diagnosis of AD.[2] There has been a growing acceptance of the use of PET imaging of amyloid beta deposition in the brain for several purposes, namely, to enable the early identification of subjects who might be at risk of developing AD dementia, to select patients for amyloid-clearing therapies and to evaluate therapeutic efficacy.[3-6] Visual interpretation of Aβ PET images using binary "positive" and "negative" scales is routinely performed. However, equivocal cases may present,[6] and the correlation between binary-scale interpretation and neurocognitive status is as yet conclusive.[5,7-9] Semiquantitative analysis of Aβ PET images using standard uptake value ratios (SUVRs) shows the advantage of providing consistency in interpretation, diagnostic and prognostic classification, and objective evaluation of longitudinal changes.[10-12] The recent development and integration of toolboxes in free software has enabled the automation of the calculation of SUVRs of brain PET images.[13-14] Nevertheless, the use of such tools is still mainly limited to research settings. The need for individual structural magnetic resonance imaging (MRI) images also does not allow some techniques to be used for patients who cannot undergo MRI.

A semiquantitative image analysis using 3-dimensional stereotactic surface projections (3D-SSP) in PET neuroimaging studies has been shown to improve the accuracy of diagnoses of different neurological abnormalities.[15] Using 3D-SSP Z-score maps, the patterns of abnormal radiotracer distribution in a subject's brain relative to a normal subject database may facilitate diagnosis. However, the results from 3D-SSP analysis of amyloid beta PET studies are relatively limited[16,17] and can differ with the normal controls and radiopharmaceuticals used. Five stages of amyloid deposition were proposed in a recent study on the frequency of the regional distribution of ^{18}F-florbetapir PET images obtained from Alzheimer's Disease Neuroimaging Initiative (ADNI)

This article was accepted: 07 March 2021
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data. The stages were based on regional brain involvement, and they were found to be very consistent with clinical diagnoses, CSF Aß42 levels and some neurocognitive test results.[18]

In the current study, we used semiquantitative data from ^{18}F-florbetapir PET images of the brain in patients with AD and mild cognitive impairment (MCI). The reference database of ^{18}F-florbetapir PET images was acquired from a cognitively normal, elderly, Thai population (Thai NDB). We demonstrated a high association between the amyloid PET results and clinical diagnoses. Negative correlations between amyloid PET results and the TMSE scores were also partly observed.

MATERIALS AND METHODS

This single centre study was approved by the Institutional Review Board as a part of the Amyloid PET Project (COA: Si137/2015). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Subjects

This study enrolled 78 subjects who had visited the Geriatric Clinic, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. The participants were aged 60 and above, and comprised 20 cognitively healthy controls (HCs), 27 patients with clinically diagnosed MCI, and 31 patients with clinically diagnosed AD. Formal consent was given by the subjects or their legally authorised representatives. Normal elderly subjects were also recruited via a poster advertisement. The ^{18}F-fluorodeoxyglucose (FDG) and 18F-florbetapir PET were performed on all subjects between September 2016 and June 2018, and within 6 weeks of their neurocognitive assessments. Exclusion criteria were as follows: an unstable medical condition, seropositivity for HIV or AIDS, alcoholism, drug abuse, primary or metastatic brain cancer, significant brain lesions, a history of amyloid-targeting medication usage, or a lack of willingness to follow the study protocol. The neurocognitive tests performed on all of the subjects comprised the Thai Mini-Mental State Examination (TMSE),[19] Clinical Dementia Rating (CDR) Scale,[20] Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-COG),[21] and Thai Activities of Daily Living (ADLs).[22] The study used established criteria from of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[23] and the International Working Group on Mild Cognitive Impairment[24] to define participants with AD, MCI and cognitively HC based on their clinical complaints, TMSE and CDR scores as of followings;

- *AD:* Subjects with dementia symptoms compatible with fulfilled criteria for probable AD; TMSE < 26; CDR ≥ 0.5.
- *MCI:* Subjects with a subjective memory complaint reported by the patient, a family member or a clinician, plus impairment on objective cognitive tasks and/or evidence of decline over time on objective cognitive tasks, with preserved activities of daily living; TMSE 24-30, CDR = 0.5.
- *HC:* Subjects without neurological or psychiatric illness, no MCI or dementia symptoms and normal activities of daily living; TMSE 24-30; CDR = 0.

PET image acquisition

The in-house productions of the ^{18}F-florbetapir tracer and imaging protocols were as previously described.[25,26] All subjects underwent both ^{18}F-FDG and ^{18}F-florbetapir brain PET/CT scans with at least a 24-hour interval between the scans, acquired in 3D-mode on a Discovery STE PET/CT scanner (GE Healthcare, Milwaukee, Wis., USA). The acquisition and reconstruction techniques followed the scanner-specific protocols from ADNI 2 and were stated in our previous work.[26,27] The ^{18}F-FDG PET/CT scans were acquired over approximately 30 minutes following a 4.5–5.5 mCi ^{18}F-FDG injection and scanned for 30 minutes. The amyloid PET/CT scans were acquired over approximately 50 minutes following 8–10 mCi ^{18}F-florbetapir injection and scanned for 20 minutes. The subjects were positioned in the scanner using a laser light beam to ensure proper head alignment, and a computed tomography scan was acquired prior to the PET imaging for attenuation correction. Immediately after the acquisition, the images were reconstructed and corrected for scatter and attenuation using commercial software packages and inspected for adequacy of count statistics and absence of head motion. Summed images from the reconstructed ^{18}F-FDG PET/CT data and the reconstructed amyloid PET/CT data were generated for each subject, after excluding any image frames in which head motion was detected.

Image analysis

For each PET scan, the anonymised and summed DICOM image files were converted to one analysis format file using ImageJ 1.51s software (National Institutes of Health, Bethesda, Md., USA; available at http://imagej.nih.gov/ij). Each converted file was further processed using Neurological Statistical Image Analysis Program (NEUROSTAT/3D-SSP software, University of Utah, Salt Lake City, Utah, USA) to transform the reconstructed images to the stereotactic coordinate system and to co-register the ^{18}F-FDG and ^{18}F-florbetapir PET/CT images using previously validated methods, described as follows.[15-17] Each ^{18}F-FDG and ^{18}F-florbetapir PET/CT image generated by the NEUROSTAT software underwent quality control for alignment and coregistration before interpretation. The regional activities of the ^{18}F-florbetapir were extracted from the cortical grey matter to the surface of the template using the 3D-SSP method in the same manner as for ^{18}F-FDG PET/CT. The ^{18}F-florbetapir SUVRs were calculated from the cortical activity in particular brain regions normalised by the average activity of cerebellar cortex (CBL) using NEUROSTAT scaling procedures. The average values of the bilateral hemispheric global and regional cerebellar normalised SUVRs were calculated in accordance with the most validated regions for amyloid deposition found by a previous study[28], namely, the frontal cortex, parietal cortex, temporal cortex, occipital cortex, anterior cingulate, and posterior cingulate. In this study, ^{18}F-FDG PET/CT images were used mainly to assist in coregistration amyloid PET/CT images to the standard brain

template. The brain glucose metabolism in all subjects were also evaluated and classified as AD-liked, FTD-liked and other patterns (normal, undetermined or DLB)[29] to support or explain their amyloid PET/CT results, which were further discussed.

The spatially normalised ^{18}F-FDG and amyloid PET/CT scans from 20 cognitively normal volunteers (HCs; age 60–82 years) were used to create a NDB for each PET/CT study. The original scans of those HCs had been interpreted in consensus by visual assessment as being negative for both glucose hypometabolism and amyloid deposition, as per standard guidelines.[6] The PET/CT images of ^{18}F-florbetapir accumulation in the brain of each AD and MCI patient were compared with the NDB. The Z-scores ($Z = [voxel_{subject} - voxel\ mean_{NDB}]/voxel\ standard\ deviation_{NDB}$) were calculated on a voxel basis; the cortical activities were extracted to predefined surface pixels using the 3D-SSP technique, and the Z-score maps were automatically generated by computing the intensity normalised to the cerebellar cortex.[16-17]

The original transaxial images and 3D-SSP Z-score maps interpretations were performed in consensus by 2 experienced nuclear medicine specialists who were trained in ^{18}F-florbetapir PET interpretation (T.T. and C.S) without knowledge of the related clinical information. In equivocal cases, the images and maps were confirmed by a senior neuroimaging expert (S.M.). The visual assessments were classified as "positive" or "negative," following standard guidelines.[6] To evaluate abnormally increased cortical amyloid depositions, positive Z-score maps displayed on a colour-coded scale—which reflected positive tracer uptake deviations relative to the norm—were used for interpretation. The positive Z-score map pattern of each participant was staged as 0–IV, according to the recently reported criteria[18]: Stage 0, no involvement; Stage I, basal part of the temporal lobe, the anterior cingulate gyrus and the parietal operculum; Stage II, wide parts of the temporal, frontal and parietal associative cortex; Stage III, primary sensory-motor cortices and anterior medial temporal lobe; and Stage IV, posterior medial temporal lobe and the striatum. An abnormal amyloid PET/CT was considered in the regions with a Z score level of ≥ 2, which corresponds to the green colour and above on the colour scale bar (Figure 1). Each stage was then classified as "negative" (Stages 0–I) or "positive" (Stages II–IV) to assess the correlation with the binary visual interpretation. Abnormal amyloid depositions in the areas of a higher stage without involvement at the areas of a lower stage were deemed "Unstageable". Comparisons were then made of the results from each interpretation technique and the visual assessment of the original images and the semiquantitative amyloid PET results.

Statistical analyses

Statistical analyses were performed using PASW Statistics for Windows (version 18.0; SPSS Inc., Chicago, Ill., USA). Descriptive statistics were used to characterise the demographic and baseline characteristics of the study subgroups. Chi-squared tests and one-way ANOVA were applied for statistical comparisons between the study subgroups, followed by a post hoc test with pairwise comparisons. Agreement between the visual and semiquantitative amyloid PET/CT results were expressed in terms of Cohen's Kappa and percentage agreement. Pearson correlation and Spearman's correlation analyses were used to evaluate the relationships between the PET/CT results and the TMSE scores. Statistical significance was defined as $P < 0.05$.

RESULTS

The automatic co-registration of both brain PET/CT datasets was completely successful for 77 of the 78 subjects. The one unsuccessful case involved an individual with mild AD, for whom significant co-registration errors occurred. The baseline characteristics of the 77 study subjects subsequently analysed are detailed in Table I. There were no significant differences in the age, sex, or education levels of the study subgroups. Significant differences ($p < 0.05$) were observed for all neurocognitive scores, with better neurocognitive performances for the HCs than the AD subjects, and for the MCI than the AD subjects. Only the CDR score was significantly lower for the MC than the HC subgroup; though the other tests showed a lower cognitive performance for the MCI subgroup, the differences did not reach statistical significance.

The results from the visual assessments were also consistent with the clinical diagnoses: negative in 19/20 of the HCs (95%), while positive in 26/30 (87%) of the AD and 13/27 of the MCI (48%) subjects. Likewise, the stages of amyloid deposition were consistent with the clinical diagnoses: 19/20 (95%) of the HCs had negative results (Stage 0), while 24/30 (80%) of the AD and 9/27 (33.3%) of the MCI subjects had positive results (Stages II–IV). An additional 3.3% of the AD and 3.7% of the MCI participants showed a Stage I pattern, with amyloid deposition only at the anterior cingulate; this was considered negative by the definitions used in this study. There was a high agreement of amyloid positivity between the visual assessments and the Z-score maps (92.2% agreement; $\kappa = 0.845$; 95% CI, 0.785–0.905), and between the visual assessments and the global SUVRs (89.6% agreement; $\kappa = 0.793$; 95% CI, 0.724–0.862). The main discordant amyloid PET/CT results were found in 6 patients (4 MCIs; 2 ADs), whose results were considered positive by visual assessment but negative by the Z-score map staging and SUVRs.

Significant differences were observed between the global and regional SUVRs of the HCs and AD subjects, and of the AD and MCI subjects: the AD subgroup had significantly higher SUVRs than the MCI subgroup ($p < 0.001$–0.003) and the HC subgroup ($p < 0.001$; Figure 2). However, there were no significant differences between the regional nor the global SUVRs of the HC and MCI subgroups. From an ROC curve analysis, the best cutoff of cerebellar normalised SUVR to discriminate between HC and AD was 1.15, with a sensitivity of 83.3% and a specificity of 90%. The results of the different methods used to interpret the ^{18}F-florbetapir PET/CT images for all clinical diagnoses are illustrated in Figure 3. Negative correlations between the results of the ^{18}F-florbetapir PET/CT imaging and the TMSE scores were observed in all subgroups, regardless of the interpretation method. However, the correlations from the visual assessments and the staging by the Z-score map patterns were not statistically significant.

Table I: Demographics and characteristics of subjects of clinical diagnostic groups

	HC (n = 20)	MCI (n = 27)	AD (n = 30)	P-value
Age, years, mean (SD)	69.35 (5.10)	68.67 (6.09)	71.70 (6.31)	0.139
Sex (% female)	65%	48.15%	50%	0.468
Education, years, mean (SD)	11.85 (5.76)	14.70 (4.50)	13.13 (10.66)	0.455
Onset, months, mean (SD)	N/A	19.96 (10.55)	38.33 (17.69)	< 0.001[a]
TMSE, score, mean (SD)	27.65 (1.81)	27.15 (1.61)	22.07 (4.65)	< 0.001[a,b]
CDR, score, median (IQR)	0	0.5 (0)	0.75 (0.5)	< 0.001
ADAS-COG, score, mean (SD)	5.18 (2.02)	8.91 (4.07)	19.67 (9.92)	< 0.001[a,b]

Abbreviations: HC, cognitively healthy control; MCI, mild cognitive impairment; AD, Alzheimer's disease; TMSE, Thai Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating–Sum of Boxes, ADAS-COG, Alzheimer's Disease Assessment Scale–Cognitive subscale; SD, standard deviation; IQR, interquartile range: a, significant difference found between HC and AD; b, significant difference found between AD and MCI

Table II: Correlation between visual assessments, stages from Z-score map patterns, and global cortical and regional SUVRs obtained from 18F-florbetapir PET data, with neurocognitive performance (evaluated with the TMSE scores)

Method	Region	Correlation coefficient		
		Method	Region	Correlation coefficient
Visual assessment		-0.387	-0.190	-0.154
Stage		-0.387	-0.250	-0.239
SUVR	Cerebral cortex	-0.323	-0.347*	-0.216
	Parietal	-0.328	-0.343*	-0.142
	Temporal	-0.366	-0.341*	-0.158
	Frontal	-0.286	-0.381*	-0.209
	Occipital	-0.346	-0.143	-0.350*
	Anterior cingulate	-0.071	-0.413*	-0.039
	Posterior cingulate	-0.340	-0.316	-0.070

* P-value of < 0.05

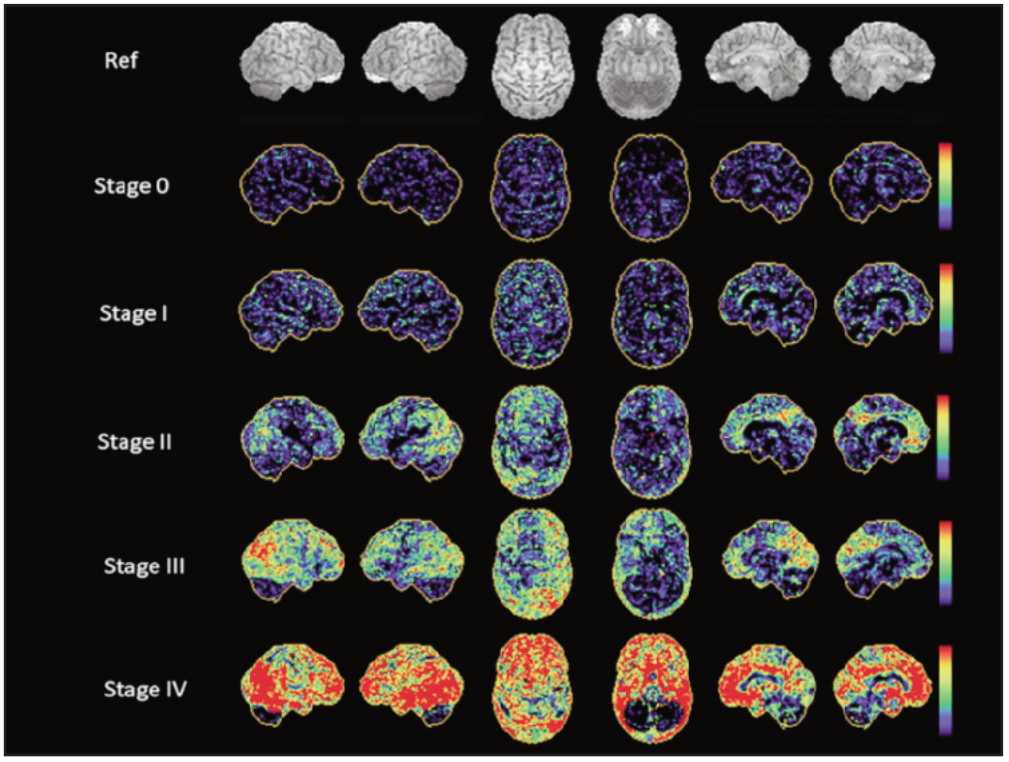

Fig. 1: In vivo staging of amyloid beta deposition using individual Z-score image patterns from 18F-florbetapir PET, compared with normal database applied from previously proposed staging system, according to regional amyloid deposition.15 From left to right, the image views are right lateral, left lateral, superior, inferior, right medial and left medial. The range of the Z-score colour codes was set from 0 (black) to 5 (red).

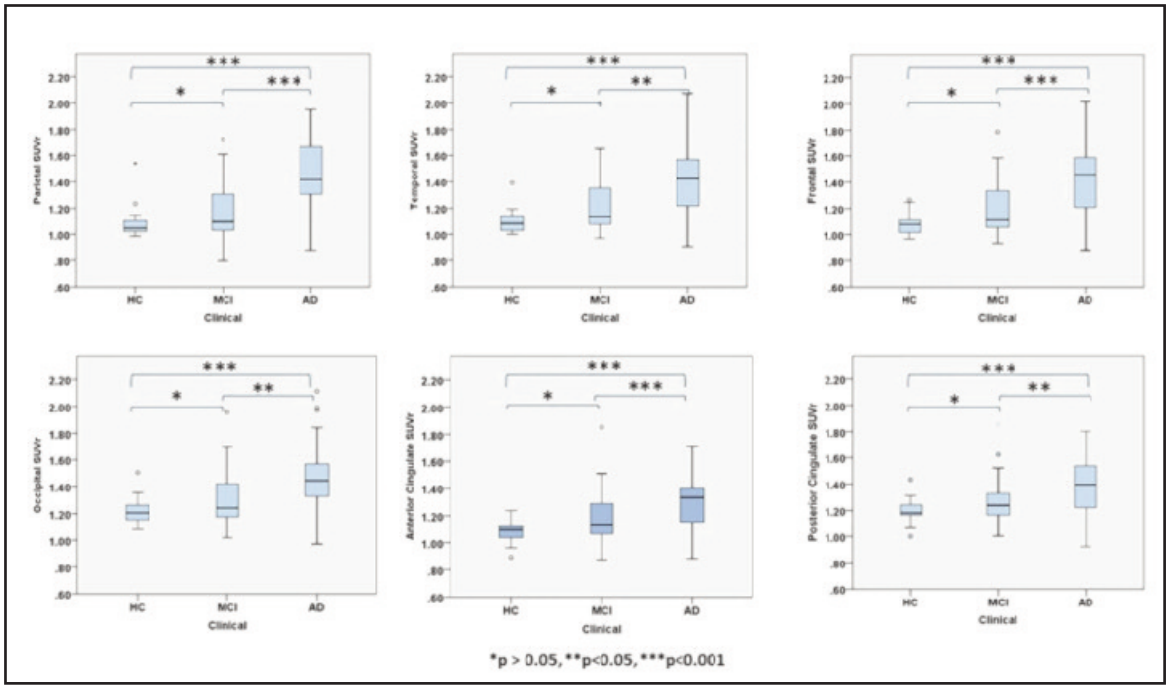

Fig. 2: Comparison of regional SUVRs and global cerebral cortex SUVRs from 18F-florbetapir PET (normalized by cerebellar cortex) of the clinical groups, showing overall higher SUVRs in AD than MCI and, in turn, than HC. Significant differences in the SUVRs were found between AD and MCI, and between AD and HC, but not between HC and MCI.

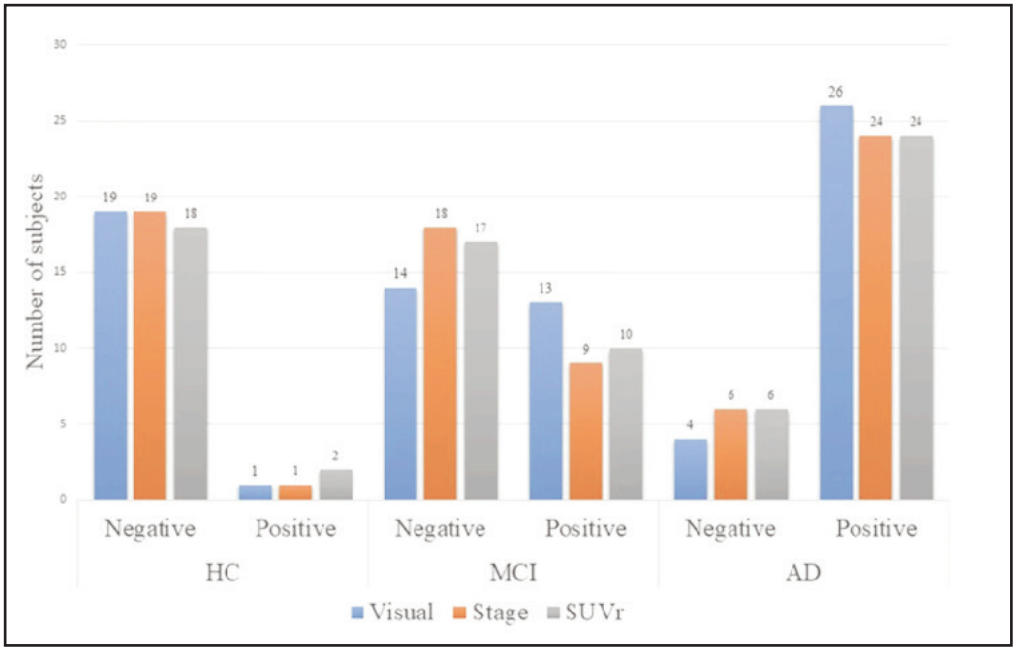

Fig. 3: Comparison of results of 18F-florbetapir brain PET from different interpretation methods, using the visual assessment and summary of stages obtained from 3D-SSP Z-score map patterns (the stages defined in Figure 1 were reclassified as follows: stages 0–I = negative, and stages II–IV = positive). The global cortical SUVR cutoff for amyloid positivity was > 1.15. A concordance of the results between the visual assessment and summed stages was observed, with HC > AD > MCI.

Significant negative correlations were partially demonstrated between both the global and regional SUVRs and the TMSE scores, with a medium strength of correlation (r = -0.341 to -0.454). In the MCI subgroup, significant correlations between the amyloid depositions and the TMSE scores were observed at all regions other than the posterior cingulate and occipital regions. As to the AD subgroup, a significant correlation was found only between the occipital SUVR and the TMSE scores.

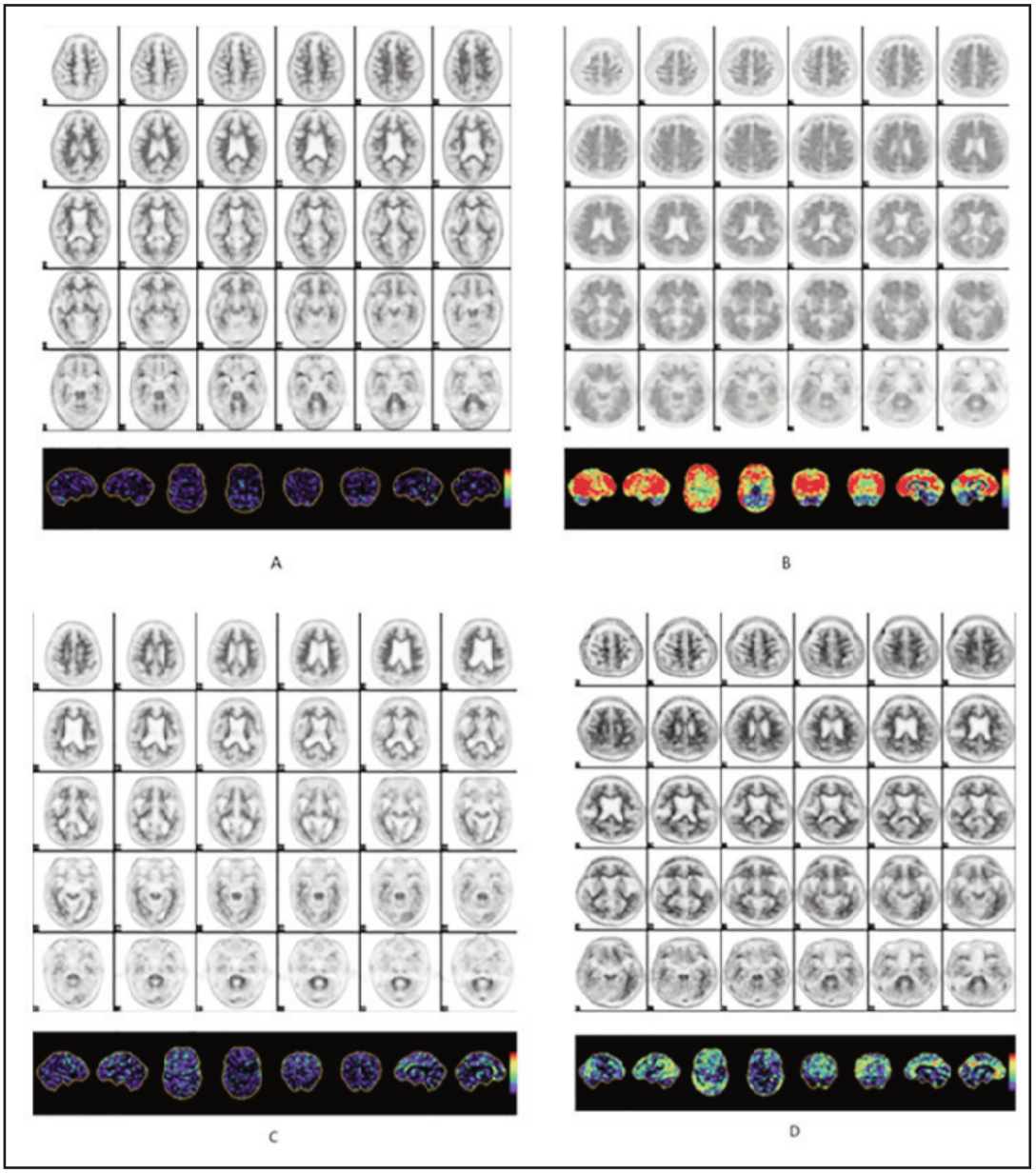

Fig. 4: Examples of trans-axial and 3D-SSP Z-score map images of 18F-florbetapir PET. (A): A normal-cognitive, elderly individual with a clearly negative amyloid PET. (B): A moderate-AD patient with a clearly positive amyloid PET. (C): In equivocal cases, 3D-SSP imaging may be helpful in identifying the very early stage (stage I) of amyloid deposition in a patient with MCI and (D): A confirmed stage II amyloid deposition in a patient with clinically mild AD whose findings from the visual assessment were considered equivocal as the only focal abnormality was detected in the trans-axial images.

In this cohort, there was no significant correlation between the SUVRs and TMSE scores of the cognitively HCs (Table II).

DISCUSSION

The recommended interpretation criteria for amyloid PET/CT imaging based on visual assessment is simple. Nevertheless, this interpretation technique has the potential for variability among readers in equivocal cases as well as the limitation for assessing correlation with detailed neurocognitive performance. The limitations of subjective visual assessments may be overcome with additional, automated, semiquantitative, analytical approaches; however, some of those require individual MRIs for anatomical co-registration. In the current study, we utilised a semiquantitative method of 3D-SSP Z-score mapping using freely accessible automatic software and a Thailand-specific NDB. We also drew on a recently proposed staging pattern[18] that provides an objective and more detailed interpretation of ^{18}F-florbetapir PET/CT imaging data than conventional binary interpretation. We expected that the Z-score mapping-based staging approach would improve the visual assessment of ^{18}F-florbetapir PET/CT imaging results, especially in equivocal cases. Furthermore, we expected that the staging approach may help to stratify

the severity of amyloid deposition and to identify minor longitudinal changes in regional amyloid deposition. These outcomes would be of benefit for clinical follow-up and the evaluation of the therapeutic efficacy of amyloid-clearing agents. We also expected to further demonstrate a correlation between the Z-score mapping-based stages and the degree of cognitive impairment.

In this study, we found a high association between the results of all the interpretation techniques of the amyloid PET/CT images and the clinical diagnoses, and a high concordance between the results interpreted by visual assessment and both semiquantitative approaches. However, equivocal cases may occur occasionally in real clinical practice, the examples are as shown in Figure 4. In our future study, we plan to investigate if the 3D-SSP technique has advantages over visual assessment by improving the level of diagnostic agreement and confidence in the interpretation of amyloid brain PET/CT images among readers with different experience levels and for diagnostic and prognostic values.

We found an overall higher SUVR in AD than in MCI, and in turn, than in HC. This is consistent with the results of previous studies, with analyses using either the 3D-SSP technique for amyloid PET/CT scans (without staging) or a radiotracer other than florbetapir,[16] or different analytical methods for ^{18}F-florbetapir PET/CT.[30,31] Nevertheless, significant differences in the SUVRs in our study were only found between AD and MCI, and between AD and HC, with no significant difference detected between the SUVRs of HC and MCI. In this cohort, the SUVR cutoff that best discriminated HC from AD (1.157) is slightly higher than the 1.1 recommended by previous studies.[29,31,32] This finding may support our hypothesis about the potential differences in amyloid PET/CT results among the population, although our cutoff is still within the range (1-1 – 1.34) used previously.[30,33,34]

There was no significant correlation between the TMSE scores and amyloid PET/CT using visual assessment. Although stronger correlations were demonstrated in MCI and AD with the Z-score map stages, they still did not meet statistical significance. Significant negative correlations between the TMSE scores and the SUVRs were partially demonstrated, with a medium strength of correlation; the MCI subgroup showed an overall stronger correlation and more regional brain involvement than the AD subgroup. These findings support our hypothesis that amyloid causes more negative neuropathological effects in the early stages rather than in the late stages of the disease. Our results support data from previous studies which found that the Aβ burden correlated with disease severity and cognitive impairment at the preclinical and prodromal stages,[35] but not at the AD stage.[36] Interestingly, a significant correlation between the occipital SUVRs and TMSE scores was noted in AD. In the present cohort, there was no significant correlation between the SUVRs of amyloid PET/CT with the TMSE scores in HCs.

In a recent study, Mattsson et al.[37] proposed a staging system of Aβ accumulation using a combination of CSF Aβ42 and ^{18}F-florbetapir PET/CT scan from ADNI data to evaluate the early, intermediate and late regions of Aβ accumulation. The early composite region in their study (precuneus, posterior cingulate, insula, medial and orbitofrontal cortices) overlaps the involved areas in Stages I–II in our study, while the late composite region (the lingual, pericalcarine, paracentral and postcentral cortices) also overlaps with Stages III–IV in our study. The ambiguous stage rate found in their staging system was 1.6%, which was similar to the 1.3% unstageable rate in our study. Their longitudinal study revealed an association between the higher stages and lower CSF Aβ42 concentrations, greater CSF P-tau and CSF T-tau and accelerated cognitive decline and brain atrophy. Therefore, they concluded that their staging system may be useful for monitoring the course of AD. The aspect of longitudinal change is also being explored in our ongoing study.

The lack of a strong correlation between amyloid accumulation in terms of the SUVRs and neurocognitive scores in our study supports the need for other biomarkers, e.g., ^{18}F- FDG PET/CT or Tau PET/CT, to identify the cause of cognitive decline. It also highlights the need for additional analysis of amyloid PET/CT results with more detailed neurocognitive scores representing different cognitive domains, which might be more sensitive for determining the correlation with corresponding regional brain changes in PET/CT. In our cohort, of the 6 patients with clinically probable AD whose amyloid PET/CT were negative by the Z-score mapping, four also showed negative amyloid PET/CT by visual assessment. The global cortical and regional SUVRs in these patients were within the range of the mean ± SD of the HC subgroup. The additional ^{18}F-FDG PET/CT showed a normal study in 2 patients, an FTD pattern in 2 patients, a DLB pattern in 1 patient and a vascular change in 1 patient. These findings support the potential value of incorporating imaging biomarkers to improve the accuracy of diagnoses and the management of patients with dementia syndrome.[38] In 2 patients with MCI with a negative amyloid PET/CT but a positive ^{18}F-FDG PET/CT, indicating an early-to-mild AD pattern, these findings might be explained by either a neurodegenerative disease from a suspected non-Alzheimer's disease pathophysiology, or the degree of amyloid brain deposition is lower than the detectable threshold of PET/CT imaging. In contrast, 1 HC and 1 AD participant presented a positive amyloid PET/CT, but without any signs of neurodegeneration by either ^{18}F- FDG or MRI. It is known that positive cerebral amyloid deposition can be detected by PET/CT or autopsy in the cognitively normal elderly population.[28] However, long-term follow-up is currently underway to see if amyloid positivity can predict future changes in neurocognitive performance and the related neuroimaging findings. The detailed results from multimodal imaging including ^{18}F-florbetapir PET/CT, ^{18}F- FDG PET/CT and MRI together with the discordance between imaging findings and clinical diagnoses observed in the preliminary results mentioned above will be further clarified in our future publications. The ongoing research also aims to establish the longitudinal changes in, and the clinical significance of, the very early pattern of amyloid deposition (Stage I), which was detected in approximately 3% of our AD and MCI patients.

The main limitation of this study is the lack of a gold standard due to the unavailability of brain autopsy and CSF results to confirm the AD pathologies. A brain autopsy can

only be done in the post-mortem period, while a lumbar puncture for a CSF analysis is considered an invasive procedure. Diagnoses based on clinical criteria and neurocognitive tests alone are known to have limited accuracy, which might explain the relatively low amyloid positivity rate (up to 87%) by ^{18}F-florbetapir PET/CT in our AD subgroup. Moreover, there was an overlapping TMSE score range in the HC and MCI subgroups, which might explain the finding that there was no statistical difference in the TMSE scores of these subgroups. The relatively low range for the TMSE scores[24-30] in the criteria for the HC subgroup in our study was based on previous data for non-demented, elderly Thais, who had median TMSE scores of 27 (IQR 25–29) and 23 (IQR 19–26) for the literate and illiterate participants, respectively.[39] Therefore, to differentiate between the HC and MCI participants, we also used clinical complaints of cognitive impairment as well as other test scores in addition to the TMSE scores. With this limitation, we did not focus on comparing the diagnostic performance of amyloid PET between visual and semiquantitative techniques (staging by Z-score map pattern and SUVR) in this initial study; however, the reference tests used in our cross-sectional study to identify the patient subgroups were similar to those of other studies.[11,28,31,32] A longitudinal study on changes in neurocognitive performance and neuroimaging findings in this cohort is still being performed to evaluate if any parameters may serve as prognostic indicators of neurocognitive decline. Another limitation is that the 3D-SSP FDG-amyloid technique needs ^{18}F-FDG PET/CT to co-register ^{18}F-florbetapir PET/CT to the standard brain template, which leads to concerns pertaining to additional patient radiation dose, time and cost of the study, although the benefit of incorporating results from FDG PET may outweigh this limitation. On the one hand, the co-registration of ^{18}F-florbetapir PET/CT to the standard template without the use of a structural MRI scan can be considered to be an advantage, especially in patients for whom an MRI cannot be performed. A new version of 3D-SSP analysis for amyloid PET/CT without the need for ^{18}F-FDG PET/CT is being developed and validated to overcome these limitations. Despite all the 3D-SSP limitations mentioned, this technique offers the ability to objectively evaluate cerebral amyloid deposition using a fully automated, PET/CT-based approach, with operator convenience and independence, a saving of time, and economic effectiveness.

CONCLUSION

The 3D-SSP analysis of ^{18}F-florbetapir PET/CT images enabled a fully automated, semiquantitative analysis of cerebral amyloid deposition using a normal database specific for our population. The technique provided objective patterns of amyloid distribution in the brain and semiquantitative results that were associated with the diagnosis and neurocognitive performances in MCI and AD patients.

ACKNOWLEDGEMENTS

The authors thank Professor Juri Gelovani for setting up the amyloid PET tracer production; Professor Opa Vajragupta and Associate Professor Supatporn Tepmongkol for their helpful comments; Angkana Jongsawadipatana, Phattaranan Phawaphutanon and Dollaporn Polyeum for data collection. This work was partly funded by National Research Council of Thailand through Health System Research Institute (grant nos. 58–036, 60–065, and 62–044), Research Development Fund, Faculty of Medicine Siriraj Hospital (grant Nos. R016236003 and R016134004) and the International Atomic Energy Agency under CRP E13043 (grant no. 19256).

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ORIGINAL ARTICLE

^{18}F-FDG PET/CT for the pre-surgical localization of epileptogenic focus among paediatric patients with drug resistant epilepsy in Malaysia: perspective of a nuclear medicine physician

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ABSTRACT

Background: Scalp video electroencephalography monitoring (VEM) and brain MRI sometime fail to identify the epileptogenic focus (EF) in patients with drug resistant epilepsy (DRE). ^{18}F-FDG PET/CT has been shown to improve the detection of EF in patients but is not widely used in Malaysia. Thus, the objective of this study was to identify whether ^{18}F-FDG PET/CT conferred an added benefit in the pre-surgical evaluation of DRE.

Methods: Retrospective review of 119 consecutive paediatric patients referred for ^{18}F-FDG-PET/CT at the Department of Nuclear Medicine of the National Cancer Institute, Putrajaya. All had DRE and underwent evaluation at the Paediatric Institute, Hospital Kuala Lumpur. Visually detected areas of ^{18}F-FDG-PET/CT hypometabolism were correlated with clinical, MRI and VEM findings.

Results: Hypometabolism was detected in 102/119 (86%) ^{18}F-FDG-PET/CT scans. The pattern of hypometabolism in 73 patients with normal MRI was focal unilobar in 16/73 (22%), multilobar unilateral in 8/73 (11%), bilateral in 27/73 (37%) and global in 5/73 (7%) of patients; whilst 17/73 (23%) showed normal metabolism. In 46 patients with lesions on MRI, ^{18}F-FDG-PET/CT showed concordant localisation and lateralization of the EF in 30/46 (65%) patients, and bilateral or widespread hypometabolism in the rest. Addition of ^{18}F-FDG PET/CT impacted decision making in 66/119 (55%) of patients; 24/73 with non-lesional and 30/46 patients with lesional epilepsies were recommended for surgery or further surgical work up, whilst surgery was not recommended in 11/46 patients with lesional epilepsy due to bilateral or widespread hypometabolism. 25 patients subsequently underwent epilepsy surgery, with 16/25 becoming seizure free following surgery.

Conclusion: ^{18}F-FDG-PET/CT has an added benefit for the localization and lateralization of EF, particularly in patients with normal or inconclusive MRI.

KEYWORDS:
Focal seizures, Lateralization, Malaysia, MRI negative epilepsy, Positron emission tomography

INTRODUCTION

Epilepsy is a common chronic neurological disorder, with prevalence of lifetime epilepsy is estimated at 7.8 per 1000 persons in Malaysia.[1] For the majority of people with epilepsy, seizures is controlled with medication but 30% of patients will continue to have seizures despite appropriate medication, thus posing significant burden to the patient, their families and to the overall healthcare system. Drug resistant epilepsy (DRE) in children is defined as seizures persisting despite maximally tolerated doses of at least two appropriately chosen anti-epileptic drugs (AEDs), with an average frequency of one seizure per month, for more than 18 months and less than 3 months of seizure free period during these 18 months.[2] The percentage of children with drug resistant epilepsy seen in the neurology clinic of the Paediatric Institute, Hospital Kuala Lumpur was reported at 45%. This figure likely reflects its' function as a tertiary referral centre.[3]

The diagnosis and management of DRE is essential, given the adverse effect of recurrent seizures on early brain development, learning, memory and neurological outcome. For some well selected children, the definitive treatment is for the surgical excision of the cortical area of ictal onset and initial seizure propagation, which is known as the epileptogenic focus (EF) or zone.[4] Young children with DRE and surgically remediable lesions are considered good candidates for aggressive surgical treatment due to the fact that they have increased neuroplasticity of the developing brain, hence the ability for better recovery post-surgery.[5-7] Furthermore, early surgical intervention with successful resection of EF will give satisfactory long-term social, psychologic and cognitive development.[6,7] A recent meta-analysis on paediatric epilepsy surgery confirmed that epilepsy surgery was more effective than medical therapy to control seizures.[8]

Pre-surgical evaluation aims to localize precisely the EF, to optimise seizure-free outcome and minimise unnecessary brain tissue resection, which may contribute to neurological deficits in a growing child. Brain magnetic resonance imaging (MRI) and scalp video electroencephalography (EEG) monitoring (VEM) are crucial to lateralize and localize

This article was accepted: 08 May 2021
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the EF as well as ascertain the candidacy for surgery in refractory seizures.[4] Patients with clear lesions on MRI and concordant scalp EEG findings require no further investigations. However, additional investigations may be required when there are no lesions discernible on MRI (non-lesional epilepsy) or when there is discordant or inconclusive MRI and video EEG findings.[9]

Currently, the 'gold standard' of pre-surgical localisation of the EF and functional cortex is intracranial electroencephalogram (iCEEG). iCEEG has high sensitivity and specificity compared to scalp EEG, but is invasive, sample-limited, costly and risky with potential complications such as subdural, intracranial haematomas, bleeding, and osteomyelitis/infections.[10] Therefore, other non-invasive tools have been used to help with localisation of the EF, including ^{18}F-FDG PET/CT, single photon emission CT (SPECT) and magnetoencephalography (MEG).[9]

^{18}F-FDG PET/CT can provide an assessment of the physiological and pathophysiological processes in patients by measuring the molecular and biochemical changes that occur in the brain prior to the onset of structural changes, which may not be easily discernible on computed tomography (CT) and MRI. The measurement of cerebral glucose metabolism acts as a surrogate biomarker of neuronal pathology in various neurology disease conditions including dementia.[11] As healthy brain cells highly metabolise glucose, they avidly take up ^{18}F-FDG, which is a glucose analog.[12] However in DRE, ^{18}F-FDG uptake is reduced in affected brain regions, thus focal or diffuse hypometabolism is observed. Regions of hypometabolism of ^{18}F-FDG on PET/CT scans have been significantly correlated with regions of almost continuous epileptiform discharges on iCEEG and often concordant with histopathological examination (HPE) results of cortical malformative tissue.[13] ^{18}F-FDG PET/CT is therefore useful for determining the suitability of the patients to undergo surgery - especially if the children have normal or inconclusive MRI, bilateral lesions or when there are discordant results in the foci detected by scalp EEG and MRI.[14] However, the role of ^{18}F-FDG PET/CT in the clinical management of paediatric DRE has yet to be established as a standard of care in Malaysia.

Thus, the aim of this study was to identify whether ^{18}F-FDG-PET/CT has an added benefit for the detection of EF in DRE compared with MRI and scalp EEG in patients with normal MRI. We also assessed the detection rate of EF on ^{18}F-FDG-PET/CT as evidenced by foci of hypometabolism in patients with inconclusive MRI or discordant data. We then identified the clinical factors that were significantly associated with the detection of foci of hypometabolism on ^{18}F-FDG-PET/CT in DRE patients in our institution.

MATERIALS AND METHODS

Study design and subject recruitment

A cross-sectional study was conducted among 119 paediatric patients (aged 18 years and less) with DRE who were referred for ^{18}F-FDG-PET/CT from October 2015 to November 2016 at the National Cancer Institute, Putrajaya, Malaysia. The diagnosis of refractory epilepsy was made by the respective paediatric neurologists based on the consensus by the International league Against Epilepsy (ILAE) Commission on Therapeutic Strategies.[15] The medical records of all patients were reviewed. Important clinical information such as demographic data, age of seizure onset, duration and frequency of seizures, seizure type, the number of AEDs taken, the presence of developmental delay or autism, as well as information as to whether surgical intervention was performed were recorded and entered in the database. All patients underwent Video EEG Monitoring (VEM) and MRI brain as pre-surgical evaluation of DRE. Only patients with normal or inconclusive MRI were subjected to an ^{18}F-FDG-PET/CT scan.

Video electroencephalography (EEG) monitoring (VEM)

All 119 patients underwent scalp VEM using the 10-20 system at the same centre. Ictal and interictal events were reviewed and interpreted by trained neurologists, and categorized into normal, focal, lateralised or bilateral/poorly localised epileptiform patterns.

Magnetic resonance imaging (MRI) of the brain

MRI scans were performed using a 1.5T Ingenia (Philips, Amsterdam, Netherlands) scanner using the institutional standard epilepsy protocol. The MRI scans of the recruited study subjects were dichotomised into normal or lesional but inconclusive MRI. An inconclusive MRI scan was defined as either i) having discordance with the EEG results, ii) focal or unilateral MRI detected lesions with subtle changes and unclear margins, or iii) multiple or bilateral cerebral lesions.

^{18}F-FDG PET/CT scan protocol

Informed consent was sought from parents of patients prior to performing the ^{18}F-FDG PET/CT scan. The parents signed the parental agreement form after receiving an explanation regarding the procedure. The patients were required to be fasted for 4-6 hours prior to the scan. Anti-epileptic drugs were continued on the day of the examination.

Fasting blood sugar (FBS) level was checked on the day of the examination. The acceptable range of the FBS was 4 to 10mmol/L. The patients were then administered with 6MBq/kg of ^{18}F-FDG intravenously and directed to lie still with their eyes open in a quiet and dimly lit room. Hydration and urination were encouraged to reduced radiation exposure to radiosensitive organs and excessive activity was discouraged. Sedation using chloral hydrate or intravenous midazolam was given to children less than three years old or uncooperative children by the accompanied doctor prior to scan acquisition and ensured continuous cardiac monitoring. The image acquisition began with CT scan imaging for the purpose of attenuation correction and anatomical localisation, using a low dose of 140 kV and 180mA. This was followed by standard PET acquisition using a Discovery ST (General Electric Company (GE), Boston, USA) scanner, which had an intrinsic resolution of 20 mm in full width at half maximum (FWHM). The emission image was acquired for 25 minutes with a two-dimensional acquisition mode (2D), 60 minutes after the radiotracer injection. Slices of the trans-axial brain images were reconstructed using a filtered back-projection method. The reconstructed images were corrected for attenuation using attenuation maps. The trans-axial

images were then realigned to yield sagittal and coronal images.

^{18}F-FDG PET/CT image interpretation and analysis
Two senior nuclear medicine physicians visually assessed the regional ^{18}F-FDG metabolism seen on the scans by consensus. The visualized hypometabolic region(s) on the ^{18}F-FDG-PET/CT scans were determined to be the EF. ^{18}F-FDG-PET/CT findings were divided into two categories, i.e., normal and abnormal. Normal denoted that there was homogeneously avid FDG metabolism throughout all the cortical regions. Abnormal was defined as localized or non-localized area(s) of FDG hypometabolism. The site of hypometabolism was categorized into focal unilobar, multilobar unilateral, bilateral or global. The site of hypometabolism was further categorized into three regions, namely temporal lobe, extra-temporal represented by the frontal, parietal and occipital lobes, and temporal-plus represented by temporal with extra-temporal lobe involvement. ^{18}F-FDG hypometabolism patterns were dichotomized to localized or lateralised versus not localized or lateralised when studying the associated factors. The patients were subsequently followed-up at the HKL epilepsy clinic to review their clinical data and decide on the further management of their condition by the treating physician.

Statistical analysis
Statistical analysis was performed using online Graphpad Quickcalcs software (https://www.graphpad.com/quickcalcs/). Descriptive analysis was used to display the demographic data and the pattern of ^{18}F-FDG hypometabolism. Various clinical factors associated with FDG hypometabolism were analysed using chi-square and Fisher's exact tests. A p value of < 0.05 was considered statistically significant.

RESULTS

Demographic and clinical data
The 119 patients who fulfilled the inclusion and exclusion criteria 74 males were and 45 females. Their ethnicity comprised of 68% Malays, 19% Chinese and 13% Indians. The age of patients at the time of ^{18}F-FDG-PET/CT study ranged from 1 to 18 years old with mean age of 10.3 years. The minimum and maximum ages of seizure onset were 0.8 and 13 years old, respectively (mean: 3.6 years old). The mean duration from seizure onset to the ^{18}F-FDG-PET/CT study was 6.7 years.

Focal seizure was the commonest seizure type, noted among 62 patients (52%). This was followed by focal seizures with secondary generalisation in 21 patients (18%), mixed seizure types (including spasms) in 21 patients (18%), generalized seizures in 8 patients (7%) and epileptic spasms as the only seizure type in 7 patients (5%). All had DRE, with 41% of patients experiencing daily seizures. 85 patients (74%) had developmental delay, learning disability, or autistic spectrum disorder.

There was no significant difference in the demographic and clinical features between patients with normal or abnormal MRI, except for epilepsy duration, which was slightly longer with patients with abnormal MRI (7.6 vs 6.1 years, p=0.047) (Table I).

MRI results and aetiology
Brain MRI did not show any clear lesions in 73 children (61%). 46 patients (39%) showed lesions on their MRI, with features of atrophy/ encephalomalacia in 15/46 patients (33%), presumed perinatal stroke in 9/46 (20%), cortical malformation in 15/46 (33%), hippocampal atrophy in 5/46 (11%), developmental tumour in one (2%) and Rasmussen encephalitis in one (2%) (Figure 1).

The aetiologies for the MRI lesions were judged to be acquired in 21 patients; consisting of hippocampal atrophy in five patients and sequelae of: traumatic/non-traumatic intracranial haemorrhage in 5 patients, neonatal hypoglycaemia in four patients, hypoxic-ischaemic injury in three patients, meningitis/encephalitis in two patients, hemiconvulsive-hemiplegic epilepsy syndrome and Rasmussen encephalitis in one patient each. The aetiologies were judged to be congenital in 25 patients, consisting of presumed perinatal stroke in 9 patients, focal cortical dysplasia in 6 patients, multilobar dysplasia in 5 patients, hemispheric dysplasia in one patient, tuberous sclerosis complex in three patients and developmental tumour in one patient.

^{18}F-FDG PET/CT results
^{18}F-FDG PET hypometabolism was detected in 102 patients (86%), whereas the remaining 17 patients had normal 18F-FDG PET/CT scans. As for the site of 18F-FDG hypometabolism, the commonest type was the temporal-plus type (51%), followed by extra-temporal type (25%), and temporal-only type hypometabolism (24%). The pattern of distribution of ^{18}F-FDG hypometabolism in patients with normal MRI were focal unilobar in 16/73 (22%), multilobar unilateral in 8/73 (11%), bilateral in 27/73 (37%) and global in 5/73 (7%) of patients. The distribution of ^{18}F-FDG hypometabolism in patients with lesional MRI were focal unilobar in 8/46 (17%), multilobar unilateral in 22/46 (48%), bilateral in 14/46 (33%) and global in 2/46 (4%) of patients (Figure 2).

Factors associated with patterns of ^{18}F-FDG-PET/CT hypometabolism
In patients with no lesions on their MRI, localised or lateralised ^{18}F-FDG PET/CT hypometabolism were significantly associated with lateralised seizure semiology and focal or lateralised interictal EEG abnormalities. Young age (less than three years) at seizure onset and presence of developmental delay, learning disability or autistic features were associated with a non-lateralised PET hypometabolism. In patients with lesions on their MRI, localised or lateralised pattern of ^{18}F-FDG PET/CT hypometabolism concordant with the lesions were associated with localised/lateralised EEG abnormalities and congenital (as opposed to acquired) lesions (Table II).

Impact of ^{18}F-FDG PET/CT findings on decision-making for surgical intervention
Overall, the addition of ^{18}F-FDG PET/CT assessment, impacted 66 (55%) of the patients; 24/73 with non-lesional and 30/46

Table I: Comparison of demographic and clinical data between patients with normal and lesional MRI (AEDs=anti-epileptic drugs, DD= developmental delay, LD=learning disability, ASD=autistic spectrum disorder, SD=standard deviation)

	Total (n=119)	Normal MRI (n=73)	INCONCLUSIVE MRI (n=46)	P value
Sex				
Male	75	45	30	
Female	44	28	16	
Ethnicity				
Malay	70	45	25	
Chinese	30	16	14	
Indian	19	12	07	
Mean age seizure onset in years (SD)	3.6 (3.52)	3.9 (3.58)	3.3 (3.57)	0.410
Mean age at PET in years (SD)	10.3 (4.97)	9.9 (4.70)	10.8 (5.37)	0.328
Mean epilepsy duration in years (SD)	6.7 (3.96)	6.1 (3.52)	7.6 (4.47)	0.047*
Seizure frequency				
Daily (%)	49	29 (59%)	20 (41%)	0.706
Weekly (%)	36	27 (75%)	9 (25%)	0.064
Monthly (%)	34	17 (50%)	17 (50%)	0.14
Mean number of current AEDs (SD)	2.3 (0.79)	2.2 (0.77)	2.4 (0.80)	0.226

Table II: Factors associated with focal/ lateralised versus non-lateralised ^{18}F -FDG PET hypometabolism (EEG= electroencephalogram, AEDs=anti-epileptic drugs, DD= developmental delay, LD=learning disability, ASD=autistic spectrum disorder). **Ictal EEG only for 55/73 patients with normal MRI, and 36/46 with inconclusive MRI.

		Normal MRI (n=73)				inconclusive MRI (n=46)			
		Focal/ lateralised PET (n=24)	Non-lateralised PET (n=49)	Total	P value	Focal/ lateralised PET (n=30)	Non-lateralised PET (n=16)	Total	P value
SEIZURE	Lateralised	13 (54%)	11 (46%)	24	0.009*	16 (76%)	5 (24%)	21	0.217
SEMIOLOGY	Not lateralised	11 (22%)	38 (78%)	49		14 (56%)	11 (44%)	25	
INTER-ICTAL	Focal/ lateralised	13 (50%)	13 (50%)	26	0.036*	22 (88%)	3 (12%)	25	0.031*
EEG	Not focal/ lateralised	11 (23%)	36 (77%)	47		8 (38%)	13 (62%)	21	
ICTAL EEG**	Focal/ lateralised	8 (36%)	14 (64%)	22	0.591	17 (81%)	4 (19%)	21	0.071
	Not focal/ lateralised	16 (29%)	39 (71%)	33		7 (47%)	8 (53%)	15	
SEIZURE ONSET	<3 yrs	7 (18%)	33 (82%)	40	0.003*	16 (57%)	12 (43%)	28	0.210
	>3 yrs	17(52%)	16 (48%)	33		14 (78%)	4 (22%)	18	
SEIZURE DURATION	<3 yrs	7 (18%)	33 (82%)	40	0.003*	16 (57%)	12 (43%)	28	0.210
	> 5 yrs	11 (28%)	28 (72%)	39		20 (67%)	10 (33%)	30	
SEIZURE FREQUENCY	Daily	6 (21%)	23 (79%)	29	0.082	11 (58%)	8 (42%)	19	0.531
	Weekly/ monthly	18 (41%)	26 (59%)	44		19 (70%)	8 (30%)	27	
AEDS	<2	6 (22%)	21 (78%)	27	0.198	14 (70%)	6 (30%)	20	0.756
	>2	18 (39%)	28 (61%)	46		16 (62%)	10 (38%)	26	
DD/LD/ASD	Yes	12 (24%)	37 (76%)	49	0.037*	24 (71%)	10 (29%)	34	0.292
	No	12 (50%)	12 (50%)	24		6 (50%)	6 (50%)	12	
LESION	Congenital	NA	NA			23 (82%)	5 (18%)	28	0.011*
	Acquired	NA	NA			7 (39%)	11 (61%)	18	

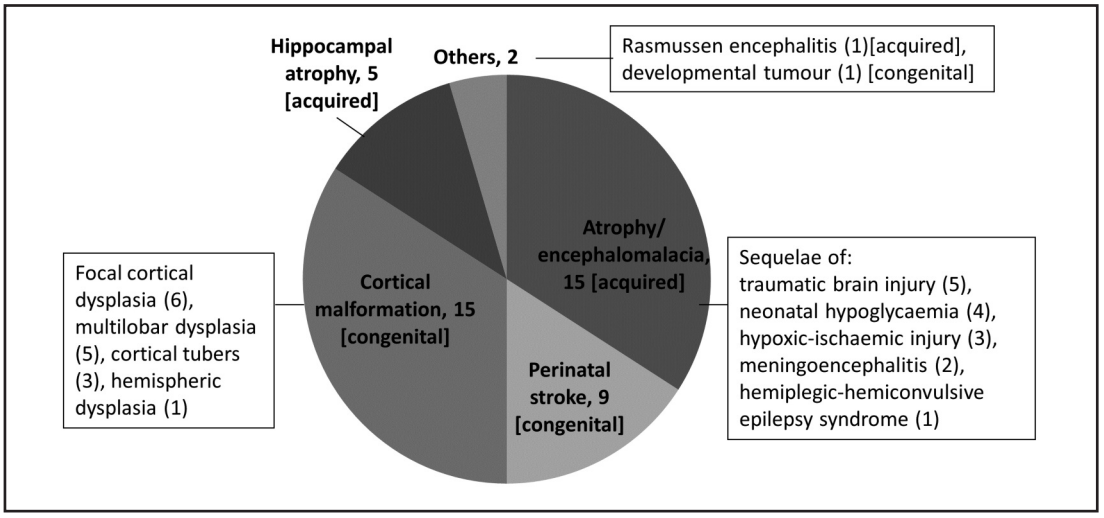

Fig. 1: MRI findings and aetiologies in patients with lesional epilepsy (n=46), classified into congenital (25/46) and acquired (21/46) categories.

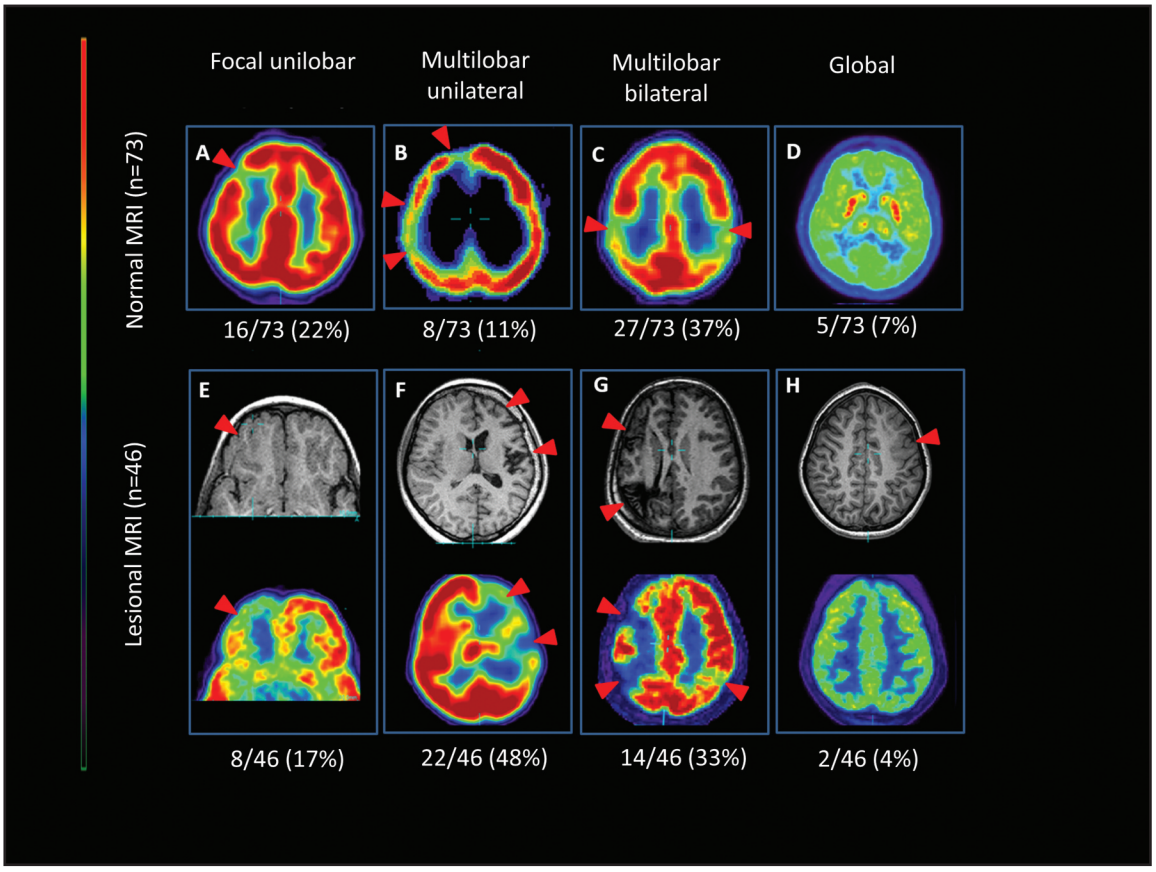

Fig. 1: Patterns of ^{18}F-FDG PET hypometabolism seen in 56/73 patients with normal MRI (top row, A-D) and all patients with lesional MRI (bottom row, E-H). (E) T1-weighted axial MRI showing abnormal grey-white differentiation over the right orbitofrontal region and concordant focal hypometabolism, suggestive of focal cortical dysplasia, (F) T1-weighted axial MRI showing left frontotemporal atrophy in a patient with traumatic brain injury and concordant hypometabolism, (G) T1-weighted axial MRI shows multilobar encephalomalacia involving the right hemisphere in a patient with history of HSV encephalitis – PET detected additional left parietal hypometabolism where no clear lesion was seen on the MRI, (H)) T1-weighted axial MRI showing thickened cortex and broad gyri in a patient with a poorly defined left frontal focal cortical dysplasia – PET was not helpful as it showed global hypometabolism.
Colour scale: red = highest level of ^{18}F-FDG uptake, dark blue/violet = lowest level of ^{18}F-FDG uptake. Red arrowheads denote areas of abnormalities.

patients with lesional epilepsies were recommended for surgery or further surgical work up, based on localised/ lateralised ^{18}F-FDG PET hypometabolism and concordant pre-surgical data. A total of 11/46 (24%) of patients with lesional epilepsy was not recommended for surgery due to bilateral or non-localising ^{18}F-FDG PET findings. A further 2 patients were recommended surgery despite non-concordant ^{18}F-FDG PET findings; one boy with a left frontal dysplasia who showed global hypometabolism (likely due to frequent seizures prior to the ^{18}F-FDG PET/CT scan) and another with left temporal dysplasia who showed bilateral temporal hypometabolism. The ^{18}F-FDG PET/CT scan findings in the rest of the patients recruited in this study did not significantly influence the decision-making for surgery.

At the time of analysis, 25 patients (including 7 with no clear lesions on the MRI) underwent epilepsy surgery. Seven and 2 patients had frontal and parietal lesionectomies respectively, assisted by intra-operative electrocorticographic monitoring, whilst one had an extensive resection of a parieto-occipital tuber. Eight patients had anterior temporal lobectomies, including one who had an additional frontal resection. Functional hemispherotomy was performed in 4 patients and temporo-parieto-occipital disconnection in 3 patients.

16/25 patients (64%) remained seizure-free, achieving Engel class I surgical outcome after a median follow-up of 20 months post-operatively. In contrast, only 13/94 (14%) patients who were continued on AED medical therapy were seizure-free. Histopathology of five out of seven patients with normal MRI who had surgery revealed cortical dysplasia.

DISCUSSION

We were able to show that in Malaysia, ^{18}F-FDG PET/CT provided useful additional information in patients with DRE who were being considered for epilepsy surgery. In patients with DRE and normal MRI, localised or lateralised ^{18}F-FDG PET hypometabolism indicative of the EF was seen in 24/73 (33%) of patients. In patients with DRE and poorly defined MRI lesions or discordant pre-surgical data, concordant hypometabolism and MRI abnormality was seen in 30/46 (65%) of patients, whilst confirmation of bilateral abnormalities was observed in 11/46 (24%) of patients. Thus overall, addition of ^{18}F-FDG PET/CT investigation impact on more than half of the patients in our cohort (65/119, 55%), allowing for greater confidence in the selection and rejection of epilepsy surgery candidates.

The utility of interictal ^{18}F-FDG PET/CT as a tool for localization and lateralization of seizure focus has been demonstrated by many previous studies.[13,16,18] The reported sensitivity of ^{18}F-FDG PET/CT for identifying seizure focus ranged from 45-90%, with generally higher sensitivity in temporal versus extratemporal foci.[16] It is particularly useful for detection of hypometabolic area in a subtle cortical dysplasia which may not be apparent on standard MRI imaging, and showed good correlation with intracranial EEG and histopathology findings. The role of ^{18}F-FDG PET/CT in the pre-surgical evaluation of refractory epilepsy in Malaysia has been explored by Lim et al., in 2017.[17] In that study, 13/16 patients who underwent stage two evaluation for epilepsy surgery had ^{18}F-FDG PET/CT scan – at least 5/13 patients had cortical dysplasia confirmed on histopathology; however the concordance between ^{18}F-FDG PET/CT and other investigative modalities was not stated. In our study, histopathology confirmed focal cortical dysplasia in 71% of patients with normal MRI and focal ^{18}F-FDG PET hypometabolism who underwent epilepsy surgery. A total of 16 patients became seizure free following surgery, with others experiencing variable degrees of seizure reduction, suggesting correct ^{18}F-FDG PET and MRI identified EF in the majority of patients. Not surprisingly, we found that lateralised seizure semiology (evidence of clinical seizure starting on side of the body) and focal/ lateralised interictal EEG abnormalities were associated with concordant focal/ lateralised ^{18}F-FDG PET hypometabolism.

In our experience, not only was ^{18}F-FDG PET/CT useful in detecting focal areas for resection, it was also useful to look for hypometabolism in the regions outside the presumed EF, the presence of which would make one cautious about recommending epilepsy surgery. It should be noted however, that a significant number of patients in our study, both with or without MRI lesions, showed bilateral ^{18}F-FDG PET hypometabolism. ^{18}F-FDG PET hypometabolism beyond the epileptogenic foci may reflect seizure propagation, for example, the spread of ^{18}F-FDG PET/CT abnormalities in patients with temporal lobe epilepsy (TLE), that extend beyond the anterior and mesial regions, was observed in 32% of TLE patients.[18] Hypometabolism in other cortical regions may also be observed due to presence of independent EF that may not apparent on brain MRI.[19] Additionally, other clinical factors may contribute to ^{18}F-FDG PET hypometabolism, such as presence of development delay and learning disability[20], anti-epileptic medications (especially phenobarbitone), duration of seizures and specific epilepsy or genetic syndromes.[19] In our study, young age (less than 3 years) at seizure onset (but not seizure duration), acquired lesions (as opposed to congenital lesions) and presence of developmental delay, learning disability or autism, were associated with bilateral ^{18}F-FDG PET hypometabolism.

Technical factors may also influence the degree and diagnostic accuracy of ^{18}F-FDG PET/CT study in DRE. It is mandatory to ascertain recent episodes of seizures prior to ^{18}F-FDG PET study – seizures just prior to or during acquisition may increase the influx of glucose into the EF, which may in turn result in contrary ^{18}F-FDG PET hypermetabolism instead of hypometabolism.[21] Adherence to pre-injection preparations such as optimal fasting of at least 4-6 hours will reduce endogenous insulin excretion and ensure optimal FDG uptake into the brain cells. Lying quietly with eyes closed in dimly lit room with avoidance of activities like reading, talking or listening few minutes before and during uptake time will prevent increase of FDG metabolism in visual, language-motor cortical as well as auditory areas. During image acquisition, careful precaution must be made to avoid head movement by using a head rest and reminding older children to avoid voluntary movements of head as much as possible. Presence of motion artifact may compromise the image quality and interpretation. In certain patients requiring sedation, careful attention to timing of sedation is crucial. Sedation must not be given too early or too close

(within 20 minutes) to FDG injection as it may interfere with FDG metabolism and biodistribution in the brain, leading to erroneous findings.[22,23]

There are currently 21 centres in Malaysia with dedicated PET-CT scanners offering their services mainly for oncological cases. To date, only two government hospitals, one university hospital and four private hospitals in Malaysia are offering ^{18}F-FDG-PET/CT for neurological studies, specifically epilepsy. The limited use of ^{18}F-FDG PET/CT imaging for epilepsy investigation is probably partly due to the low request for such imaging from the treating neurologists. Furthermore, not many nuclear medicine specialists in Malaysia are well-versed with ^{18}F-FDG PET/CT imaging interpretation and reporting in cases of epilepsy. The relatively higher cost (compared to MRI) and radiation exposure may also limit its' routine use in evaluation of patients with DRE. At the same time, improvement in MRI quality have improved lesion detection and may obviate the need for ^{18}F-FDG PET/CT scan for some patients with DRE.[9]

The limitation of this study is our resources, in which we were unable to utilise any neurology image processing software in order to perform a semi-quantitative assessment to identify epileptogenic foci. Semi-quantitative assessment using voxel-based analysis with statistical parametric mapping or three-dimensional stereotactic surface projection sequence such as Neurostat is an important tool that have been proven to have added benefit to the physician in the interpretation of the area of hypometabolism for epileptic focus detection.[24] Moreover, our subjects were children in which there is no establishment of control database for this age group. We recommend that future studies should deploy the semi-quantitative processing software methods to improve the diagnostic accuracy of ^{18}F-FDG PET/CT in drug resistant epilepsy.

CONCLUSION

^{18}F-FDG-PET/CT is a non-invasive, neuroimaging tools that can improve the detection of EF in DRE, especially in patients with normal or inconclusive MRI and clinical data. Recognition of the indications and limitations of this important imaging modality may improve the care of patients with DRE in Malaysia.

ACKNOWLEDGEMENT

The authors would like to thank the Director-General of Health, Ministry of Health Malaysia for the permission to publish this original research. The authors also thank the Hospital Director of Hospital Kuala Lumpur, Ministry of Health, Malaysia and Director of the National Cancer Institute, Ministry of Health Malaysia, Putrajaya for giving permission to use the patients' clinical data and anonymised images in this publication. Surgeries were performed by Dr Benedict Selladurai at Ara Damansara Medical Centre and Dr Azmi bin Alias at Hospital Kuala Lumpur.

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ORIGINAL ARTICLE

Clinicopathological features and treatment outcome of paediatric differentiated thyroid cancer treated with Radioactive Iodine-131 therapy in Hospital Kuala Lumpur, Malaysia

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ABSTRACT

Background: Radioactive iodine ^{131}I (RAI) therapy is one of the definitive treatments for paediatric differentiated thyroid cancer (DTC) initiated at nuclear medicine departments. In Malaysia, there is a need to identify the standardisation of treatment regimes to align with international standards. We aimed to evaluate the clinicopathological features and the patient response to RAI therapy among paediatric DTC cases at Hospital Kuala Lumpur (HKL), Malaysia.

Methods: A retrospective, longitudinal study was conducted among paediatric DTC patients treated with RAI in HKL and followed up between 2000-2016. Sixty-five patients were studied (mean period: 58.8±36 months). The clinicopathological data of the patients was recorded, and descriptive analysis was made. The association between categorical and continuous data with disease status was assessed using chi-square and Kruskal-Wallis tests, p-value <0.05 taken as statistically significant.

Results: Most patients were female (78.5%), and adolescents comprised 89.2%. Pre-pubertal age, those presenting with cervical nodal involvement, extra-thyroidal extension and lymphovascular invasion were significantly associated with distant metastases at presentation. There was no mortality reported during the follow-up period. Sixty per cent of patients achieved remission, while 40% had persistent disease. The persistent disease was significantly correlated with distant metastasis at presentation (p=0.025).

Conclusions: Paediatric DTC manifests with a more extensive disease burden at presentation and requires multiple RAI doses. Despite this, it carries an excellent overall prognosis.

KEYWORDS:
Differentiated thyroid carcinoma, paediatric thyroid cancer, radioactive iodine, radionuclide therapy, treatment outcome

INTRODUCTION

Well-differentiated thyroid carcinoma (DTC) is a follicular cells-derived type of cancer that is iodine-avid and sensitive to thyroid-stimulating hormone (TSH). DTC in the paediatric population is rare, accounting for approximately 1.4% of all paediatric malignancies.[1] DTC has been reported as the 8th most common cancer in adolescents aged 15 – 19 years old and the second most common cancer among young females.[2] Compared to adults, paediatric DTC is more aggressive and has a higher risk of recurrence.[3] Nevertheless, this condition has an excellent long-term prognosis, having 30-year survival rates of 90–99%.[4] Treatment generally involves surgery, i.e. total thyroidectomy (TT), post-operative TSH suppression, and radioactive iodine ^{131}I (RAI) therapy.[5] Performing central compartment neck dissection (CND) based on an extensive *en-bloc* resection of lymph nodes by a high-volume thyroid surgeon is ideal for reducing the risk of recurrence, compared to the previously practised selective 'berry picking' approach.[6] In fact, between 38-45% of patients who undergo prophylactic CND are detected with microscopic metastasis, which can alter the risk stratification and management plan of these patients.[5]

Proper risk stratification is the basis for classifying patients into the appropriate treatment regime and follow-up programme. The classification of patients is made based on the risk of having persistent or metastatic disease. Based on the histopathological examination (HPE) of the operated specimens, the patients who have disease limited to the thyroid gland, with or without the presence of micro-metastasis to a small number of central neck nodes, are considered low risk.[7,8] Intermediate risk patients have extensive central neck lymph node involvement or minimal lateral neck lymph node involvement.[7] Based on the American Thyroid Association (ATA) 2015 guidelines, high-risk paediatric patients comprise of those with extensive regional disease or locally invasive disease, i.e., tumours with extrathyroidal extension (ETE) such as extra-capsular/ prevertebral fascia invasion; carotid artery/mediastinal vessels encasement; irrespective of whether or not they have distant metastasis.[9]

In the nuclear medicine departments that receive referrals for administering RAI therapy in Malaysia, dynamic risk stratification is performed by utilizing a ^{131}I whole-body scan (WBS), which is performed after the radioactive ablation is

This article was accepted: 18 May 2021
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administered. The dynamic risk stratification is also aided by monitoring serial serum thyroglobulin (Tg) during follow-up clinic visits. Traditionally, RAI is administered as an adjuvant therapy, i.e. radioiodine remnant ablation (RRA), to destroy any residual thyroid tissue in the thyroid bed following TT. RRA enables post-ablation Tg estimations to be a good biomarker for the detection of early biochemical recurrence.[8] By monitoring post-RRA and post-RAI Tg levels, a dynamic risk assessment can be performed to detect the potential development of locoregional recurrence or the occurrence of distant metastases.

For those with high-risk disease, the aim of the treatment is to achieve TSH suppression at the level of <0.1mIU/L by giving levo-thyroxine (LT_4) supplementation therapy, which is a synthetic version that mimics the endogenously produced thyroid hormone thyroxine (T4). While on LT_4 therapy, the serum Tg levels are monitored 3-6 monthly for 3 years and then once every year. TSH suppression is recognised as an important foundation for DTC treatment, particularly for paediatric patients who are stratified as high-risk for developing recurrence.[9]

A patient with cervical nodal or extensive locoregional disease that is not amenable to surgery, and those having distant metastases are indicated to receive RAI therapy. In the group with the intent to treat using RAI (normally those who are in the intermediate-risk and high-risk groups), TSH-stimulated Tg (attained by temporarily withholding LT_4), and diagnostic ^{123}I WBS or ^{131}I WBS findings are monitored. Furthermore, 6-12 monthly ultrasound neck surveillance is also recommended.[8]

Studies pertaining to RAI therapy for paediatric DTC have been published from America, Europe, South Asia, and West Asia.[10-14] However, there are no reports currently available from Malaysia. Thus, the aim of this study was to determine the clinical and pathological features of the paediatric DTC patients that were referred to the Nuclear Medicine Department of Hospital Kuala Lumpur (HKL), a tertiary referral centre in Malaysia and to assess the treatment response and outcome after administration of RAI.

MATERIALS AND METHODS

Study design

This is a retrospective, longitudinal cohort study, of consecutive paediatric DTC patients who had received treatment in HKL between the period of 1st January 2000 to 30th June 2016. The method adopted was convenience sampling. Thus, all the paediatric patients with operated DTC who were referred to us were recruited during the sampling period. The clinicopathological data and treatment information of the patients were retrieved from the clinic database, whereby referrals were received from all over Malaysia.

Our inclusion criteria for subject recruitment were all patients diagnosed with DTC, aged ≤18 years old, and who either underwent total or hemithyroidectomy followed by completion thyroidectomy, with or without neck node dissection and subsequently referred to our department for RAI during the sampling period. Exclusion criteria were patients who defaulted follow-up. Several attempts were made to arrange for reappointment for the defaulters; however, these patients refused follow-up due to logistic reasons. We confirmed that there were no deaths among the defaulters by telephone calls to the families of patients and also checks on hospital registries during the study period.

In our centre, all referrals for RAI therapy were vetted by our team of nuclear medicine physicians. The policy for institution of therapy is that all operated DTC patients will be administered with RAI for remnant ablation or therapy for cervical nodal or distant metastases. Furthermore, based on the evaluation of multifocality, bilateral lobe involvement, and potential for ETE these factors would influence the decision to treat with RAI.

Baseline blood investigations were also done before giving RAI therapy, which included serum Tg and anti-Tg, and Thyroid Function Test, i.e., T4 and TSH. We ensured that the TSH level was well stimulated > 30mIU/L. Other blood tests prior to giving RAI included checking for the Full Blood Count, Renal Profile, Liver Function Test, as well as serum calcium and phosphate levels.

We administered RAI therapy based on administering a fraction of the recommended adult dose, which is the empirical fixed-dose technique using 3700–7400 MBq (100–200 mCi) ^{131}I. Hence, we adjusted the recommended ^{131}I adult dose to a fraction of the dose, taking into consideration the paediatric patient's age and body weight.

Post therapy WBS was performed at least 3 days post RAI to evaluate the extent of the disease. If the disease was localised, the patient was followed-up with a diagnostic WBS with stimulated serum Tg level monitoring in 6 months. If there was no evidence of disease (NED)/ remission, the patient was followed up every 6 months by monitoring the serum Tg levels alone.

Conversely, if there was evidence of metastatic disease on post therapy WBS, further RAI doses were given at a 6 - 12 monthly interval. Current practice, is that if the cumulative administered RAI dose exceeds 600mCi, the interval of RAI is spaced out and other treatment strategies are actively sought, e.g., re-surgery. Prior to adapting some of the ATA 2015 guideline recommendations, patients with persistent disease that was not amenable to surgery were continued with multiple RAI doses. Nevertheless, from 2016 onwards, patients who demonstrated stable persistent disease were treated with TSH suppression alone and cessation of RAI, especially when the cumulative dose exceeded 600 – 1000 mCi. In the instance of markedly elevated serum Tg, an effort to exclude dedifferentiated disease was made by performing ^{18}F-Fluorodeoxyglucose positron emission tomography/ computed tomography (^{18}F-FDG PET/CT) scans for selected patients.

This study received ethical clearance from the Malaysian Medical and Research Ethics Committee (MREC) [Ethical clearance reference number: NMRR-16-1310-31677 (IIR)].

Data collection

The extracted data included the patients' demographic information, type of surgical history, tumour histology, tumour size based on direct microscopic measurements of the tumour margin, initial staging and risk assessment, RAI therapy history, and imaging history. Among the clinicopathological information extracted included the presence of ETE. ETE was defined as tumour cells that invaded beyond the thyroid capsule into perithyroid soft tissue or organs. Multifocality was recorded, which was defined as more than one focus of cancer in a single thyroid lobe. Moreover, the presence of unilateral vs. bilateral DTC was also recorded. We extracted data for the number of lymph nodes microscopically examined and the number of nodes positive for metastatic disease. Information on the dose and frequency of administering RAI was also recorded.

Post RAI therapy, the patients were classified as having: (1) no evidence of disease (NED) / remission, (2) persistent disease that included stable and dedifferentiated disease, (3) recurrent disease and (4) progressive disease (PD). NED was defined as a negative diagnostic ^{131}I WBS, performed 6 months following RAI with negative serum Tg. Stable disease was defined as a positive ^{131}I WBS at follow-up with similar or less iodine-avid disease than the initial scan. In certain patients with negative ^{131}I WBS despite having rising serum Tg (> 10ng/mL), dedifferentiated disease was suspected based on the ^{18}F-FDG PET/CT scan. Recurrence was defined as locoregional recurrence or distant metastasis detected by ^{131}I WBS or other imaging modalities, after an initial period of being disease-free or NED. Whereas, PD was defined as evidence of increasing number of foci of iodine-avid disease in a ^{131}I WBS or any imaging that fulfilled the Response Evaluation Criteria In Solid Tumors (RECIST) criteria.[13]

Statistical analysis

Statistical analysis was performed using SPSS V22.0. Descriptive statistics displayed the demographic data of the cohort. Continuous data was described using the minimum and maximum values, and the mean and standard deviation (SD). Kruskal–Wallis test and chi-squared test were used to compare categorical and continuous variables. Baseline characteristics were compared using Pearson's correlation for continuous variables and chi-square test for categorical variables. The association between categorical and continuous data with disease status at presentation was assessed using chi-square and Kruskal-Wallis test (for non-parametric data) and Pearson's correlation (for parametric data). A p-value of < 0.05 was considered statistically significant.

RESULTS

Initially, 67 patients fulfilled the study criteria; however, 2 patients defaulted follow-up. Hence, 65 patients were analysed. The characteristics of patients are detailed in Table I. Majority of the patients were females (51/65; 78.5%). The mean age at diagnosis was 14.9 ± 3.7 years (range 4 – 18 years). All the patients underwent thyroid surgery, which included TT in 22 patients (33.8%), TT and CND in 30.8%, and staged surgery in the remaining 35.4% of patients. Fifty patients (76.9%) had classical papillary thyroid carcinoma, 6 patients (9.2%) had follicular variant of papillary thyroid carcinoma and 6 patients (9.2%) had follicular thyroid carcinoma. There were 3 patients (4.6%) with mixed follicular and papillary thyroid carcinoma, well differentiated thyroid carcinoma NOS, and microcarcinoma with evidence of multifocality, bilateral lobe involvement, and tumour close to the surgical margin, respectively. Thirty (46.2%) patients were classified as group N0, 10 patients (15.4%) as group N1a, and 25 (38.5%) as group N1b.

All the DTC patients received treatment with at least one dose of RAI. Of the 65 patients, 13 of them had only remnant disease at the thyroid bed, whereas 33 patients had locoregional disease detected after the first RRA. There were 19 (29.2%) patients with high-risk (M1 stage of disease). Almost all the patients in the M1 group presented with distant metastases to the lungs (94.7%), except for one patient who had metastasis to the bones alone. There were 24 (36.9%) patients stratified as low-risk, 10 (15.4%) patients as intermediate-risk and 31 (47.7%) patients as high-risk, based on the 2015 ATA classification.

Distant metastasis at presentation was significantly associated with pre-pubertal age (p=0.002), presence of cervical lymphadenopathy at initial presentation (p=0.018), bilateral thyroid lobe cancers/ multicentric DTC (p=0.015), multifocal malignancy (p=0.021), ETE (p=0.006), and presence of lymphovascular invasion (p=0.001), as shown in Table II. Large tumour size of >4cm but with no evidence of ETE did not carry any significant risk of metastatic disease at presentation (p=0.131).

The mean time to first RAI therapy after completion of surgery was 96 days. The mean number of times for RAI per patient was 4.26 ± 3.4 (1 -16 times). In several selected patients who had persistently positive post-treatment ^{131}I WBS, RAI therapy was repeated within 6 – 12 months after their initial treatment with RAI (Figure 1). All patients were placed on TSH suppression therapy following RAI. The cumulative RAI dose (CRD) was 30-2040 mCi (mean±SD: 469.8±449.4 mCi). Difference in mean CRD in the remission and persistent disease group was significant (p=0.010), i.e., 297±328 mCi and 729±487 mCi, respectively.

No mortality was reported during our study period. Overall, there were 39/65 (60%) of patients who achieved remission. Among the patients who achieved remission, 49% were from low-risk, 15% from intermediate-risk and 36% from high-risk groups, respectively. Meanwhile, 40% had persistent disease. Twenty-one out of 26 patients in the persistent disease group showed stable disease: 12 patients had persistent locoregional disease, and 9 had persistent lung metastasis. The remaining 5 patients in the persistent disease group had rising Tg levels and negative ^{131}I scans. These patients underwent ^{18}F-FDG PET/CT scans and were identified to have dedifferentiated disease, as shown in Figure 2. Persistent disease was significantly correlated with distant metastasis at presentation (p=0.025). There were no patients detected with recurrence or progressive disease.

Long term adverse events were reported in 2 patients who developed bone marrow suppression, i.e., in one patient with

Table I: Demographics and clinicopathological characteristics among paediatric DTC

Characteristics	Total patients n=65	
	n	% of total
DEMOGRAPHICS AND CLINICAL CHARACTERISTICS		
Gender		
Male	14	21.5
Female	51	78.5
Age at diagnosis (range)	14.9 years ± 3.7 (4- 18)	
Age group		
< 10 years old	7	10.8
≥ 10 years old	58	89.2
Ethnic		
Malay	49	75.4
Chinese	8	12.3
Indian	4	6.2
Others	4	6.2
Presenting complaint		
Thyroid nodule	50	76.9
Cervical lymphadenopathy	7	10.8
Thyroid nodule and cervical lymphadenopathy	7	10.8
Others (e.g., syncopal attack)	1	1.5
Family history of thyroid cancer		
Yes	6	9.2
No	59	90.8
Surgery		
Total thyroidectomy and neck dissection	20	30.8
Total thyroidectomy	22	33.8
Staged surgery (Hemithyroidectomy followed by completion)	23	35.4
HISTOPATHOLOGICAL		
Tumour histology		
Papillary thyroid carcinoma	50	76.9
Follicular thyroid carcinoma	6	9.2
Follicular variant of papillary thyroid carcinoma	6	9.2
Microcarcinoma	1	1.5
Others	2	3.1
Bilateral lobes involvement		
Yes	23	35.4
No	42	64.6
Focality		
Multifocal	30	46.2
Unifocal	35	53.8
Tumour size		
T1a	1	1.5
T1b	23	35.4
T2	16	24.6
T3	21	32.3
T4a	4	6.2
T4b	-	-
Extrathyroidal extension		
Yes	4	6.2
No	61	93.8
Lymphovascular invasion		
Yes	42	64.6
No	23	35.4
Regional nodes metastasis		
N0	30	46.2
N1a	10	15.4
N1b	25	38.5

Footnote: Categorical variables are represented as number (n) and percentage (%). Continuous variables are represented as mean±SD. T: tumour staging. N: lymph node staging.

Table II: Factors associated with distant metastasis at presentation

Clinicopathological characteristics	Total (n=65)		Distant metastasis at presentation				p value
	No	%	No (n=46)	Yes (n=19)			
			No	%	No	%	
Male gender	14	21.5	9	19.6	5	26.3	0.529
Malay race	49	75.4	36	78.3	13	68.4	0.591
Age group < 10 years old	7	10.8	1	2.2	6	31.6	0.002
Presenting with Cervical lymphadenopathy	14	21.5	6	13.0	8	42.1	0.018
Family history of thyroid cancer	6	9.2	4	8.7	2	10.5	0.571
Tumour histology							
Follicular thyroid carcinoma	6	9.2	5	10.9	1	5.3	0.662
Bilateral thyroid lobes involvement	23	35.4	12	26.1	11	57.9	0.015
Multifocality	30	46.2	17	37.0	13	68.4	0.021
Tumour size >4cm	25	38.5	15	32.6	10	52.6	0.131
Extrathyroidal extension	4	6.2	0	0	4	21.1	0.006
Lymphovascular invasion	42	64.6	24	52.2	18	94.7	0.001

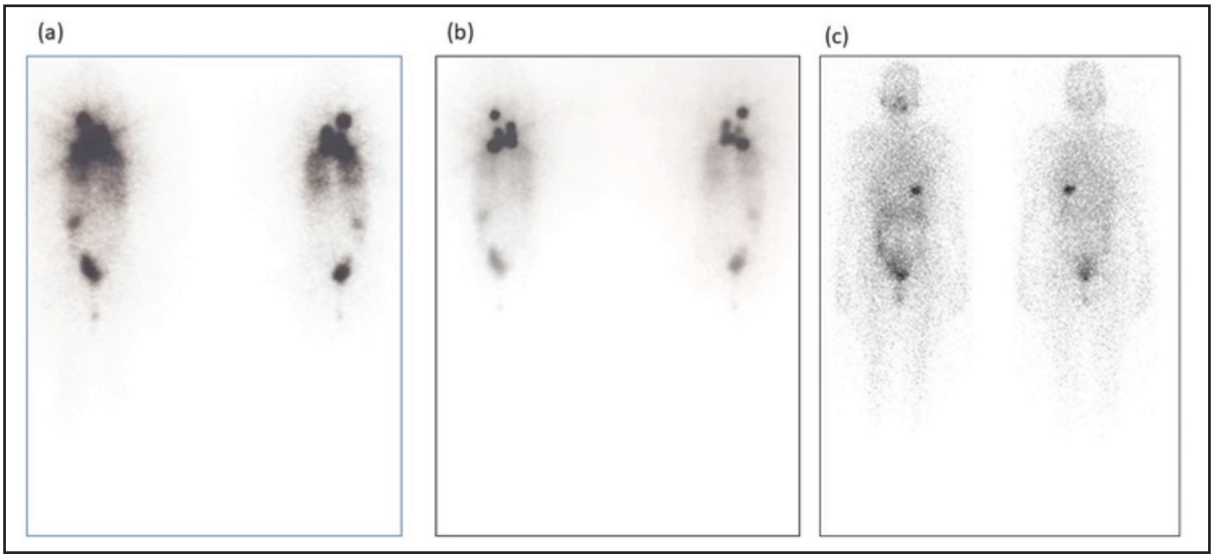

Fig. 1: (a) A 4-year-old girl with papillary thyroid carcinoma having cervical nodal metastasis, who underwent total thyroidectomy and modified right neck dissection. At presentation there was intense locoregional disease with diffuse lung metastasis on the ^{131}I WBS (Serum thyroglobulin, Tg was 50 ng/mL). (b) ^{131}I WBS for the same patient after the 3rd RAI therapy showed reduced tracer uptake in the thyroid bed, cervical nodes and lung indicating response to treatment. (Serum Tg became reduced to 24 ng/mL). (c) ^{131}I WBS after the 5th RAI therapy, with a cumulative dose of 150 mCi, showed physiological uptake, indicative of complete metabolic response. (Serum Tg dropped to < 1 ng/mL).

a total CRD of 2040 mCi and another in a patient with a total CRD of 1080 mCi. Nevertheless, the bone marrow suppression spontaneously resolved several months after the cessation of RAI therapy. Throughout their follow-up, a total of eleven patients underwent other adjunct therapy in addition to RAI therapy, namely eight patients underwent surgery for lymph node excision, and three patients underwent radiotherapy to the neck. One out of these 11 patients underwent RAI 16 times and had radiotherapy to the neck, followed by surgical excision of the neck nodes. Subsequently, this patient was referred to the National Cancer Institute in Putrajaya, Malaysia, for dosimetry-guided RAI of 500 mCi in a single dose. This patient had a total CRD of 1570 mCi. Despite having persistent disease, the patient was asymptomatic throughout and did not have any complications. Whereas, out of the 11 patients, two patients had undergone both radiotherapy and lymph node excision. Another patient with refractory disease, i.e. had persistent lung metastasis despite being administered with 8 consecutive doses of RAI, required dosimetry-based therapy of 300 mCi.

DISCUSSION

Treating paediatric DTC with RAI therapy frequently poses a challenge to physicians in nuclear medicine. There are many controversies pertaining to the factors that affect the risk of recurrence and the most appropriate treatment protocol for them. In our study population, the distribution of tumour histology that was predominantly papillary thyroid cancer and the high female-to-male ratio (5:1); are considered relatively consistent with data from other countries.[11,14,15] Although females acquired DTC more frequently than males, the latter group was noted to have an increased, albeit statistically non-significant risk for developing metastasis, similar to that noted by Kammori et al., 2015.[14]

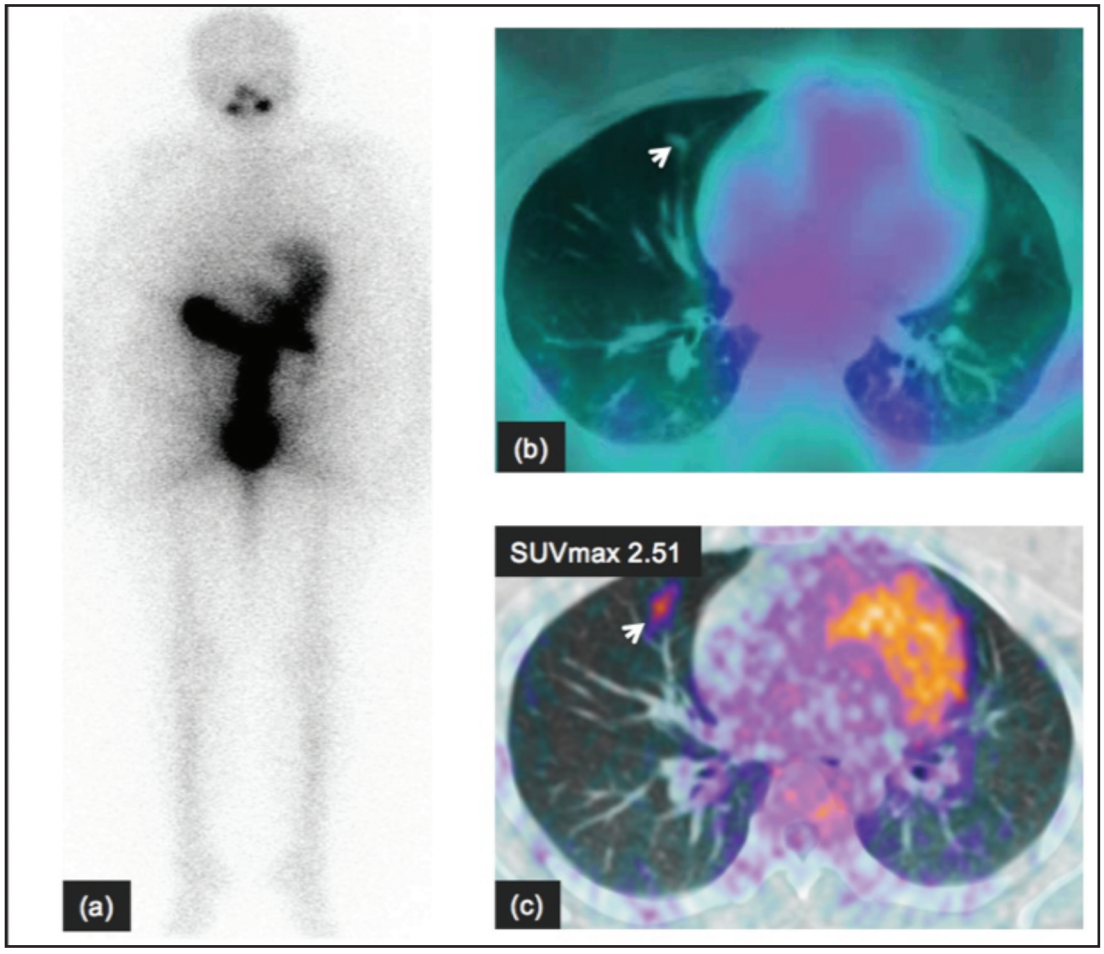

Fig. 2: (a) A 18-year-old patient with negative ^{131}I WBS despite high Tg levels. (b) A small, hypodense lung nodule (arrow) detected in the right middle lobe did not demonstrate tracer uptake on the ^{131}I SPECT/CT scan. (c) ^{18}F-FDG PET/CT scan revealed increased tracer uptake in the small lung nodule at the right middle lobe (SUVmax 2.5), indicative of dedifferentiated disease.

We noted that the distribution of patients based on risk assessment was 36.9% for low-risk, 15.4% for intermediate-risk and 47.7% for high-risk groups, respectively. This distribution is slightly different from a study published by Bhavani et al. 2018 regarding an Indian patient population, which reported that 12% of patients were from low risk, 68% of patients from intermediate risk and 20% of patients from high-risk groups, respectively.[10]

We administered RAI therapy based on an empirical dose whereby we adjusted the ^{131}I dose according to the body weight of patients. We gave a fraction of the dose based on the typical adult activity used to treat similar disease extent, considering the paediatric age and body weight of patients. We practised RRA at HKL for all cases irrespective of the initial risk assessment due to several factors. Firstly, some of our patients were referred to us from remote areas of Malaysia. Hence the patients may not have the benefit of a high-volume thyroid surgeon. Secondly, ^{123}I is not available in Malaysia, limiting our ability to perform an initial diagnostic scan as per the 2015 ATA guideline recommendations. Alternatively, we decided against performing a diagnostic scan using ^{131}I for our patients because it generally confers a higher radiation dose while having a relatively inferior sensitivity to detect disease.[9] Apart from that, the unavailability of post-operative Tg results made RRA a better option for these patients. Furthermore, based on the ATA recommendations in 2015, we practised a modified individualized approach, in which we incorporated the clinicopathological data to guide our approach in the therapy.[9] This included dose modifications by giving a fraction of the adult doses that were based on our personal experiences in paediatric practice.

The pre-pubertal age group had more advanced disease compared to the adolescent group, wherein the majority (85.7%) of patients had distant metastases at presentation. The sites of metastases were predominantly the lungs. This observation was also similar to studies conducted in India and Japan, where there was a high incidence of pulmonary metastases detected at presentation.[3,16] During the course of the treatment, the mean CRD of 469.8 mCi was prescribed for the whole study sample, with the mean CRD in the remission group being significantly lower than in the persistent disease group, i.e., 297±328 mCi and 729±487 mCi, respectively ($p<0.05$). The high CRD is due to the historical practice in HKL with a low threshold of successive RAI administrations, which has already evolved in recent years to be more in line

with the latest clinical practice guidelines. Currently, alternative treatment strategies are usually actively sought in cases that are refractory to RAI therapy. These patients are more likely to continue TSH suppression therapy alone with cessation of RAI.

In addition to RAI therapy, eleven patients had other adjunct treatment in the form of repeat MRND and external beam radiotherapy to the neck. Approximately 60% of the total patients had achieved complete remission. Unfortunately, 40% had persistent disease despite multiple RAI therapies and a multimodality treatment approach. Two patients with lung metastases had ^{131}I internal dosimetry and were given as high as 500mCi in a single dose. Despite high RAI doses to the lungs, no lung fibrosis was reported. No disease recurrence was reported in successfully treated patients. Furthermore, there was neither mortality nor any significant morbidity reported among our patients.

In our study population, the low-risk group's remission rate was higher than the high-risk group. The remission rate for patients having regional nodal metastases and distant metastases was 57.6% and 36.8%, respectively. In cases of iodine avid distant metastasis requiring multiple ablations, radioiodine administration based on the dosimetry approach should be strongly encouraged. We now recognise that dosimetry should be performed early, as RAI refractoriness is defined as CRD >600mCi. Hence, once the paediatric patients have exceeded this limit, the chances are that performing dosimetry prior to giving subsequent RAI may not be remarkably beneficial.

Furthermore, during the study period, no second malignancy was identified or reported. We routinely followed up the patients with thorough history taking, and physical examinations. Additionally, a full blood picture or peripheral blood film investigation was done for patients who had >600 mCi of total cumulative doses of RAI. Nevertheless, a longer duration of study may actually be needed to evaluate the stochastic effects of radiation.

Several selected patients benefitted from ^{18}F-FDG PET/CT scans to help assess their status of dedifferentiated disease. ^{18}F-FDG PET/CT involves the utility of non-invasive hybrid imaging using a glucose analogue radiotracer that can help to diagnose, monitor treatment, and aid in the prognostication of cancers.[17] Based on PET Response Criteria in Solid Tumours (PERCIST) 1.0, the maximum standardised uptake value (SUV_{max}), which is the measured activity of the radiotracer in a given volume of interest in the body, can be recorded from the ^{18}F-FDG PET/CT scans to determine abnormal glucose metabolism in cancerous cells.[18] Dedifferentiated DTC are more aggressive, as they develop a reduction of the sodium iodide symporter and manifest an overexpression of the GLUT1 transporter, thus becoming radioiodine refractory but more metabolically active on ^{18}F-FDG PET/CT scans.[19] Hence, there is a role for referral of patients for a ^{18}F-FDG PET/CT scan if they demonstrate persistently elevated serum Tg, but with relatively low to nil evidence of iodine-avid disease on ^{131}I WBS.[20] After identifying non-RAI avid lesion on ^{18}F-FDG PET/CT imaging, it is necessary to evaluate the feasibility of surgical or oncological therapy because these lesions are at risk of PD.

The limitation of this study is the relatively small overall sample size. Furthermore, as the condition is rare, we had a small proportion of pre-pubertal age group patients with DTC. Although the pre-pubertal age has been reported as a significant factor in previous studies, we were not able to evaluate this factor adequately due to our small sample size. In future, we recommend that efforts need to be taken to obtain more data of children treated for DTC in Malaysia. There is a need to perform multicentre studies to achieve more comprehensive information regarding DTC among children in this country. We also recommend future studies to recruit more subjects from the pre-pubertal age group to evaluate their treatment prognosis. Both gender and pubertal status should be considered in future studies when evaluating iodine-refractory disease. We also recommend that dosimetry-based RAI therapy be instituted early in the treatment protocol, especially when dealing with high-risk patients. Thus, particularly in pre-pubertal children who are more prone to develop marrow suppression and induction of secondary cancers, appropriate management strategies can be developed to achieve better treatment outcome. Furthermore, larger longitudinal studies are needed to determine the long-term survival and the sequelae of radionuclide therapy among the paediatric population.

CONCLUSION

This is the first report on the Malaysian experience in the management of paediatric DTC from the nuclear medicine perspective. Paediatric DTC manifests with more extensive disease at presentation and requires multiple RAI doses. Despite this, it carries an excellent overall prognosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENT

We would like to thank the Director-General of Health Malaysia, Ministry of Health Malaysia and Director of Hospital Kuala Lumpur, Malaysia for the permission to publish this study.

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ORIGINAL ARTICLE

Radionuclide gastric emptying scintigraphy in patients with suspected gastroparesis in Hospital Kuala Lumpur: A preliminary experience

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ABSTRACT

Introduction: Gastroparesis is a medical condition that can cause significant morbidity. Its prevalence in Malaysia is not known and is often under diagnosed. The gold standard in the assessment of gastroparesis is radionuclide gastric emptying scintigraphy (GES). The aim of this study was to evaluate the added benefit of performing GES in patients with suspected gastroparesis in Hospital Kuala Lumpur (HKL).

Methods: The clinical data and scintigraphic findings of consecutive patients referred to the Department of Nuclear Medicine, HKL for GES from July 2020 to December 2020 were retrospectively reviewed.

Results: Thirteen patients underwent the study (6 males and 7 females) with a mean age of 47.9 years (age range of 25 to 72 years). The majority of patients (n=11) were diagnosed with either type I or type II diabetes mellitus. Ten patients reported abnormal scan findings with only 3 patients had normal GES findings. Scintigraphic findings from our patients, association of symptoms with abnormal GES as well as the challenges in implementing GES in Malaysia is discussed.

Conclusion: GES provides valuable information to the referring physician in the diagnosis and management of patients with gastric motility disorders. However, its use is limited because of limited availability, cost restriction, lack of familiarity among clinicians, and lack of understanding of the test. Further effort is thus needed to enhance the availability and usage of GES in Malaysia.

KEYWORDS:
gastric emptying scintigraphy, gastroparesis, sulfur colloid

INTRODUCTION

Gastroparesis is a chronic disorder that results in delayed gastric emptying without the presence of mechanical obstruction and can greatly impact the quality of life of the patients.[1-6] It is caused by an impaired intrinsic nervous system involving the gastric motor function of the stomach which leads to abnormal peristaltic contractions and stagnation in chyme propagation.[1,3,6] The aetiology can be idiopathic or secondary to other diseases such as diabetes mellitus, infection, cancer, connective tissue disease, renal insufficiency and neurologic dysfunction.[1,3,6-8] Diagnosis is based on symptoms consistent with gastroparesis, normal upper endoscopy findings and evidence of delay in gastric emptying.[9,10]

Accurate diagnosis of this condition is essential to reduce cost and impact on the economy as reflected in patient hospitalization, multiple diagnostic tests, and ineffective therapy causing absence from work and reduction in productivity at the workplace.[1,11,12] Currently, radionuclide gastric emptying scintigraphy (GES) is still the gold standard in the diagnosis of gastroparesis.[1,8] A standard Technetium-99m (^{99m}Tc) labelled meal is ingested by the patient followed by serial scanning with a gamma camera to assess the transit of food through the stomach. Despite its inception in the 1960's,[2,8,13] the usage of this test has not been well documented or published in Malaysia. In addition, the prevalence of gastroparesis in Malaysia is not known and the disorder is often under diagnosed.

In a survey conducted by the Asian Neurogastroenterology and Motility Association on gastroparesis, it was found that the main factors in the lack of interest or under diagnosis of gastroparesis were attributed to lack of knowledge, scarcity of research, limited access to diagnostic tools and lack of effective therapy.[10] However, with the advancement of pharmacological and non-pharmacological therapies,[10] the need for awareness in GES as a reliable diagnostic test for gastroparesis is of paramount importance. Thus, the objective of this study was to evaluate the benefit of performing GES in patients with suspected gastroparesis and to assess the severity of gastroparesis at Hospital Kuala Lumpur (HKL), Malaysia. We also aimed at designing a suitable Malaysian protocol for this diagnostic technique in the future.

MATERIALS AND METHODS

Patient selection

This retrospective study was approved by the Ministry of Health Medical Research Ethics Committee (MREC approval number: NMRR-20-1008-54807) and data collection was in accordance with the Declaration of Helsinki for human

This article was accepted: 23 May 2021
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research. We reviewed the clinical data and scintigraphic findings of consecutive patients referred to the Department of Nuclear Medicine, HKL for GES from July 2020 to December 2020. Inclusion criteria were patients aged 18 years and above with no previous history of gastric surgery who were referred to our department for GES and completed the GES study. Exclusion criteria were: vomiting portion of the meal, incomplete consumption of meal and poor glycaemic control before the study. From our records, there were 14 patients referred and underwent the GES study. One patient did not complete the study due to persistent vomiting at 2 h and was thus excluded.

Radiolabelled meal ingestion protocol

The patients fasted between 6 to 10 h before the study. Medications that were deemed to a) increase gastric motility such as metoclopramide, domperidone, tegaserod and erythromycin; b) decrease gastric motility such as opiates, atropine, antispasmodic agents and phenobarbital; c) increase or decrease gastric motility like calcium channel blocker, progesterone, theophylline, phentolamine, octreotide and benzodiazepine were withheld for at least 48 h before the procedure.[2,13] Patients relevant clinical information pertaining to gastroparesis were retrospectively obtained. The fasting blood glucose levels were recorded on the morning of the procedure with a cut-off value of less than 15.3mmol/L[1,2] being eligible for the study. The standardized radiolabelled meal was then prepared based on the Society of Nuclear Medicine and Molecular Imaging (SNMMI) guidelines, consisting of 255 kcal meal (72% carbohydrate, 24% protein, 2% fiber and 2% fat).[2] The mixture of 1.0mCi of ^{99m}Tc labelled sulfur colloid and 4 oz of egg whites (60 kcal) were cooked into a firm rubbery consistency in a microwave and ingested by the patient with two slices of bread (120 kcal), 30g of jam (75 kcal) and 120ml of plain water within 10 minutes.[2,5] No additional food or drinks were allowed until the completion of the study at 4 h post meal ingestion.

Image acquisition

After ingestion of the radiolabelled meal, patients were placed in a supine position on a dual-head gamma camera. Concurrent static one-minute anterior and posterior images of the region covering the lower chest and lower abdominal region were acquired on either Siemens E-Cam Dual or Siemens Symbia T6 SPECT/CT gamma camera immediately, and at intervals of 0.5, 1, 2, 3 and 4 h post meal. The images were acquired using a low energy all-purpose collimator at 140 keV photopeak of ^{99m}Tc and 20% energy window (140 keV ± 10%).

Image analysis, data interpretation and statistical analysis

Images obtained were then processed and analysed on a dedicated E-soft Syngo workstation (Siemens Medical Systems). The stomach was identified on the immediate image and normalized to 100% as the baseline point (T0). Subsequent gastric residuals were measured at each time point using geometric mean activity and region of interest analysis, corrected for ^{99m}Tc decay. Image interpretation was performed qualitatively, considering the quantitative parameters based on the percentage (%) of gastric retention at each time point that were graphed. The normal limit of % gastric retention is based on the Consensus Recommendation of Gastric Emptying Scintigraphy, where the normal percentage of gastric retention at 1 h is 30 to 90%, ≤ 60% at 2 h and ≤ 10% at 4 h.[2] Rapid gastric emptying is define as gastric retention percentage of < 30% at 1 h while the criteria for delayed gastric emptying includes gastric retention of > 60% at 2 h or > 10% at 4 h.[2,13] This study involves descriptive analysis. The Fischer's exact test is used to assess the association between clinical symptoms and delayed gastric emptying.

RESULTS

Of the 13 patients included, they were 6 males and 7 females with the mean age of 47.9 years (age range of 25 to 72 years). In terms of ethnicity, 53.8% were Malays (n=7) with 3 Chinese and 3 Indians respectively. The majority of patients (n=11, 84.6%) were diagnosed with either type I or type II diabetes mellitus. The recorded mean of fasting blood glucose of our patients was 8.8mmol/L (range of 4.8 to 15.1mmol/L). Ten patients recorded abnormal findings with only 3 patients having normal GES findings (Figure 1). Out of the 10 patients, 1 patient showed rapid gastric emptying (Figure 2), 3 patients demonstrated delayed emptying in the early phase with normal gastric retention at 4 h, and 6 patients reported delayed gastric emptying at 4 h of study. The delayed gastric emptying can be further classified in terms of its severity based on the percentage of gastric retention at 4 h. Of the 6 patients, 4 patients showed mild delay (11% to 20% retention), 1 patient with moderate delay (21% to 35% retention) and 1 patient displayed very severe delay (> 50% retention) in gastric emptying (Figure 3). Table I summarises the characteristics of patients referred for GES, including their clinical symptoms and GES scan findings. As for the main presenting symptoms, most of the patients experienced dyspepsia or epigastric discomfort (n=9, 69.2%) and nausea-vomiting (n=8, 61.5%) before the study. Scintigraphy imaging at 1, 2 and 4 h demonstrated abnormal findings in 7 (53.8%), 9 (69.2%) and 6 (46.2%) patients, respectively. Further analysis revealed that nausea-vomiting symptom was significantly associated with abnormal scan findings at 4 h imaging ($p < 0.05$). Among those with symptoms of nausea-vomiting, 6 patients (75%) had abnormal scan findings at 4 h imaging as compared to none among those who reported no nausea-vomiting. Other parameters were not significantly associated with abnormal scan findings (Table II).

DISCUSSION

Gastroparesis is a debilitating disease that caused significant morbidity and mortality.[4] The actual prevalence of gastroparesis in Malaysia is not known and it is often under diagnosed.[4] Based on an epidemiological study, gastroparesis may present in up to 1.8% of the general population, with only a fraction (approximately 0.2%) being diagnosed.[3] Majority of patients with gastroparesis are diabetic and gastroparesis can involve up to two-third of diabetic patients.[1,2,4,7,10,14] In general, gastroparesis has a significant impact on the quality of life and affects mostly women.[6,15]

The key motor function of the stomach is gastric accommodation which facilitates delivery and storage of

Table I: Characteristics of patients referred for GES, clinical symptoms and scan findings

Case	Age	Gender	Clinical symptoms	Medical comorbidities and past surgical history	Gastric retention %			GES Conclusion
					At 1 h (normal range 30 to 90%)	At 2 h (normal range ≤ 60%)	At 4 h (normal range ≤ 10%)	
1	72	Male	Gastroesophageal reflux, epigastric pain and bloating	Diabetes mellitus, hypertension, bronchial asthma, hypothyroidism and dyslipidemia	74%	53%	3%	Normal gastric emptying study
2	68	Female	Heartburn, bloating and abdominal discomfort	Diabetes mellitus and dyslipidemia. History of total abdominal hysterectomy and bilateral salphingoopherectomy	27%	14%	0%	Rapid gastric emptying
3	25	Female	Nausea, vomiting, diarrhoea, abdominal discomfort and weight loss	Gastritis and hiatal hernia	84%	66%	3%	Delayed gastric emptying in the early phase with normal gastric retention at 4h
4	26	Female	Persistent vomiting	Diabetes mellitus, hypertension and dyslipidemia History of appendicectomy	91%	66%	16%	Mildly delayed gastric emptying
5	39	Male	Abdominal discomfort, nausea, vomiting and diarrhoea	Diabetes mellitus	96%	74%	32%	Moderately delayed gastric emptying
6	52	Male	Postprandial vomiting	Diabetes mellitus, hypertension and dyslipidemia	77%	50%	15%	Mildly delayed gastric emptying
7	63	Female	Epigastric discomfort, frequent burping and regurgitation	Parkinson's disease	80%	61%	10%	Delayed gastric emptying in the early phase with normal gastric retention at 4h
8	32	Female	Persistent nausea and vomiting	Diabetes mellitus, hypertension and dyslipidemia	61%	28%	0%	Normal gastric emptying study
9	34	Female	Persistent dyspepsia and vomiting	Diabetes mellitus	98%	71%	16%	Mildly delayed gastric emptying
10	32	Male	Cyclical vomiting syndrome	Diabetes mellitus	93%	78%	20%	Mildly delayed gastric emptying
11	66	Female	Chronic dyspepsia	Diabetes mellitus, hypothyroidism and bronchial asthma. History of appendicectomy and cholecystectomy	97%	68%	9%	Delayed gastric emptying in the early phase with normal gastric retention at 4h
12	66	Male	Dyspepsia and weight loss	Diabetes mellitus and hypertension	66%	24%	0%	Normal gastric emptying study
13	47	Male	Abdominal discomfort, vomiting, chronic diarrhoea and weight loss	Diabetes mellitus, chronic pancreatitis and hyporeninemic hypoaldosteronism	97%	94%	60%	Very severe delayed gastric emptying

h = hour, GES = gastric emptying scintigraphy

Table II: Association of gender, age, diabetes mellitus and symptoms with gastric emptying scintigraphy findings at 1, 2 and 4 hours

	One Hour		p-value	Two Hour		p-value	Four Hour		p-value
	Normal	Abnormal		Normal	Abnormal		Normal	Abnormal	
Gender									
Female	3	4	1.000	1	6	0.266	5	2	0.286
Male	3	3		3	3		2	4	
Age group									
≤40 years	2	4	0.592	1	5	0.559	2	4	0.286
>40 years	4	3		3	4		5	2	
Diabetes mellitus									
No	2	0	0.192	0	2	1.000	2	0	0.462
Yes	4	7		4	7		5	6	
Dyspepsia									
No	2	2	1.000	2	2	0.53	1	3	0.266
Yes	4	5		2	7		6	3	
Nausea-vomiting									
No	3	2	0.583	2	3	1.000	5	0	0.021*
Yes	3	5		2	6		2	6	

Fisher's Exact Test (p value <0.05 indicated a significant difference)

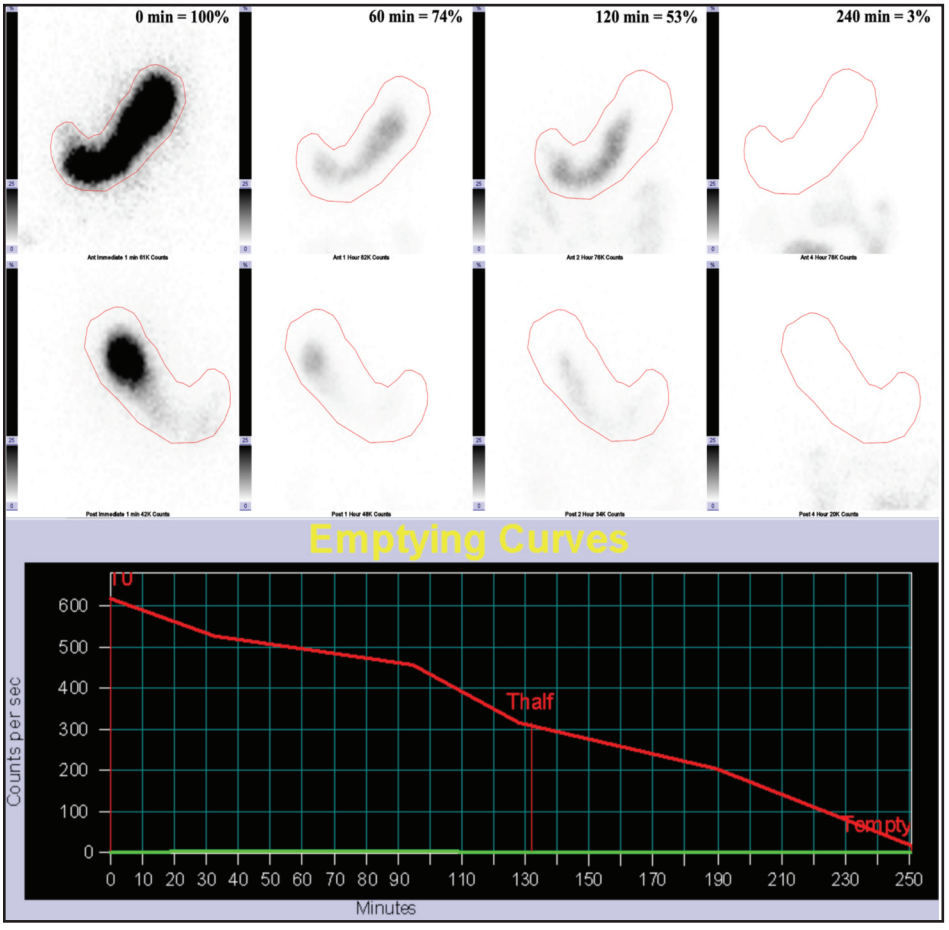

Fig. 1: A 72-year-old male diagnosed with diabetes mellitus, hypertension, hypothyroidism and bronchial asthma, complained of a 1-year history of epigastric pain and abdominal bloating. GES showed the radiopharmaceutical meal in the stomach in the immediate image with progressive emptying of radiotracer from the stomach into the small bowel as the study progress. Quantitative assessment and emptying curve showed the gastric retention at 1, 2 and 4 hours were within the normal range denoting a normal GES study.

food, followed by subsequent grinding of food into smaller fragments, also known as trituration.[1,3,4,13] The fragmented food is then liquefied by the actions of both antral contractions and digestion of gastric acid, producing a high liquid shearing force that propels the food particles, 1 to 2 mm in size against the pylorus before it empties into the duodenum.[1,3,4,13] In gastroparesis, there is impairment in extrinsic neural control, intrinsic nerves dysfunction and

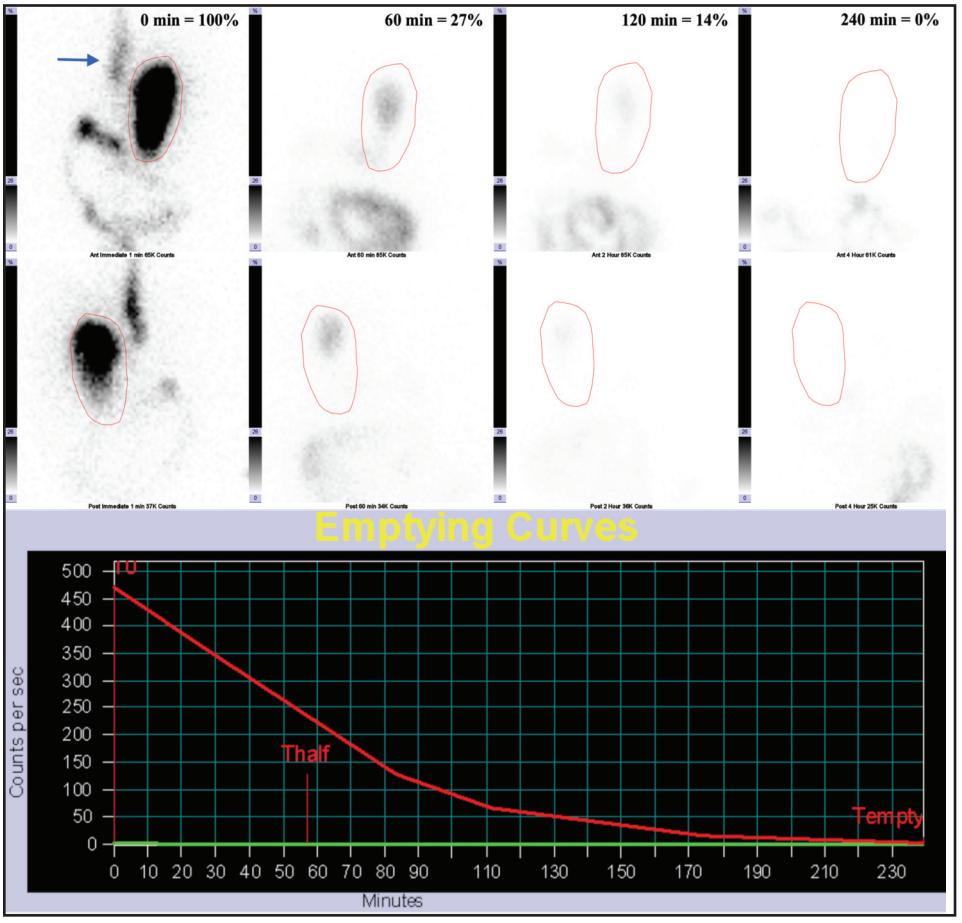

Fig. 2: A 68-year-old female with diabetes mellitus and dyslipidemia who presented with a 2-year history of heartburn, bloating and abdominal discomfort. GES showed rapid movement of tracer from the stomach into the small bowel with early visualization of the large bowel in the immediate (0 min) image. Quantitative assessment and emptying curve revealed 27% gastric retention at 1 hour (normal tracer retention range at 1 hour is 30% to 90%) indicating a rapid gastric emptying. There is also an ancillary finding of gastroesophageal reflux as evidenced by abnormal accumulation of radiotracer in the distal esophagus seen in the immediate (0 min) image (blue arrow).

interstitial cells associated with local control of gastrointestinal muscle as well as loss of function of the smooth muscles.[1,3,4,6]

The symptoms of gastroparesis include early satiety, nausea, vomiting, postprandial fullness, belching, bloating, abdominal pain and abdominal discomfort.[2–4,6,8,13] Nonetheless, patients with rapid gastric emptying and functional dyspepsia may present with almost identical symptomatology.[2,4,6] This presents a diagnostic dilemma amongst the treating physician as the treatment strategies for each of the disorder differ. Furthermore, both gastroparesis and rapid gastric emptying can present in diabetic patients.[4] In our case (Figure 2), a 68-year-old patient with diabetes mellitus who was initially thought to have gastroparesis was found to have rapid gastric emptying from GES which result in a change of the patient's treatment plan. Moreover, in our study, it was found that the clinical symptoms of nausea and vomiting were significantly associated with delayed gastric emptying (abnormal gastric retention at 4 h) (Table II). This is similar to the findings from a systematic review and meta-analysis by Vijayvargiya et al.[16], which noted a significant association between symptoms of nausea and vomiting with delayed gastric emptying. In addition, other symptoms such as abdominal pain and early satiety were also recognized to be significantly associated with gastroparesis.[16] Nonetheless, further assessment with larger sample size is needed to validate our findings.

There is a myriad of tests that can be used to diagnosed gastroparesis such as GES, gastric emptying breath test (GEBT) and wireless motor capsules (WMC).[1,3,17] GEBT does not involve radiation exposure and is easy to use. A ^{13}C-labelled substrate is added to a standard liquid or meal. When the labelled food enters the duodenum, $^{13}CO_2$ is released as the labelled food is absorbed and broken down. The release of $^{13}CO_2$ from the breath is sampled at regular intervals to generate an emptying curve.[18] However, the test is not widely available, is easily influenced by physical activity and unreliable in patients with malabsorption, chronic obstructive pulmonary disease and pancreatic insufficiency.[1,3,18] Like the GEBT, WMC can assess gastric emptying without the involvement of radiation exposure with the added advantage of evaluating intestinal and bowel motility.[1,3] The gastric emptying is measured when a change of pH is detected as the capsule enters the alkaline duodenum

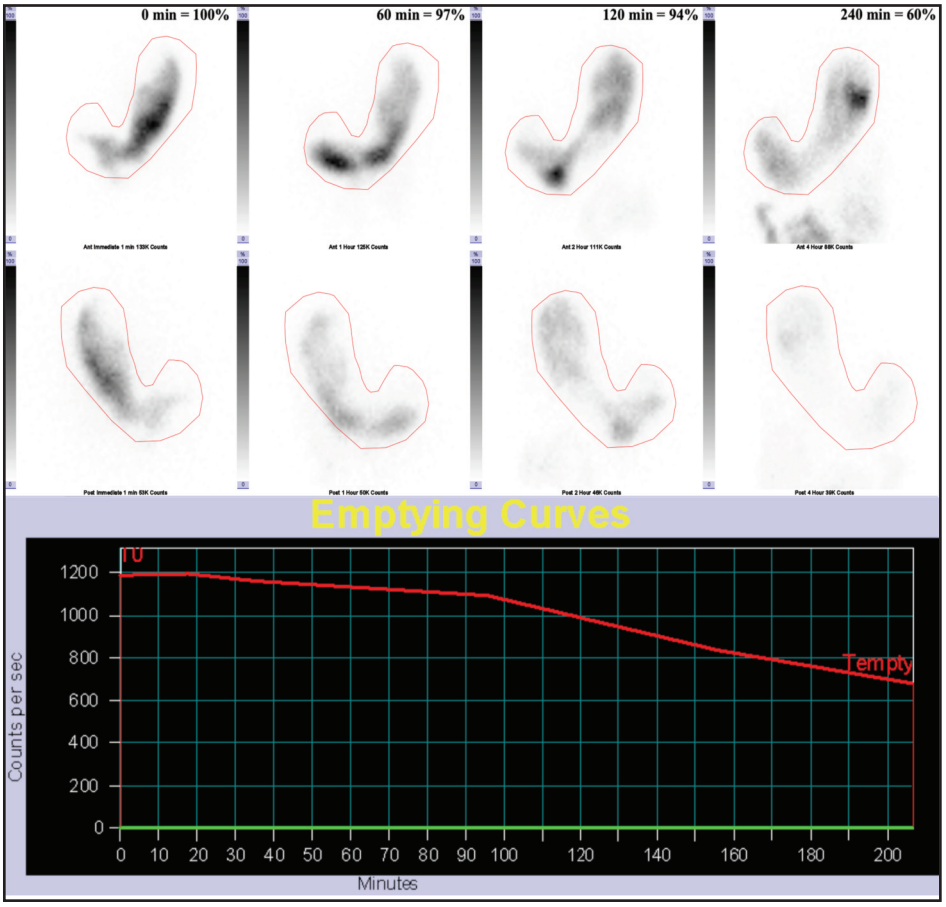

Fig. 3: A 47-year-old male with diabetes mellitus, chronic pancreatitis and hyporeninemic hypoaldosteronism. Presented with a history of chronic diarrhea, epigastric pain, vomiting and loss of weight. GES showed tracer accumulation in the stomach in the immediate image with slow transit of tracer into the small bowel as the study progress. There is significant retention of tracer by 4 hours of study with 60% gastric retention (upper limit of tracer retention is 10% at 4 hours) signifying very severe delay in gastric emptying.

from the acidic stomach.[18] However, this method is expensive, limited in availability and does not empty at a similar rate as a digestible meal.[18] Comparatively, GES has the advantage of being non-invasive, quantitative as well as physiologic in the evaluation of gastric emptying.[2] GES involves ingestion of radioisotope labelled solid meal with a short half-life and the measurement of radioactivity in the stomach at various time intervals to determine the rate of gastric emptying.[3,8] The limitations of GES include minimal radiation exposure, the prepared meal may not be palatable to the Malaysian population and long duration of study which may require patients to be in the nuclear medicine department throughout the day.

GES aims to identify patients with gastroparesis who may benefit from pharmacological or other treatments.[8,13] Common indications for performing GES are a) unexplained nausea, vomiting and dyspeptic symptoms; b) assessment of gastric motility before fundoplication for gastroesophageal reflux disease; c) evaluation of gastric motility before small bowel transplantation or colectomy for colonic inertia; and d) screening for gastroparesis in diabetic patients.[19] Since the introduction of GES in 1966, there were variations in terms of meal composition, imaging protocols and normal values of gastric emptying which hinders its clinical application. A consensus between the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine was reached in 2008 [2] to resolve the issues. The universally recognized test meal is the low fat, egg white meal which was described by Tougas et al. with image acquisition to be performed the least, at 0, 1, 2, and 4 h post radiolabelled meal ingestion.[5] The consensus is currently the accepted standard for GES and has been adapted in many centres around the world, including in HKL. Apart from diagnosing gastroparesis and rapid gastric emptying, other ancillary findings can also be found on the GES study such as gastroesophageal reflux disease (Figure 2), reduced fundus compliance, reduction in fundus accommodation, and antral dysmotility which further enhance its diagnostic utility.[2,7,17]

Although the ^{99m}Tc generator is readily available in the nuclear medicine department, the sulfur colloid kit which is tagged with ^{99m}Tc is deemed expensive and not cost-effective, limiting the study's availability. Usage of ^{99m}Tc sulfur colloid is primarily due to its properties of not being absorbed by the mucous membranes of the gastrointestinal tract and its good binding to the egg white protein.[13] Other cheaper alternatives with good labelling efficiency have been sought such as tin colloid, nanocolloid and macroaggregated albumin [14] to replace sulfur colloid. However, none of the studies were

conducted in vivo. In a study conducted by Mat Nawi et al. [20] involving 31 healthy individuals who underwent GES on two separate days using ^{99m}Tc sulfur colloid and ^{99m}Tc phytate, it was found that there was no statistically significant difference in gastric retention percentage at each time point between both radiopharmaceuticals. The in vivo study further concluded the use of ^{99m}Tc phytate as a valid alternative to the gold standard ^{99m}Tc sulfur colloid. In addition, the cost of a kit for phytate is five-fold cheaper compared to sulfur colloid with the added advantage of a more convenient radiopharmaceutical preparation.[20] The normative range of gastric retention percentage was almost identical to the one used by Abell et al., [2] hence, can be a reference point for its use in Malaysia. Usage of ^{99m}Tc phytate for GES has also been reported in other countries such as Thailand and Brazil.[21,22]

The commonly used radiolabelled meal in GES is the Western-styled meal, which consists of scrambled eggs, jam and two slices of bread. Nonetheless, the Western-styled meal may not be well accepted by other cultures including in Malaysia. Other centres from different regions of the world have modified or used different types of meal labelled with ^{99m}Tc sulfur colloid that is acceptable to the local population. This includes vegetarian solid meal comprising of Indian bread or chapatti,[17] hamburger,[23] steamed rice,[21] chocolate mug-cake[24] and scrambled tofu[24]. However, its use is not recommended until sufficient validation is available.[8] Hence, there is a need to formulate a locally acceptable and validated test meal for the GES study.

In patients who are unable to tolerate egg-white based meals or who have egg allergies, other alternatives have been proposed. In a study by Sachdeva et al. [9] comparing liquid nutrient meal (EnsurePlus) of similar caloric content to the standard egg-white meal involving 20 healthy volunteers, it was concluded that the overall gastric emptying is similar between the two meals. In another study by Solnes et al. [25] involving 21 healthy subjects using liquid nutrient meal for GES, the normal gastric emptying values were determined and compared with another group of normal volunteers which used the standard egg-white based meal. No significant differences in gastric retention percentage were found between liquid nutrient meal and the egg-white based meal group at specific time points. Both studies further advocate the use of liquid nutrient meal as an acceptable and reliable alternative to egg-white based meal in GES study. However, the main drawback of a liquid nutrient meal lies in its inability to assess the physiological aspect of trituration of the GES study.

Therapeutic strategies in gastroparesis encompassed treating the underlying cause, diet and lifestyle modifications such as multiple small meals, weight loss and avoidance of smoking and alcohol, antiemetic drugs, prokinetic agents and psychotropic medications.[1,3] For diabetic patients, the emphasis is on the normalization of blood glucose levels.[1,3] In patients who have failed pharmacological treatment, other therapy such as endoscopy, surgery and gastric electrical stimulation are utilized.[1,3] The grading in terms of severity of gastroparesis derived from GES can be used to assess treatment response and point the clinicians towards the appropriate treatment,[1,2] paving the way for personalize medicine. Mild to moderate gastroparesis can be treated with prokinetic agents in addition to dietary and nutritional modifications, while endoscopic treatment, gastric electrical stimulation and surgery can be considered in patients with severe or very severe gastroparesis as illustrated in our case (Figure 3). Prokinetic drugs may not be efficacious in those who have a normal GES study and this group of patients may likely benefit from other treatments.[5] In contrast to gastroparesis, the treatment strategies for patients with rapid gastric emptying include dietary modifications such as high protein and high fibre meals, pharmacological agents such as somatostatin analogues and acarbose, invasive procedures such as gastric pouch restriction as well as jejunostomy in malnourished patients.[4]

In our study, three patients had delayed gastric emptying in the early phase with normal gastric retention at 4 h. The early phase (0 to 2 h) reflects gastric fundus function whereas the delayed phase (2 to 4 h) signifies antral trituration as well as the movement of the meal into the duodenum.[7] Future therapies may be tailored to individually i.e. target fundus or antrum based on the early or late abnormalities characterized by a 4 h GES study.[7] At the present, patients with delayed gastric emptying in the early phase and mildly delayed gastric emptying at HKL are generally treated with pharmacological therapy along with dietary and lifestyle modification whereas two patients in the moderate to very severe delayed gastric emptying group are being considered for endoscopic treatment.

Because of limited nuclear medicine centres and resources in Malaysia, it is imperative to make use of available scan slots and gamma camera time for GES study. We therefore suggest a designated day for GES and to maximize the number of patients to be tested for that day. Close coordination and planning is thus needed amongst the referring clinician, nuclear medicine physician and nuclear medicine technologist in patient scheduling to ensure efficiency and optimal use of available gamma camera. Moreover, cheaper radiopharmaceutical alternatives can be considered if the need arises. This will inadvertently enhance the cost-effectiveness of the GES study without compromising the accuracy of the test.

LIMITATIONS OF THE STUDY

Limitations from this study is the small sample size and patients from a single institution. Thus, we were unable to generalize the findings observed in this study. In addition, this is a retrospective and cross sectional study with no long term follow up. Hence, we were unable to determine the causal relationship as well as changes in future management and patient outcome. Future prospective study with a larger sample size involving other institutions and long term follow up is thus advocated to ascertain the change or outcome of treatment in patients who underwent GES.

CONCLUSION

Gastroparesis is a relatively under diagnosed medical disorder and GES remains the gold standard in the assessment of this condition. GES provides valuable information to the referring physicians in the diagnosis of

gastric motility disorders and facilitate subsequent treatment plan. The limited availability of GES however hampers its clinical usefulness. Further effort is thus needed to enhance the availability and usage of GES in Malaysia.

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ORIGINAL ARTICLE

Problems in Malaysian children with large angle infantile esotropia: Children and parents' perspectives

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ABSTRACT

Introduction: There is limited information regarding the problems faced by children with large angle infantile esotropia (LAIE). The aim of this study was to explore the problems that children with LAIE encounter from both their perspectives and those of their parents.

Methods: This study included children who had LAIE (with angle of 40 prism dioptres or greater), aged 5 and 17 years who had attended the Ophthalmology Clinic, Hospital Universiti Sains Malaysia from March to September 2016. The children and their parents or guardians were interviewed face-to-face using a validated semi-structured interview guide. Interviews were tape-recorded and transcribed verbatim. Content analysis was performed using the NVivo 12 software.

Results: A total of 30 children and 30 parents were interviewed. The most common problems identified by the children were social interactions (73.3%, 22 children), visual functions (60.0%, 18 children), emotions (60.0%, 18 children), physical issues (40.0%, 12 children) and difficulties regarding treatment options (26.7%, eight children). The parents reported that their children were more affected in terms of visual functions (100.0%, 30 parents), social interactions (56.7%, 17 parents), emotions (43.3%, 13 parents), physical issues (20.0%, six parents), and difficulties regarding treatment options (16.7%, five parents).

Conclusion: The major problems that the children with LAIE identified were social interactions, while the parents observed that problems with visual functions was the most common issue encountered by their children. This suggests that the children affected have different perspectives from their parents and require support.

KEYWORDS:
infantile esotropia, large angle, children, parent, perspective

INTRODUCTION

Both children and adults with childhood onset of strabismus have psychosocial problems such as embarrassment, trouble making eye contact, low self-esteem, poor self-confidence, and intelligence scores that are perceived to be low.[1-3] The functional problems from which these patients suffer include rubbing their eye, photophobia, tired eyes, problems with eye focussing, double vision, difficulty in reading, difficulty with depth perception, pain or burning sensations in the eyes and vision-related problems.[1-12]

Valuable information regarding children's psychosocial and functional problems can be obtained from the close observations by their parents.[13,14] Furthermore, the parents of affected children reported adverse outcomes of strabismus on their own daily lives and family relationships. The parents were distressed by remarks of other people, worried about their children, had unsupportive relationship with their children, and had not been advised about corrective surgery.[13,14]

Few authors have described the concerns regarding strabismus from the perspectives of the children and their parents.[4-7] Based on a PubMed search, data regarding actual problems faced by children with large angle esotropia of infantile onset are limited. Hence, it is necessary to measure the daily problems of both the affected children and their parents from their own perspectives. The aim of our study, then, was to identify relevant problems that affect the daily activities of Malaysian children with large angle infantile esotropia (LAIE) and of their parents.

MATERIALS AND METHODS

This qualitative study was conducted in the Ophthalmology Clinic at Hospital Universiti Sains Malaysia (USM), Kelantan, Malaysia. Clinical data collection and procedures were conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Human Research Ethics Committee of USM. Informed consent was obtained from the parents and informed assent was attained from the affected children. Only one of each parent of the children was recruited for the interview. Purposive sampling using the maximum variation sampling was applied for this study.

The number of participants was decided according to the saturation of information given by the participants. Saturation was achieved when all the participants had given

This article was accepted: 08 June 2021
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almost the same information and the collection of new data did not shed any further light on the problems under investigation. In this study, the in-depth-interviews were conducted on 30 children who had infantile esotropia and 30 parents of these children, based on the minimum required sample size for qualitative study.[15,16]

All the children who were screened had been diagnosed with infantile esotropia greater than 40 prism diopters from 5 to 17 years of age. Children were excluded from the study if they had other types of strabismus (e.g. Duanne syndrome), secondary causes of esotropia (e.g. trauma and sensory deprivation due to congenital cataracts, corneal opacity, optic atrophy, and macular scars), organic eye diseases, neurological disorders, facial, ocular or cosmetic abnormalities, syndromic or chromosomal anomalies, known intellectual disability, abducens nerve palsy and had ocular surgery. Parents with known intellectual disability and psychological illness were also excluded.

Detailed demographic data were obtained, including birth history, onset of esotropia, visual performance, family history of esotropia, and history of prematurity. The children underwent complete clinical assessment, which involved visual acuity tests, assessment for stereopsis, cover tests, testing for extraocular motility, examinations of their pupils and convergence tests. The children were also examined carefully for signs of anomalies of the anterior and posterior segments. An identified paediatric ophthalmologist examined all the patients who had been recruited, and a trained senior optometrist performed cycloplegic refraction assessments in all patients.

Semi-structured interview guides were developed and validated separately for the versions for children and parents. Content validity was also performed for the semi-structured interview guides that had been drafted. A panel of experts was selected based on their knowledge and experience in questionnaire development and paediatric ophthalmology subspecialty. During this validity assessment, the panel of experts commented on the comprehensiveness, relevancy, and representativeness of all the items in the interview guides. The interview guides were then modified according to the experts' suggestions.

A second draft of the semi-structured interview guides was piloted with 28 new participants, that included 9 children and 19 parents for face validity. The children and parents who consented to do this were asked about the clarity and transparency of the interview guides. Based on comments and observations during the interviews, the wordings in the interview guides were then modified to simplify and shorten the sentences to produce a third semi-structured interview guides for both the children and the parents.

The third semi-structured interview guides were re-assessed in a second pilot study with new participants, including 6 children and 12 parents. This step was performed to assess the clarity and simplicity of the items. No further modifications were needed following these interviews, since the children and their parents stated that the interview guides were easy to understand and the sentences were clear. These third and final semi-structured interview guides for the children (18 items) and parents (17 items) was forward translated into English versions and back translated to Malay language.

The interviews were conducted in a quiet examination room by the primary investigator using the validated Malay versions of the final versions of the semi-structured interview guides (Appendix I) for the children and their parents. The children were encouraged to share their difficulties and describe in detail their problems they had with regard to infantile esotropia. There was no time limit set for the interviews. Both the children and parents were given adequate time to talk and express their views.

While the children were interviewed, the parents generally waited in another room, having agreed that their children might feel uncomfortable being interviewed in their presence. However, if the parents preferred to stay in the same room during the interview, they sat at the back of the room and were asked not to interrupt or interfere. With consent from their parents, the children waited in an adjacent room while the investigator interviewed the parents. The aim of this procedure was to allow freedom for both children and their parents to express their views spontaneously and avoid feeling concerned that their opinions may disturb or hurt either their parents or their children.

The interviewer used a natural tone of voice throughout the interview process. The questions were repeated slowly to ensure that the participants had a solid understanding of them and to avoid confusion or misinterpretation. The interviews were tape-recorded with the permission of both the children and their parents. All the interviews were conducted in Malay and transcribed verbatim.

Before starting the coding process, the primary investigator underwent formal training to establish a common understanding regarding the coding process. The primary investigator read the transcripts and listened to the recordings repeatedly to ensure the accuracy and relevancy of the data. The investigator read and checked the transcripts many times before the actual interview process. This was important in order to choose appropriate themes and subthemes and to ensure the relevancy and consistency of the coding.

Specific problems with regard to LAIE were identified and coded by using different words, phrases and labels to address the nature of the problems for the children and their parents. These codes were subsequently reviewed by the expert panels to verify the appropriateness of the coding.

The socio-demographic and clinical data were analysed using the Statistical Package for the Social Sciences for Windows version 24.0 (SPSS Inc, Chicago, IL, USA). The transcripts from the interviews were reviewed and coded using NVivo 12 software (QSR International, Doncaster, Australia), which allowed for the organisation and tracking of interview content and thematic analysis. The frequencies and percentages relating to the problems were calculated independently for the self-reported perceptions of the children and their parents, using SPSS version 24.0.

Table I: Demographic and clinical characteristics

Characteristics	Children n (%)	Parents n (%)
Gender		
Female	10 (33.3)	23 (76.7)
Male	20 (66.7)	7 (23.3)
Race		
Malays	27 (90.0)	29 (96.7)
Chinese	3 (10.0)	1 (3.3)
Children's age (years)		
5-8	10 (33.3)	
9-17	20 (66.7)	
Parent's age (years)		
20-30		7 (23.3)
31-40		11 (36.7)
41-50		10 (33.3)
51-60		2 (6.7)
Parent interviewed		
Father		6 (20.0)
Mother		24 (80.0)
Parent's level of education		
Primary school		2 (6.7)
Secondary school		18 (60.0)
College/University		10 (33.3)
Parent's monthly income		
Less than RM 580		2 (6.7)
RM 580 - RM 1500		11 (36.7)
RM 1500 - RM 3000		10 (33.3)
More than RM 3000		7 (23.3)
Best corrected visual acuity		
6/6-6/18	30 (100.0)	
6/24-6/60	0 (0.0)	
Worse than 6/60	0 (0.0)	
Stereopsis		
Present	3 (10.0)	
Absent	27 (90.0)	
Distant angle of deviation (Prism dioptre)		
Less than 40	0 (0.0)	
40-45	10 (33.3)	
More than 45	20 (66.7)	
Near angle of deviation (Prism dioptre)		
Less than 40	0 (0.0)	
40-45	5 (16.7)	
More than 45	25 (83.3)	
Spherical Equivalent (Dioptre)		
Less than +1.00	20 (66.7)	
+1.00 to +1.75	8 (26.7)	
+2.00 to +3.00	2 (6.6)	

RESULTS

A total of 30 children and 30 parents were interviewed. The majority of the children were aged from 9 to 17 years (66.7%, 20 children), were males (66.7%, 20 children), and were of Malays (90.0%, 27 children). The majority of the parents involved were mothers (80.0%, 24 parents), aged from 31 to 50 years (70.0%, 21 parents), with secondary school education (60.0%, 18 parents) and had a monthly income of less than RM 3,000 (76.7%, 23 parents). All children had corrected visual acuity from 6/6 to 6/18 (20/20 to 20/60). Only 10.0% of the children had binocular single vision. The majority had angles of deviation that were greater than 45 prism dioptres at distance (66.7%, 20 children) and near (83.3%, 25 children). Furthermore, 66.7% of the children presented with low hypermetropia. Table I shows the tabulation of these figures.

Five broad problems were identified among the children, aged from 5 to 17 years, who had infantile esotropia: social interactions (73.3%, 22 children), visual functions (60.0%, 18 children), emotions (60.0%, 18 children), physical issues (40.0%, 12 children) and difficulties with treatment options (26.7%, 8 children) (Table II). The children noted 32 specific problems. Being teased by friends (60.0%, 18 children) was the most frequently reported among these problems, followed by feeling anxious (40.0%, 12 children) and experiencing blurred vision for distance (33.3%, 10 children).

From the interviews with the parents regarding their children's problems, five broad issues were also identified. However, unlike their children, the parents perceived that the most frequent problem was with regard to visual functions

Table II: Problems of children with LAIE

Problems (Themes and subthemes)	Child n (%)	Parent n (%)
Visual Functions		
Blurred vision for distance	10 (33.3)	14 (46.7)
Whiteboard writings	5 (16.7)	1 (3.3)
Focusing	5 (16.7)	7 (23.3)
Bumping into objects	3 (10.0)	7 (23.3)
Gadget	3 (10.0)	7 (23.3)
Reading	3 (10.0)	5 (16.7)
Writing	3 (10.0)	3 (10.0)
Searching object	3 (10.0)	4 (13.3)
Turning back	3 (10.0)	1 (3.3)
Outdoor activities	3 (10.0)	1 (3.3)
Field of view	3 (10.0)	0 (0.0)
Closing one eye	3 (10.0)	0 (0.0)
Head tilt	0 (0.0)	12 (40.0)
Climbing stairs	0 (0.0)	5 (16.7)
Watch television	0 (0.0)	4 (13.3)
Walking	0 (0.0)	3 (10.0)
Eating	0 (0.0)	2 (6.7)
Photophobia	0 (0.0)	1 (3.3)
During school examination	0 (0.0)	1 (3.3)
Emotions		
Anxiety	12 (40.0)	5 (16.7)
Shy	8 (26.7)	1 (3.3)
Negative perception	5 (16.7)	5 (16.7)
Fear	5 (16.7)	3 (10.0)
Hope to be normal	5 (16.7)	0 (0.0)
Angry	3 (10.0)	5 (16.7)
Stress on appearance	3 (10.0)	1 (3.3)
Positive perception	3 (10.0)	1 (3.3)
Sad	3 (10.0)	0 (0.0)
Depressed	0 (0.0)	2 (6.7)
Refuse to talk	0 (0.0)	2 (6.7)
Physical Issues		
Eye strain	8 (26.7)	1 (3.3)
Ocular discomfort	3 (10.0)	0 (0.0)
Headache	3 (10.0)	1 (3.3)
Tearing	3 (10.0)	3 (10.0)
Moving eye	0 (0.0)	1 (3.3)
Double image	0 (0.0)	1 (3.3)
Social Interactions		
Teasing by friends	18 (60.0)	13 (43.3)
Public insecurity	5 (16.7)	1 (3.3)
Eye contact	3 (10.0)	1 (3.3)
Interaction	3 (10.0)	3 (10.0)
Teacher's bias	0 (0.0)	3 (10.0)
Treatment Options		
Patching	8 (26.7)	3 (10.0)
Surgery	8 (26.7)	3 (10.0)
Spectacle	3 (10.0)	3 (10.0)

(100%, 30 parents), followed by social interactions (56.7%, 17 parents), emotions (43.3%, 13 parents), physical issues (20%, 6 parents) and difficulties with treatment options (16.7%, 5 parents). The parents observed 39 specific problems (Table II). The most common reported among these problems were blurred vision for distance (46.7%, 14 parents), being teased by friends (43.3%, 13 parents), and head tilts (40.0%, 12 parents).

DISCUSSION

The available data is focussed on children with exotropia and combination esotropia/exotropia and their parents in India and the United States of America.[4-6] Only a limited amount of data is available regarding the concerns and perspectives of children with esotropia.[7] Therefore, we conducted a hospital-based study which acts as a referral centre for strabismus consultation in the states in the East Coast of Peninsular Malaysia. We recruited children with LAIE, and 66.7% of these children had esotropia greater than 45 prism dioptres for distance fixation. Table III summarises the above reports,[4-7] and also includes the outcome of our study.

The children in our study reported social interactions as their most common problem. They suffered from being teased by friends at schools and found it difficult to mix in society.

Table III: Published reports regarding children and parents' perspective

Author / Year	Country	Type of strabismus	Number of children/parents	Main concern by children (Percentage)	Main concern by parents (Percentage)
Hatt et al. (2008)[6]	United States of America	Intermittent Exotropia	24 children (aged 5-17 years old) 24 parents	Worry (42%) Troubled by blurriness (33%) Comments from others (33%)	Comments from others (63%) Appearance to others (38%) Troubled by need to correct exotropia (25%)
Kothari et al. (2009)[4]	India	Horizontal comitant strabismus	Guardians of 93 children (aged 4-16 years old)	Not reported	Extremely distressed due to people's remarks (55%) Severely ostracized (57%) Severe difficulty in communication (38%) Difficulty to cope (50%) Severe difficulty in communication (38%)
Liebermann et al. (2016)[7]	United States of America	Childhood esotropia	40 children (aged 5-17 years old) 40 parents	Visual Function (80%) Treatment (78%) Emotion (65%) Social (58%) Physical (58%) Worry (45%)	Visual Function (83%) Treatment (85%) Emotion (67%) Social (68%) Physical (32%) Worry (7%)
Hatt et al. (2016)[5]	United States of America	Intermittent exotropia	35 children (aged 5-13 years old) 35 parents	Rubbing the eye (83%) Problems with eyes in the sun (63%) The eyes feeling tired (63%)	Not reported
Current study (2021)	Malaysia	Infantile esotropia	30 children (aged 5-17 years old) 30 parents	Social interactions (73.3%) Visual functions (60.0%) Emotions (60.0%) Physical issues (40.0%) Treatment options (26.7%)	Visual functions (100.0%) Social interactions (56.7%) Emotions (43.3%) Physical issues (20.0%) Treatment options (16.7%)

Large angles of deviation in children with infantile esotropia are easily noticeable, and this is supported by reports that esotropia is perceived to be more disturbing than exotropia by non-strabismic adults and children.[8,17,18] Paysse et al. confirmed that a negative attitude toward strabismus appears to emerge at approximately 6 years of age.[19]

Our finding contradicted those of Liebermann et al. who reported that the majority (80%) of the children with esotropia experienced visual functions as their major problem.[7] This observation probably resulted from the study involving different types of esotropia with variable angle of deviations. Liebermann et al. recruited patients with small angles of deviation (less than 10 prism dioptres) in the majority (74%) of their cases along with cases involving accommodative or partial accommodative types of esotropia (47%).[7] A different observation was also reported by Hatt el al., who conducted a similar study on children with intermittent exotropia.[6] The majority of the children reported worrying as their major problem. This can be explained by the history of intermittent exotropia. Children with this type of exotropia become noticeable after two to three years of age or later in life and have good stereopsis at near and breaks into tropia only when they are tired, not focused or suffering from febrile illness. Their eye conditions may not be so obvious to their peers and friends until they break their fusion abilities.[9-11] This clearly suggest that type, severity and onset of strabismus contributes to the psychosocial effects with regard to the affected children.

In contrast to the reports by their children, the parents in our study described visual functions as the most common problem faced by their children. Other problems included blurred vision for distance (46.7%), head tilts (40.0%), bumping into objects (23.3%), watching television (13.3%) and searching for objects (13.3%). The parents also noted that their children had near vision problems including focusing on and difficulties using electronic gadget (23.3%), reading (16.7%), writing (10.0%), eating (6.7%) and school examinations (3.3%). This finding is slightly different from that of Liebermann et al., who reported that treatment options (85%) was their main concern.[7] One possible explanation for this is that our study was conducted in a government hospital that provides low-cost treatment and consultation. Hatt et al. reported that parents (63%) of children with intermittent exotropia were also concerned about comments made by others.[6]

In our study, we observed that there were a few concerns that were mentioned only by the parents. These included head tilts (40.0%), while climbing stairs (16.5%), watching television (13.3%) and walking (10.0%). Liebermann et al. also noted in their study that 2% of the parents mentioned anxiety in their children, although this was not noted by the children in their study. However, self-confidence and relationships (17% in each subtheme) were mentioned by parents only in the study by Hatt et al.[6] This is an interesting observation in relation to our study, in which visual functions were still the main concern noticed by the parents of children with large angle esotropia, even though visual functions were not mentioned by the children. This observation contradicts the outcome of other studies where the parents reported more concerns with regard to emotions.[6,7]

Both the children with infantile esotropia (60.0%) in our study and their parents (43.3%) agreed that teased by friends was an issue of great concern. A similar study on childhood esotropia reported that this issue was stated by 48% of the children and 38% of their parents.[7] In contrast, other studies reported fewer comments about being teased, with 33% in children with intermittent exotropia and 63% in their parents.[6] Kothari et al. reported that 55% of parents were extremely distressed by remarks that people made.[4] This issue merits attention, and we have been unable to find published reports on the long term consequences regarding this. However, we encountered a study by Olson et al., who reported that congenital esotropia increases the odds 2.6 times of developing mental illness by early adulthood in comparison to a control group.[20] The authors evaluated a cohort of patients who had been diagnosed with congenital esotropia at ages 10 to 30, and reported that the prevalence of major depression was 50% and 19% for anxiety.[20]

Our study found a vast difference in the major concerns between the children with LAIE and their parents. There are a few possible explanations for this. Firstly, age gap may contribute to the differences in perceptions between the children and their parents. Secondly, the children may be more concerned with their social relationships, while the parents focus more on health, family and safety. Thirdly, the parents' perceptions were based on observation of their children at home or during the time they spent together, and may not include times when the children run into difficulties with friends, at school or in public places. Therefore, it is advisable for the parents to improve their communication and understand the difficulties faced by their children who have infantile esotropia.

In addition, conducting interviews with very young age groups, especially those aged less than eight years, can be problematic. These young children took more time to understand the questions. They also became silent and refused to talk to strangers, and this attitude may have affected the results. To minimize these problems, a simpler and shorter semi-structured interview guide was developed in this study to help these young children to understand better and hence to cooperate more fully.

CONCLUSION

Children with LAIE who were treated in Hospital USM reported that social interaction was their major problem. However, their parents perceived that visual functions were the main issue encountered by these children. The parents need to improve communication with their children to gain a better understanding of the actual problem and help these children with LAIE to overcome the obstacles they face.

FUNDING

This work was supported by Universiti Sains Malaysia Research Grants (Usains Research Grant 2016/401/PPSP/3410015 and Research University Grant 1001/PPSP/812104).

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Appendix I: Interview questions for children with infantile esotropia

A. For children

1. When do you notice about your squint eyes?
   Sejak bila anda sedar mata anda juling?

2. Tell me how your eyes feel?
   Apa yang anda rasa mengenai mata anda?

3. What things would you like to do, but can't do because of your eyes?
   Apa perkara yang anda mahu lakukan, tetapi tidak dapat dilakukan disebabkan mata anda?

4. Do you feel difficult to climb up the stairs?
   Adakah anda merasa sukar semasa menaiki tangga?

5. Do you feel difficult to jump over the drain?
   Adakah anda merasa sukar untuk melangkah longkang?

6. Do you feel difficult to estimate depth when you go swimming?
   Adakah anda merasa sukar untuk menganggar jarak kedalaman semasa berenang?

7. Do you have any problem at school because of your eyes?
   Adakah anda mengalami masalah di sekolah kerana mata anda?

8. What do other children say about your eyes?
   Apakah yang kawan-kawan anda perkatakan mengenai mata anda?

9. Do you have any problem during your conversation with others?
   Adakah anda mempunyai masalah semasa bercakap dengan orang lain?

10. Do your teachers give comment regarding your eyes?
    Adakah guru-guru memberi komen mengenai mata anda?

11. What do other grown-ups mention about your eyes?
    Apa yang orang-orang dewasa perkatakan mengenai mata anda?

12. What do your parents say to you about your eyes?
    Apa yang ibu bapa perkatakan mengenai mata anda?

13. How do you feel about your eyes?
    Apa perasaan anda mengenai mata anda?

14. How do your parents feel about your eyes?
    Apa perasaan ibu bapa terhadap mata anda?

15. Do you know about the treatment of your eyes?
    Adakah anda tahu mengenai rawatan tentang mata anda?

16. What do you think about the treatment of your eyes?
    Apa yang anda fikir mengenai rawatan mata anda?

17. Is there anything else that bothers you about your eyes?
    Adakah terdapat perkara lain yang mengganggu disebabkan mata anda?

18. What is your wish after your squint surgery?
    Apa harapan anda selepas menjalani pembedahan mata juling?

B. For Parent

1. When did you notice your child had squint eyes?
   Sejak bila anda menyedari mata anak anda juling?

2. How much do you notice your child's eye is wandering?
   Berapa kerapkah mata anak anda kelihatan juling?

3. What activities do you associate with your child's eye wandering in? What makes it worse or better?
   Apakah yang anak anda lakukan semasa mata anak anda kelihatan juling?Apa yang menyebabkan keadaan tersebut semakin buruk atau baik?

4. Did your child tell you how do his/her eyes feel?
   Pernahkah anak anda memberitahu perasaan tentang keadaan matanya?

5. What do you child do or not do because they have squint?
   Apa yang anak anda lakukan, atau tidak lakukan kerana mata juling?

6. In what ways does the squint affect your child?
   Apa yang mengganggu anak anda berkaitan matanya?

7. Does your child have difficulty to climb up the stairs?
   Adakah anak anda sukar menaiki tangga?

8. Does your child have difficulty to jump over the drain?
   Adakah anak anda sukar melangkah longkang?

9. Does your child feel difficult to estimate depth when you go swimming?
   Adakah anak anda berasa sukar untuk menganggar jarak kedalaman semasa berenang?

10. What bothers you most about your child's eyes?
    Apakah yang paling mengganggu anda mengenai mata anak anda?

11. In what ways does the squint affect your child's ability to interact with other children or adults?
    Bagaimanakah keadaan mata anak anda memberi kesan dalam pergaulannya dengan rakan-rakan atau orang dewasa?

12. How do other people react when they notice your child has squint?
    Apa reaksi orang lain mengenai mata anak anda?

13. How do you feel about your child having squint eyes?
    Apakah perasaan anda bila anak anda mengalami mata juling?

14. Do you know about the treatments of the squint eyes?
    Adakah anda tahu mengenai kaedah-kaedah rawatan mata juling?

15. What are the main issues or concerns for you regarding the treatment or management of your child's eyes?
    Apakah perasaan anda mengenai rawatan mata anak anda?

16. Is there anything regarding your child's eyes that makes you unhappy?
    Adakah terdapat perkara mengenai mata anak anda yang menyebabkan anda tidak gembira?

17. Can you describe any other ways that squint affects you or your child that we have not discuss?
    Adakah terdapat perkara yang mengganggu mengenai mata anak anda yang kita belum dibincangkan?

ORIGINAL ARTICLE

Retrospective study of pelvic and para-aortic lymph nodes positivity in stage 1A to 2A cervical cancer patients

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ABSTRACT

Background: The significance of pelvic and para-aortic lymph nodes (retroperitoneal lymph nodes) metastasis in the five-year survival of early stage cervical cancer (CC) patients is well established. The previous International Federation of Gynaecology and Obstetrics (FIGO) 2009 staging of CC was clinical and excluded advanced radiological assessment in assigning a stage. However, with the current FIGO 2018 staging, advanced radiological assessment and pathological findings were allowed to assign a stage which would alter the subsequent management. This pilot study aims to obtain local data on the correlation between radiological retroperitoneal lymph node positivity and histological lymph node positivity in early stage CC (stage 1A2 to 2A1) and seeks to correlate independent prognostic factors for recurrence to histological lymph node positivity.

Materials and Methods: In this retrospective cross-sectional analysis, clinical data, including clinical staging, Computed Tomography (CT) scan findings and histopathological results were collected and analysed in the Department of Obstetrics and Gynaecology, Hospital Ampang, Ministry of Health Malaysia.

Results: A total of 31 patients had surgery for CC from 1st August 2018 till 31st August 2020. Radical hysterectomy was done on 23 of them as primary treatment for early stage cervical cancer. Both pelvic and para-aortic lymph node dissection was done in 6 patients while 17 patients had only pelvic lymph node dissection. All patients had thoraco-abdomino-pelvic CT scans done preoperatively. Among the 82.6% patients with no enlarged pelvic lymph nodes on CT scan, all were confirmed by histology to be negative of malignancy. In the remainder 17.4% of patients with enlarged pelvic nodes on CT scan, three quarters had histology positive pelvic nodes for malignancy (p=0.002). Among patients with no enlarged para-aortic lymph nodes on CT scan, 83.3% had histologically negative para-aortic nodes. Among patients with clinical tumour diameter 2- 3.9 cm, 14.3% had positive pelvic nodes while a quarter of patients with clinical tumour diameter ≥ 4cm had histological positive pelvic nodes. None of the patients with tumour diameter < 2cm had positive pelvic nodes (p=0.993). Positive pelvic lymph nodes involvement was present in 37.5% of those with positive lymphovascular space invasion (LVSI). All patients with negative LVSI had no histological positive pelvic nodes (p=0.103). Among patients with tumour invasion involving the inner third of the stroma, 16.7% had histological positive pelvic nodes while 18.2% with outer third stromal invasion had positive nodes (p=0.977). None of the patients had histologically positive para-aortic lymph nodes with negative pelvic lymph nodes. Among patients with clinical stage 1B2, 20% would have been upstaged to stage 3C based on radiological imaging and final histology confirmation.

Conclusion: This study shows that in early stage CC, there is a statistically significant correlation between CT scan findings of enlarged pelvic lymph nodes and histological positive pelvic lymph nodes.

KEYWORDS:
Cervical cancer, radical hysterectomy, para-aortic lymph nodes, pelvic lymph nodes, computed tomography, FIGO staging

INTRODUCTION

In Malaysia, CC is ranked the third most common cancer in women after breast and colorectal with an age-standardised incidence rate per 100,000 of 6.2%.[1] Between 2011-2016, 3,981 cases of CC was reported with 59% detected in stage 1 and 2.1 In 2018, approximately 570,000 new cancer cases were diagnosed with more than 300,00 death reported worldwide.[2] Approximately 85% of new cases and 90% of deaths occur in low-resource countries or among people from low socioeconomic sections of society.[3] The occurrence of metastatic lymph nodes is an important factor that has implication on treatment and therapeutic outcomes in cervical cancer patients.[4] Therefore, accurate detection of lymph nodes metastases is paramount as it is correlated with a reduction in the five-year survival rate, despite of adjuvant radiotherapy to the surgery.[4]

The FIGO 2009 staging mainly depends on clinical and radiographic examination.[3] This staging was recently revised by FIGO Gynaecologic Oncology Committee to enable imaging and pathological findings, where available, to determine the stage and was presented in FIGO XXII World Congress of Gynaecology and Obstetrics in Rio de Janeiro in October 2018.[3] In FIGO 2009 staging, radiological node status did not determine stage. However, pre-treatment staging has shown that 18% of patients with stage 1B to 4A CC had para-aortic lymph node metastasis.[3,5] With the new FIGO 2018 staging, nodes positive patients was assigned to Stage 3C as lymph node involvement confers a worse prognosis.[3,6] Patients with pelvic lymph nodes positive and para-aortic lymph nodes positive was assigned to stage 3C1 and stage

This article was accepted: 04 June 2021
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3C2 respectively.[3] Thus, stage 3C has been added and defined as the presence of nodal metastases on histology or advanced imaging such as CT scan, Magnetic Resonance Imaging (MRI), or Positron Emission Tomography(PET).

Studies using the sentinel lymph node mapping technique, confirms that any of the pelvic or para-aortic lymph nodes groups, may contain the first draining lymph node and resulting it to be the first site of nodal metastasis.[7,8,9] This demonstrates the possible occurrence of skipped lymph nodes involvement where there are para-aortic lymph nodes involvement without the involvement of pelvic lymph nodes. Clinical tumour size, depth of stromal invasion (DSI) and LVSI are independent prognostic factors for recurrence.[10] Increasing DSI is proportionate with the risk of pelvic lymph node metastasis. The risk of pelvic lymph node involvement is as high as 7% for stage 1A2 disease.[11] The incidence of LVSI was positively associated with DSI and lymph node metastasis. Lymph node metastasis is an independent factor that affects postoperative overall survival.[12] Survival is correlated with retroperitoneal lymph node involvement.[10] Early stage CC patients without pelvic nodes involvement treated with surgical treatment have five years' survival of 90%.[10] Pelvic lymph nodes involvement decreases the survival rate to 50-60% while para-aortic lymph nodes involvement decreases the rate further to 20-45%.[10]

The purpose of this pilot study was to obtain local data with regards to the correlation between radiological lymph node positivity versus histological proven lymph node positivity. It also seeks to correlate independent prognostic indicators for recurrence with histologically proven pelvic node positivity as well as the percentage of skipped para-aortic lymph nodes positivity without involvement of pelvic lymph nodes. Lastly, this study also seeks to determine the percentage of patients with stage 1A2 to 2A1 CC who are upstaged to stage 3C (FIGO 2018) based on radiological and histological results.

MATERIALS AND METHODS

Study design and population

This is a retrospective cross-sectional study conducted in a tertiary hospital, Hospital Ampang (HA), Ministry of Health Malaysia, Selangor. The medical records of patients with histologically proven cervical squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma who had undergone primary radical or modified radical hysterectomy and bilateral pelvic lymphadenectomy including dissection up to the level of para-aortic lymph nodes were reviewed. Patients with pre-operative FIGO 2009 stage 1A2 to 2A1 CC were included while patients with pre-operative staged as 1B3 following FIGO 2018 were re-staged to 1B2 and were included. These patients were operated in HA during the study period between 1st August 2018 till 31st August 2020.

The preoperative diagnosis of CC was obtained via cervical punch biopsy, Large Loop Excision of Transformation Zone (LLETZ), Loop Electrosurgical Excision Procedure (LEEP) biopsy or cone biopsy. Patients with previous neoadjuvant chemotherapy or radiotherapy (including haemostatic radiotherapy), known HIV infection, concurrent pregnancy on diagnosis, recurrent cervical cancer, palliative nodal debulking, inadvertent diagnosis of CC post-surgery where the surgery was done for a seemingly benign condition as well as those with neuroendocrine or sarcoma of cervix as final histopathological result were excluded.

Clinical data including CT scan reports and histopathological reports of patients fulfilling the criteria above were obtained from the electronic-hospital information system (e-HIS) using standardized data collection forms. This study was conducted in compliance with Malaysian Good Clinical Practice Guideline and was registered with the National Medical Research Register, Malaysia. The ethical approval for this study was obtained from the Medical Research and Ethical Committee (MREC), Ministry of Health Malaysia (NMRR-20-1457-55599).

Patient selection and surgery

The medical records of 31 patients who had surgery done for CC cancer was reviewed. Eight patients were excluded from the study due to the following reasons. Three had cervical neuroendocrine carcinoma and one had cervical carcinosarcoma as the final histopathological diagnosis. Two patients had exenteration and were staged as 3A and 4A respectively. One patient had neoadjuvant chemotherapy and was staged as stage 3A while another had extrafascial hysterectomy done for stage 2A2 with ovarian metastasis. The records of the remainder 23 patients were reviewed and were all clinically staged by trained Gynae-oncology Fellows and Consultant. Clinical staging was done either in the clinic or in the operation theatre under anesthesia. All patients had pre-operative histologically confirmed diagnosis of CC obtained either from certified pathologists in Hospital Serdang (HS), Ministry of Health Malaysia, Selangor or pathologists from private laboratories in Malaysia. All patients had either Type B or C radical hysterectomy according to Querleu and Morrow classification.[3] All post-operative specimens were sent to HS for histopathological analysis.

Radiological lymph node positivity

The preoperative CT scan reports of the thorax, abdomen and pelvis of the patients were reviewed. All reports were done either by in-house certified radiologists or radiologists from private medical centers in Malaysia. Lymph node positivity was taken as a short axis diameter ⩾10mm, single or multiple occurring either unilaterally or bilaterally with or without central necrosis.[13,14]

DSI and LVSI

The formal histopathological report of the patients was reviewed. DSI and LVSI were obtained after microscopic examination by certified pathologists and were reported as depth of invasion over the cervical wall thickness in millimeters. Accordingly, the depth of invasion was then categorised into inner third, middle third, and outer third infiltration. The lymphovascular space invasion was classified as either positive or negative based on the report.

Statistical Analyses

All analyses of the collected data were carried out using the statistical software Statistical package for Social Science (SPSS) Version 25. Armonk, NY: IBM Corp. Categorical data

were expressed as frequencies and percentages. Cross tabulation was used to demonstrate the association between the variables. Additionally, Fisher's exact test, Phi coefficient and Cramer's V were calculated to indicate, in quantitative terms, the extent of the association. Parametric testing was not feasible as the sample size was below 50. All p-values are two-sided and p values <0.05 were considered statistically significant.

RESULTS

The median age of the 23 patients was 56 years (range, 31-69 years). Majority of the patients were Malaysian Chinese (78.3%) followed by Malays (17.4%). There was a solitary patient of Thai descent in this study. Overall, 95.7% of the patients were parous. Following FIGO 2009 staging, stage 1B2 disease was the most common (65.2%), followed by stage 1B1 (21.7%) and stage 2A1 (13.0%). There were no patients with stage 1A2 in this cohort. Squamous cell carcinoma was the most common histologic cell type (56.5%), followed by adenocarcinoma (39.1%) and adenosquamous carcinoma (4.3%) (Table I). The median number of pelvic lymph nodes removed was 27 bilaterally (range 2- 52).

All 23 patients had pelvic lymph nodes dissection done as part of the radical hysterectomy inclusive of 6 patients with additional para-aortic lymph nodes dissection. No enlarged pelvic lymph nodes were noted on CT scan in 82.6% of them. All the patients with no enlarged pelvic lymph nodes had no histological pelvic lymph nodes involvement. Among those with enlarged pelvic nodes on CT scan, three quarter had histologically confirmed malignancy spread to the lymph nodes (p=0.002). The False Positive Value (FPV), False Negative Value (FNV), Positive Predictive Value (PPV), Negative Predictive Value (NPV), Sensitivity and Specificity are 5%, 0%, 75%, 100%, 100% and 95% respectively. Among the six patients with both pelvic and para-aortic lymph node dissection done, none had enlarged para-aortic lymph nodes on CT scan. Subsequently, 83.3% (5/6) of them were confirmed by histology to be negative of malignancy. The NPV for para-aortic nodes on CT scan is 83.3% (Table II).

In patients with clinical tumour diameter 2- 3.9 cm, 14.3% had positive pelvic nodes on histology. In contrast, 25% of patients with clinical tumour diameter ≥ 4cm had histological positive pelvic nodes. None of the patients with tumour size < 2 cm had histology positive pelvic nodes (p=0.993). In this study, 37.5% of patients with positive LVSI had histological pelvic lymph node involvement. All the patients with negative LVSI had no pelvic lymph node involvement (p=0.103). The NPV, PPV and specificity is 100%, 75% and 83.3% respectively. With regards to DSI, 16.7% and 18.2% of those with inner and outer third stromal involvement respectively had histological pelvic lymph node involvement (p=0.977) (Table III).

There were no patients with positive para-aortic lymph nodes with negative pelvic lymph nodes. In patients who were initially staged as 1B1 and 1B2 (FIGO 2009), 20% (1/5) and (3/15) had histological positive pelvic lymph nodes respectively (p=0.614). None of the patients staged 2A1 had positive pelvic nodes (Table IV). The incidence of patients with clinical stage 1B2 with enlarged pelvic lymph nodes on CT scan and histological positive pelvic lymph nodes were 20% (Table V).

DISCUSSION

Our data is consistent with the latest Malaysia National Cancer Registry 2012-2016 with regards to the highest incidence of CC between age 50-65 years and among Malaysian Chinese followed by Malays.[1] Squamous cell carcinoma was the most common histology followed by adenocarcinoma and adenosquamous which was also consistent with published data.[15]

Published meta-analysis regarding the diagnostic performance of CT scan showed that the specificities were more than 90% (high specificity) in the detection of lymph nodes metastases but has a sensitivity of less than 60% (low sensitivity).[4] In our data, the correlation between CT finding of enlarged pelvic nodes and histological proven metastasis to the pelvic lymph nodes are statistically significant with a specificity of 95% (p=0.002). However, compared to the published data on CT scan imaging in predicting pelvic lymph nodes metastasis, our data differed in NPV (90.1% vs 100%), sensitivity (51.4% vs 100%) and PPV (41.3% vs 75%).[14] The difference compared to our data is mainly attributed to skewed representation as none of the patients in this cohort with no enlarged CT pelvic lymph nodes had positive pelvic node on histology. However, our results of the high specificities and NPV do concur with the available data.

The correlation between CT findings of enlarged para-aortic nodes to histological involvement of para-aortic nodes could not be computed because in this smaller sample size of six patients, none of the patients had enlarged para-aortic nodes resulting in absence of false positive and true positive values.

Our results indicate that larger diameter tumours are associated with an increased risk of lymph node metastasis although it did not achieve statistical significance. As these clinical tumour diameters of 2-3.9cm and ≥ 4cm correspond to FIGO 2018 stages 1B2 and 1B3 respectively, it can be implied that the incidence of pelvic lymph node metastasis in stage 1B2 and 1B3 is 14.3 - 25%. This corresponds to available literature where the risk of pelvic lymph nodes metastasis in cervical stage 1B to 2A is 16-25%.[10] The absence of patients at stage 2A1 with histology positive lymph nodes indicates that patients with larger tumour volume has higher risk of pelvic lymph nodes involvement compared to clinical stage alone.

The presence of LVSI and DSI is known to be positively associated with lymph node metastasis.[12] Although our data has shown correlation with regards to DSI and pelvic lymph node positivity, it has failed to achieve statistical significance due to sample limitations.

There were no patients with histological para-aortic lymph node involvement skipping the involvement of the pelvic lymph nodes. Taking the data on sentinel lymph nodes into consideration, it is expected that a larger sample of patients may yield a result reflective of the actual occurrence demonstrated by available studies.

Table I: Demographic data, pre-operative stage and type of cervical cancer

Variable	Patients (n= 23)	Final Histology			p-value
		Adenocarcinoma	Squamous cell carcinoma	Adenosquamous carcinoma	
Age group					0.254
31-40	4 (17.4%)	1 (11.1%)	3 (23.1%)	0 (0)	
41-50	2 (8.7%)	2 (22.2%)	0 (0%)	0 (0)	
51-60	11 (47.8%)	3 (33.3%)	8 (61.5%)	0 (0)	
61-70	6 (26.1)	3 (33.3%)	2 (15.4%)	1 (100)	
Race					0.099
Chinese	18 (78.3%)	9 (100%)	9 (69.2%)	0 (0)	
Malay	4 (17.4%)	0 (0%)	3 (23.1)	1 (100)	
Others	1 (4.3%)	0 (0%)	1 (7.7)	0 (0)	
Parous					0.435
Yes	22 (95.7%)	1 (11.1%)	0 (0)	0 (0)	
No	1 (4.3%)	8 (88.9%)	13(100)	1 (100)	
Pre-Op Stage FIGO 2009					0.231
1B1	5 (21.7%)	2 (22.2%)	2 (15)	1 (100)	
1B2	15 (65.2%)	7 (77.8%)	8 (61.5)	0 (0)	
2A1	3 (13.0%)	0 (0%)	3 (23.1)	0 (0)	
CT Pelvic node					1.000
Negative	19 (82.6%)	7 (77.8%)	7 (77.8%)	1 (100)	
Positive	4 (17.4%)	2 (22.2%)	2 (15.4)	0 (0)	
CT Para-aortic node					-
Negative	6 (100%)	2 (33.3%)	4 (66.7%)	0 (0%)	
Positive	0 (0%)	0 (0%)	(0%)	0 (0%)	
LVSI					0.253
Negative	15 (65.2%)	4 (44.4%)	10 (76.9%)	1 (100%)	
Positive	8 (34.8%)	5 (55.6%)	3 (23.7%)	0 (0%)	
DSI					0.534
Inner	6 (26.1%)	2 (22.2%)	4 (30.8%)	0 (0%)	
Middle	6 (26.1%)	3 (33.3%)	3 (23.1%)	0 (0%)	
Outer	11 (47.8%)	4 (44.4%)	6 (46.2%)	1 (100%)	
Pelvic Node Status					0.392
Negative	20 (87.0%)	7 (77.8%)	12 (92.3%)	1 (100%)	
Positive	3 (13.0%)	2 (22.2%)	1 (7.7%)	0 (0%)	
Pelvic Nodes removed					0.868
1-10	1 (4.3%)	0 (0%)	1 (7.7%)	0 (0%)	
11-20	6 (26.1%)	2 (22.2%)	4 (30.8%)	0 (0%)	
21-30	6 (26.1%)	3 (33.3%)	2 (15.4%)	1 (100%)	
31-40	7 (30.4%)	3 (33.3%)	4 (30.8%)	0 (0%)	
41-50	2 (8.7%)	1 (11.1%)	1 (7.7%)	0 (0%)	
51-60	1 (4.3%)	0 (0%)	1 (7.7%)	0 (0%)	
Para-aortic Nodes					0.333
Negative	5 (83.3%)	1 (50%)	4(100%)	-	
Positive	1 (16.7%)	1 (50%)	0 (0%)	-	
Para-aortic nodes removed					0.983
< 5	4 (66.7%)	1 (50%)	3 (75%)	-	
> 5	2 (33.3%)	1 (50%)	1 (25%)	-	

n = frequency; % = percentage

Table II: Comparison between CT lymph nodes positivity with histological retroperitoneal lymph nodes positivity

	Histological pelvic node n= 23		Histological para-aortic node n= 6		Total	p-value
	Negative	Positive	Negative	Positive		
CT Pelvic Node						
Negative	19 (82.6%)	0 (0%)	0 (0%)	0 (0%)	19 (82.6%)	0.002
Positive	1 (4.3%)	3 (13.0%)	0 (0)%	0 (0%)	4 (17.4)	
Total	20 (87.0%)	3 (13.0%)			23(100)	
CT Paraortic Node						
Negative	0 (0%)	0 (0%)	5 (83.3%)	1 (16.7%)	6 (100%)	
Positive	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Total	0 (0%)	0 (0%)	5 (83.3%)	1 (16.7%)	6 (100%)	
FPV	0.05		-			
FNV	0.0		-			
Sensitivity	1.0		-			
Specificity	0.95		-			
PPV	0.75		-			
NPV	1.0		0.833			

n = frequency; % = percentage

Table III: Prognostic factors in comparison with histologic pelvic nodes

	Histological pelvic node n= 23		Total	p-value
	Negative	Positive		
Clinical tumor size				0.993
<2 cm	5 (21.7%)	0 (0%)	5 (21.7%)	
2-3.9 cm	12 (52.2%)	2 (8.7%)	14 (60.9%)	
≥4 cm	3 (13.0%)	1 (4.3%)	4 (17.4%)	
Total	20 (87.0%)	3 (13.0%)	23 (100%)	
LVSI				0.103
Negative	15 (65.2%)	0 (0%)	15 (65.2)	
Positive	5 (21.7%)	3 (13.0%)	8 (34.8)	
Total	20 (87.0%)	3 (13.0%)	23 (100)	
DSI			0.977	
Inner	5 (21.7%)	1 (4.3%)	6 (26.1)	
Middle	6 (26.1%)	0 (0%)	6 (26.1)	
Outer	9 (39.1%)	2 (8.7%)	11 (47.8)	
Total	20 (87.0%)	3 (13.0%)	23 (100)	

n = frequency; % = percentage

Table IV: FIGO 2009 cervical cancer stage in comparison with histological pelvic nodes

	Histological pelvic node; n= 23			p-value
	Negative	Positive	Total	
Preop stage				
1B1	4 (17.4%)	1 (4.3%)	5 (21.7%)	0.614
1B2	12 (52.2%)	3 (13.0%)	15 (65.2%)	
2A1	3 (4.3%)	0 (0%)	3 (13.0%)	
Total	19 (82.6)%	4 (17.4%)	23 (100%)	

n = frequency; % = percentage

Table V: Pre-operative stage in comparison with radiologic and histologic pelvic lymph nodes positivity

n= 23	CT pelvic node positive + histological pelvic node positive	CT pelvic node positive + histological pelvic node negative	p-value
Pre-op stage			0.250
1B1	5 (22%)	0	0
1B2	15 (65%)	3	0
2A1	3 (13%)	0	1

n = frequency; % = percentage

Pre-op stage 1B2	n = 15	Total	p-value
CT positive pelvic node			
Negative	12 (80%)	15 (100%)	0.327
Positive	3 (20%)		
Histological pelvic node			
Negative	12 (80%)	15 (100%)	0.614
Positive	3 (20%)		

n = frequency; % = percentage

The incidence of positive pelvic lymph nodes in clinical stage 1B of 20% in this cohort corresponds with published data. The majority of patients in this cohort are in stage 1B2. Sub-analysing this sub-group of patients revealed that the incidence of patients with both enlarged pelvic lymph nodes on CT scan and positive histological involvement is 20% respectively. This implies that 20% of patients in this cohort with clinical stage 1B2 would be upstaged to 3C1 disease based on the CT scan imaging and the final histology of the pelvic lymph nodes. Our study also shows that in stage 1A2 to 2A1, based only on CT scan findings, 17.4% are upstaged to stage 3C1 (FIGO 2018). In comparison, based on final histology, 13.0% were upstaged to stage 3C1 and 4.3% were upstaged to stage 3C2 (FIGO 2018).

Stage 3C is classified as locally advanced disease which is associated with poorer survival outcome compared to those without lymph nodes involvement.[3] Concurrent chemoradiation is the standard contemporary treatment which consist of weekly cisplatin during the course of external beam radiation therapy.[3] Ongoing trial on additional adjuvant chemotherapy after chemoradiation are ongoing to assess the overall survival of this group of patients.[16] Although extended beam radiotherapy to these nodes is required together with chemotherapy to improve disease control, it has been proven that the benefit is minimal even with concomitant platinum-based chemotherapy as the rates of local and distant failure remain high in these patients.[17] Hence in our data, 4.3% of these patients would be at risk of recurrence or distant failure based on clinical staging versus the current staging.

Finally, our data also revealed the apparent deficiency of the FIGO 2009 staging which omitted the retroperitoneal lymph nodes as part of the staging. Based on our data, 17.4% of apparent stage 1A2 to 2A1 who should have been upstaged to stage 3C1 (FIGO 2018) would have been missed and thus omitted from adjuvant treatment which would have resulted in a higher risk of recurrence.

STUDY LIMITATIONS AND CONCLUSION

This study is limited by its retrospective nature and reduced sample size as the cohort of the study duration was at the transition between the FIGO 2009 and FIGO 2018 CC staging. Although the FIGO 2018 staging was published in October 2018, the change in surgical practice to include dissection of the para-aortic lymph nodes as part of radical hysterectomy for cervical cancer only started in November 2019 in HA. Hence a prospective study with similar objectives would be expected to yield a more accurate data representation. Looking forward, a follow-up study on the progression free survival and survival outcome of this cohort in this institution would be of importance.

Despite the limitations mentioned, this study has shown a statistically significant correlation between enlarged pelvic lymph nodes detected on CT scan and histological positive nodes. With the inclusion of radiological and histological retroperitoneal lymph nodes in the current FIGO 2018 staging, these patients would be up-staged to stage 3C. This has two main implications to clinical practice, namely the requirement to perform retroperitoneal lymph node dissection up to the level of the para-aortic which would necessitate retraining and establishment of the required dissecting skills to perform the procedure safely. The second implication is that the requirement to perform at least a thoraco-abdomino-pelvic CT scan for staging which may not be available in certain centers or affordable for some patients due to cost and availability especially in low resource countries.

ACKNOWLEDGEMENTS

The authors would like to thank the Director-General of Health Malaysia for permission in publishing this article. The authors would also like to thank Associate Professor Dr. Joanne BY Lim, University of Nottingham Malaysia for her assistance with the statistical analysis in this study.

DISCLOSURES

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

CONFLICT OF INTEREST

All the authors declare no conflict of interests.

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Associated genetic polymorphisms and clinical manifestations in systemic lupus erythematosus in Asian populations - A systematic literature review

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is a chronic and life-threatening autoimmune disease. Its prevalence and clinical manifestations are known to be particularly severe in the Asian populations. Although genetics is known to play an important role in SLE susceptibility and clinical manifestations, the specific polymorphisms associated with these phenotypes in Asia are unclear. Therefore, we aim to review the association of SLE genetic polymorphisms with lupus manifestations across Asian populations and their role in the pathogenesis of SLE.

Methods: A systematic search was conducted on PubMed, EBSCOHost, and Web of Science. We identified 22 case-control studies that matched our inclusion and exclusion criteria. Information such as study characteristics, genetic polymorphisms associated with SLE, and organ manifestations was extracted and reported in this review.

Results: In total, 30 polymorphisms in 16 genes were found to be associated with SLE among Asians. All included polymorphisms also reported associations with various SLE clinical features. The association of rs1234315 in TNFSF4 linking to SLE susceptibility (P=4.17x10-17 OR=1.45 95% CI=1.34-1.59) and musculoskeletal manifestation (P=3.35x10-9, OR=1.37, 95%CI= 1.23–1.51) might be the most potential biomarkers to differentiate SLE between Asian and other populations. In fact, these associated genetic variants were found in loci that were implicated in immune systems, signal transduction, gene expression that play important roles in SLE pathogenesis.

Discussions and conclusions: This review summarized the potential correlation between 30 genetic polymorphisms associated with SLE and its clinical manifestations among Asians. More efforts in dissecting the functional implications and linkage disequilibrium of associated variants may be required to validate these findings.

KEYWORDS:
Systemic Lupus Erythematosus; Single Nucleotide Polymorphisms; Genetic Predisposition to Diseases; Phenotypes; Disease risk

INTRODUCTION

Systemic lupus erythematosus (SLE) is a debilitating disorder and genetically inheritable. The genetic contribution to the development of SLE is estimated to be 69% of heritability in monozygotic twin studies.[1] Majority of genetic association studies had suggested that the genetic risk for SLE shows modest effect sizes, ranging from 1.15-2.0.[2] Meanwhile, the key pathogenesis of SLE is the aberrant innate immune responses such as the defect in apoptosis and the loss of tolerance towards self-antigens. This has led to the auto-antibody formation and repository of immune complexes in the blood vessels, causing the infiltration of autoantibodies and deposition of inflammatory cells to affect various targeted organs.

The prevalence of SLE in Asians, particularly in the Eastern part of Asia, was reported to be two times higher compared to Caucasians (between 24.9 and 37.6/100,000 persons).[3] Asians with SLE are frequently at higher risk for severe with life-threatening complications such as renal and cardiovascular involvement.[4] However, the genetic predisposition of SLE in terms of disease susceptibility can vary according to different populations and ethnic groups.[5] The disparity in SLE genetics between populations may cause the Asians to be more severe than other Non-Asian populations.[6] Besides, the complexity of SLE genetics contributed to the penetrance of various targeted organ damage. Features such as lupus nephritis and cutaneous rashes are regularly found in SLE individuals.[7]

Although more than 100 SLE loci have been identified from the candidate gene approach and genome-wide association studies (GWAS) in European and Asian populations, there are high potential of biases in the association study of genetic polymorphism with SLE susceptibility and organ manifestation in Asia. The corroborations which featured Asians to have higher risk variant frequencies of SLE compared to Europeans/Caucasians might explain on why Asians are more severe than other Non-Asian populations. Therefore, this review will examine the best depiction of genotype-phenotype associations for SLE in Asians in comparison with Non-Asian populations and the functional implications of each locus in SLE.

This article was accepted: 26 April 2021
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MATERIALS AND METHODS

2.1 Search Strategy

This review is registered in the PROSPERO database (CRD42020162670). The pipeline of this review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A broad search of the literature was performed on three renowned two databases, namely PubMed, EBSCOHost and Web of Science (WoS) from January of 2010 up to June of 2020. The main keywords of this study were adapted from Population-Exposure-Comparative-Outcome-Timeframe (PECOT) framework which is explained in the study design. From the framework, we decided to come up with 'Systemic Lupus Erythematosus', 'Polymorphisms' and 'Asians' as the main keywords for literature search. The synonyms of every keyword were obtained from the Medical Subject Headings (MeSH). All keywords and respective synonyms were used with truncation and standard Boolean Operators such as '*and*' and '*or*' where relevant.

2.2 Study Design Framework

The study design was devised based on the PECOT framework. P represented the population originated from Asia with SLE and their known complications; E represented the exposure of having the outcome; and C represented the comparable elements with the exposed group. O represented the outcome of interest of the study while T represented the timeframe of study from 2010 to 2020. The focus of this study was to determine the relationship between the genetic association underlying SLE and the organ manifestations in Asian populations. The case-control studies were included for further analyses.

2.3 Article Screening

The filtering of selected evidence was executed in two consecutive phases: 1) Review of title and abstract information and 2) Review of full text. Full text of selected evidence was retrieved from Mendeley Web by adhering to the guideline from the University of Western Australia (https://guides.library.uwa.edu.au/mendeley). Once the literature filtering was completed, the total of final searched reports were narrowed down to prevent abundant searches and to eliminate biases, hence additional inclusion and exclusion criteria were incorporated. Published reports were included for quality assessment and data extraction if they matched with every aspect in the formulated inclusion criteria:

1. Case-control studies that were from original research article between 2010 and 2020
2. All texts were written in English
3. Cases and controls consisted of ethnic groups originating from all parts of Asia.
4. Cases and controls were classified using ACR/SLICC classification criteria.
5. Single nucleotide variant (SNV) was used as a marker in the genotyping analysis
6. Statistical outcomes such as OR and p-Value were included.
7. Genotype-phenotype association analysis was performed
8. There was no conflict of interest with any authorities.

We excluded papers that were

1. Published before the year of 2010
2. Not original research articles, such as mini reviews, case reports, meta-analyses, and editorials.

2.4 Methodological Quality

The quality of the texts and analyses was evaluated by risk of bias assessment tool before the identified publications were finalized and confirmed to be used in this study. The utilization of risk of bias assessment tool is to attain transparency of the data synthesis for an evidence and to detect if there are any potential bias that might affect the entirety of synthesis. In this study, the modified Newcastle-Ottawa Scale (NOS) was selected as the tool to determine the bias of our identified publications since NOS is regularly applied to assess the quality of case-control in genetic studies. For the assessment, an asterisk is marked for every points of view: (1) the selection of the study groups, (2) the comparability of the groups, and one or two asterisks were marked for the (3) ascertainment of either the exposure or outcome of interest. The score has a range between zero and nine. A score of 5 and higher was deemed reliable to be used after the quality assessment by conforming to the standards of the NOS, whereas the lower scores indicated high potential of bias. The quality assessment was carried out by two independent researchers and any disagreements were resolved through discussion.

2.5 Data Extraction

Data from selected evidences were independently extracted by two authors using a piloted extraction form implemented by University of Wisconsin, USA (https://researchguides.ebling.library.wisc.edu/systematic-reviews) from selected articles included: (1) first author's name and publication year, (2) countries, (3) ethnic or race, (4) disease type, (5) sample size of cases and controls with their mean ages, (6) associated SNPs, (7) minor allele frequencies (MAF), (8) statistical finding of genetic association analysis, (9) associated genes, and (10) genotype-phenotype association analysis. Data extraction was carried out by two independent researchers to minimize the rate of extraction errors and the time taken to complete the extraction, and any eventual disagreements were agreed upon by all the authors.

2.6 Data Analysis

Upon information extraction, meta-analysis was decided as an unlikely option to answer the research question. This was due to different polymorphisms/variants being found from the various study selection and outcome measurements among the included articles. Therefore, a narrative synthesis of the evidence was chosen to analyze these studies in which we tabulated every single nucleotide polymorphism (SNP) association with outcome (SLE) and disease risk information as a preliminary synthesis. In addition, we also correlated the association between outcome-associated SNP with SLE complication (gene-phenotype association) in a tabulated form to demonstrate the main objective of this study.

2.7 Genotype-phenotype Association Study

SLE-associated variants were made associated with most common organ manifestations. Risk effect (OR) >1 and

significant value of P<0.05 indicated that SNPs were to be associated with high risk of SLE, while risk effect (OR) <1 and significant value of P<0.05 indicated that SNPs were to be associated with low risk of SLE.

2.8 The Identification of SLE-associated Loci with Respective Biological Pathways

The interpretation of functional role for each locus were divided into five main biological pathway categories (Immune System, Signal Transduction, Metabolism, Gene Expression and Extracellular Matrix Organization) according to the Reactome pathway database (www.reactome.org).

RESULTS

3.1 Literature Search

The overall flow of work throughout the literature search is illustrated in Figure 1. In total, 22 articles were included for data synthesis. Unclear publications such as research reports, conference papers, dissertations and theses, clinical trials, government documents, census data, standards, patents, and other research outputs were excluded because they did not meet the formulated inclusion and exclusion criteria.

3.2 Study Characteristics

Most studies were carried out in mainland China (N=11), followed by Taiwan and India (N=3), Hong Kong and Korea (N=2), Japan (N=1) (Table I). The sample size varied greatly across the studies, ranging from 190 to 8,076 subjects (95 to 3,339 patients and 95 to 4,737 controls). The mean age of SLE patients ranged from 20.5 ± 10.9 years to 42.8 ±13.9 years, and the mean age of controls ranged from 29.2 ± 11.0 years to 40.0 ± 8.6 years. In total, 16 studies examined only one SNP, while the remaining six studies investigated multiple polymorphisms.

A total of 30 polymorphisms (located in/near 20 genes) were reviewed. Among these 30 polymorphisms, there were three polymorphisms significantly associated with lower SLE risk (OR<1.00), while the remaining 27 were positively associated with SLE risk (OR>1.00). All the included studies reported associations with various SLE phenotypes. The top three leading phenotypes were lupus nephritis/renal disorder, lupus arthritis and lupus rashes which were described in 19 studies. This was followed by photosensitivity, hematologic disorders, and vasculitis (two studies each), serositis (one study) and oral ulcers (one study).

3.3 Study Quality Assessment

Nine studies[9,15,16,20,22,23,24,25,27] were classified as having a high methodological quality (8-10 stars) while the other 13 studies[8,10,11,12,13,14,17,18,19,21,26,28,29] reported moderate methodological quality (5-7 stars). In selection, it is obvious in most primary articles that case groups were selected upon self-reports or independent validation by several rheumatologists using the defined ACR or SLICC classification criteria. Besides, the reported cases were selected randomly in a consecutive time with lucid description. For controls, it was reported in most articles that controls were recruited from the same area as cases with a clear endpoint. In comparability, most authors clearly controlled the confounders such as age and gender, either in the study design, analysis, or both. The authors also claimed to be blinded by the detailed information of case and controls while performing genotyping and similar techniques used to genotype both cases and controls. In fact, there is a lack of clarity on the success rate of genotyping for both groups in most primary articles. This is crucial to be included as a high rate of more than 95% will provide higher inclination towards success genotyping and can eliminate potential biases.[12,20,23]

3.4 Genotype-Clinical Outcome Associations

Genetic polymorphisms associated with SLE were implicated in the association with clinical manifestations. Table II shows the details of study characteristics. The most reported clinical features were renal, musculoskeletal, and cutaneous involvements.

We further analyzed the implication of SLE-associated loci with the key pathways (Immune system, signal transduction and gene expression) that play role in the development of SLE autoimmunity (Figure 2). A total of 12 loci were linked with immune system, and 4 loci were linked with signal transduction and gene expression.

DISCUSSION

4.1 Exclusion Criteria for Literature Searching

Limits were applied because we intended only to report on the SNPs replicated in all Asian SLE studies since the inception of GWAS of SLE in Asia that was published in late 2009.[30] This was because prior studies before SLE GWAS were criticized for producing high rates of false positives which can bias in the genetic association of a particular or biologically known variant.

4.2 Synthesis of Research Findings

From the preliminary synthesis, rs1234315 in *TNFSF4* may be the most potential biomarkers to elucidate the genotype-phenotype association in Asian predominantly in East Asia. In fact, rs1234315 demonstrated genome-wide significance ($P<5x10^{-8}$) to both SLE susceptibility and musculoskeletal disorders is of a great implication for the reporting of genotype-phenotype association for SLE in Asia. Rs1234315 lies in a region about 2 kb distant from the 5'UTR of the *TNFSF4* gene which encodes for OX40L protein, a type II transmembrane protein expressed on several immune cells such as B and T lymphocytes. Increased OX40L-OX40 receptor binding would lead to abnormal signaling for the activation of cytokines and contribute to high plasma cell development in SLE. Of late, the genetic association of rs1234315 with SLE was only found in Chinese population with individuals harboring T risk allele were seen higher in SLE patients (51.2%) compared to healthy controls, according to Zhang and colleagues (32.5%).[17] Likewise, a subgroup analysis by ethnicity was found significant in Asian patients (P<0.01, OR=1.39, 95% CI= 1.32–1.46) but not in European (P=0.06, OR=0.84, 95% CI= 0.71-1.00) with different direction of genetic risk score.[31] A similar evidence was also shown in a meta-analysis study in which T allele of rs1234315 was significantly related to SLE susceptibility in Asian population (P<0.001, OR=1.39, 95% CI=1.33–1.46).[32] These two evidences have emphasized on the substantial difference between SLE genetics between Asian and Caucasian which remarks the

Table II: Genotype-phenotype Association in Study Characteristics

First Author (Year)	Country	Ethnics	Disease	Sample Size (Mean Age)		Associated Single Nucleotide Polymorphism (SNP)	Minor allele frequencies (MAF) (%)			Genetic associations			
				Case	Controls		Allele	Case	Controls	OR	95% CI	P-Value	Gene
Zhu, 2014[8]	China	Chinese	SLE	741 (37.87± 11.05 years)	731 (34.38± 12.42 years)	rs7396562 (C/T)	T	59.9	53.1	1.32	1.14-1.53	$1x10^{-3}$	Single immunoglobulin IL-1-related receptor *(SIGIRR)*
Liu, 2015[9]	China	Chinese	SLE/ LN	792 (38.37± 12.24 years)	777 (34.06 ± 11.28 years)	rs3788013 (C/A)	C	70	65.1	1.26	1.08-1.46	$3x10^{-3}$	Ubiquitin associated, central Src-homology 3 *(UBASH3A)*
Zhang, 2017[10]	China	Northern Han Chinese	SLE/ LN	500 (31.9 ± 11.2 years)	500 (40.0 ± 8.6 years)	rs1456896 (A/G)	A	25.45	33.17	0.69	0.52-0.91	$9.32x10^{-3}$	*IKAROS* family of zinc finger1 *(IKZF1)*
Kawasaki, 2010[11]	Japan	Japanese	SLE	364 (42.8 ± 13.9 years)	513 (34.1 ± 9.9 years)	rs7708392 (G/C)	C	76.5	23.5	1.40	1.13-1.74	$2x10^{-3}$	*TNFAIP3* interacting protein 1 *(TNIP1)* and TNF alpha-induced protein 3, *(TNFAIP3)*
Zhou, 2015[12]	China	Chinese	SLE	500 (32.06± 11.5 years)	900 (31.56± 8.4 years)	rs3093024 (A/G)	A	42.2	39.9	1.10	1.02–1.20	$1.57x10^{-2}$	C-C Motif Chemokine Receptor 6 *(CCR6)*
Yang, 2011[13]	Hong Kong	Chinese	SLE	612 (N/A)	1160 (N/A)	rs7329174 (A/G)	G	28.3	21.9	1.41	1.22–1.63	$7.18x10^{-6}$	E74-Like Factor 1 *(ELF1)*
Yu, 2010[14]	Taiwan	Taiwan Han Chinese	SLE	138 (20.5 ± 10.9 years)	138 (N/A)	rs2243250 (T/C)	C	24.5	16.7	1,65	1.06-2.56	$3x10^{-2}$	Interleukin-4 *(IL-4)*
						rs2070874 (T/C)	C	24.3	17.0	1.58	1.02-2.46	$4x10^{-2}$	
						rs2243291 (C/G)	G	25.9	17.2	1.73	1.12-2.68	$1x10^{-2}$	
Wen, 2017[15]	China	Han Chinese	SLE	1047 (34.02 ± ± 11.53 years)	1205 (34.75 ± 12.97 years)	rs7726414 (C/T)	T	9.23	6.78	6.78	1.16-1.30	***3.03x10**$^{-12}$	Intergenic of Transcription factor 7 *(TCF7)*
						rs244689 (A/G)	A	37.07	31.48	1.23	1.11-1.36	$6.75x10^{-5}$	Protein Phosphatase 2 Catalytic Subunit Alpha *(PPP2CA)*
Wang, 2015[16]	China	Han Chinese	SLE	2208 (33.58 years)	2208 (31.16 years)	rs4649038 (T/C)	T	42	39	1.10	1.01-1.20	$2.93x10^{-2}$	Runt-related transcription factor 1 *(RUNX3)*
Zhang, 2011[17]	China	Han Chinese	SLE	1344 (31.8 years)	4315 (31.8 years)	rs1234315 (C/T)	T	51.2	39.5	1.45	1.34-1.59	$*4.17x10^{-17}$	Tumour necrosis factor superfamily 4 *(TNFSF4)*
						rs1234315 (C/T)							
Li, 2012[18]	Hong Kong	Hong Kong Chinese	SLE	612 (N/A)	2193 (N/A)	rs704853 (A/C)	A	16.6	21.8	0.73	0.62-0.86	$6.94x10^{-5}$	CD247 *(CD3Z, TCRZ)*
Zhang, 2018[19]	China	Han Chinese	SLE	730 (36.06± 13.16 years)	779 (36.66± 12.74 years)	rs10491322 (A/G)	G	5.27	3.34	1.61	1.13–2.31	$9x10^{-3}$	Protein phosphatase 2CA *(PPP2CA)*
						rs7704116 (C/T)	T	7.33	4.75	1.59	1.17–2.15	$3x10^{-3}$	

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First Author (Year)	Country	Ethnics	Disease	Sample Size (Mean Age)		Associated Single Nucleotide Polymorphism (SNP)	Minor allele frequencies (MAF) (%)			Genetic associations			
				Case	Controls		Allele	Case	Controls	OR	95% CI	P-Value	Gene
Joo, 2013 [20]	Korea	Korean	SLE	601 (32.36 years)	984 (37.36 years)	rs3765456 (G/A)	A	N/A	N/A	1.34	1.09-1.66	$3x10^{-2}$	*CD40*
Li, 2018 [21]	China	Han Chinese	SLE	584 (37.14± 12.35 Years)	628 (36.63± 11.27 years)	rs1143679 (G/A)	A	0.94	0.24	3.97	1.11-14.28	$2x10^{-2}$	*CD11b/ITGAM*
Umare, 2019 [22]	India	Indian	SLE	200 (28.0± 10.0 years)	201 (29.2± 11 years)	IL-18 (-1297 T/C) (rs360719)	C	44.0	30.6	1.80	1.30-2.40	$2x10^{-3}$ (P corrected)	Interleukin-18 *(IL-18)*
Yang, 2017 [23]	China	Han Chinese	SLE	1470 (37.63 ± 14.54 years)	2283 (36.84 ± 14.67 years)	rs1042522 (G/C)	G	58.10	55.12	0.89	0.81-0.97	$1x10^{-2}$	Tumour protein p53 *(Tp53)*
Umare, 2017 [24]	India	Indian	SLE	200 (28 ± 10 years)	201(29.2 ± 11 years)	–2518 A/G (rs1024611)	G	35.0	22.1	1.9	1.30-3.00	$2.3x10^{-3}$	Monocyte Chemoattractant Protein-1 *(MCP-1)*
Cai, 2010 [25]	China	Han Chinese	SLE	1420 (30.44 years)	4461 (34.44 years)	rs2230926 (T/G)	G	7.2	4.5	1.65	1.39-1.99	$2.03x10^{-8}$	*TNFAIP3*
Chang, 2011 [26]	Taiwan	Taiwanese	SLE	N/A	N/A	c.1567 C/T	C	39.3	28.7	1.60	1.17-2.20	$3x10^{-3}$	Lumican *(LUM)*
Chen, 2020 [29]	Taiwan	Taiwanese	SLE	95 (33.7± 12.5 years)	95 (36.1± 14.3 years)	rs2844455 (G/A)	A	40.5	28.4	1.72	1.12-2.63	$1.3x10^{-2}$	Complement 2 *(C2)*
Baek, 2019 [28]	Korea	Korean	SLE	280 (35.7± 7.8 years)	260 (28.1± 7.4 years)	rs2271715 (C/T)	C	53.0	58.7	1.64	1.01-2.66	$3.6x10^{-2}$	Milk fat globule epidermal growth factor 8 *(MFGE8)*
						rs3743388 (G/C)	G	52.7	60.8	1.71	1.05-2.80		
Umare, 2020 [29]	India	Indian	SLE	200 (28± 10 years)	201 (29.2± 11 years)	rs1800896 (A/G)	G	28.0	19.2	1.60	1.18-2.28	$1.1x10^{-2}$	Interleukin 10 *(IL-10)*
						rs1800871 (C/T)	C	47.5	39.8	1.40	1.03-1.81	$9.8x10^{-2}$	
						rs1800872 (C/A)	A	46.8	33.2	1.70	1.30-2.30	$1x10^{-3}$	

SLE, Systemic lupus erythematosus; LN, Lupus nephritis; OR, Odd-ratio; CI, Confidence Interval; N/A, Not available
*P-Value indicates significance if the value is less than 0.05

Table II: Genotype-phenotype Association in Study Characteristics

SLE feature	Description	Gene	Variant	Odds ratio	Population	References	PValue
Cutaneous	Malar rash	*SIGIRR*	rs7396562	1.36	Chinese	[8,16,25]	$5x10^{-2}$
		RUNX3	rs4649038	1.18	Han Chinese		$9x10^{-4}$
		TNIP3	rs2230926	1.58	Chinese		$3x10^{-5}$
Cutaneous	Photo sensitivity	*SIGIRR*	rs7396562	2.38	Chinese	[8,26,27]	$<1x10^{-3}$
		LUM	c.1567 C/T	2.05	Taiwanese		$3x10^{-2}$
		C2	rs2844455	2.00	Taiwanese		$5x10^{-2}$
Cutaneous	Discoid rash	*p53*	rs1042522	1.25	Chinese	[23]	$4x10^{-2}$
Oral ulcer	N/A	*CD247*	rs704853	0.78	Hong Kong	[18]	$5x10^{-2}$
Serositis		*IL-10*	rs1800896	2.7	India	[29]	$2x10^{-2}$
Renal	Lupus nephritis	*IKZF1*	rs1456896	0.80	Chinese	[10-14,16,20-22,24-26]	$2x10^{-3}$
		TNIP3	rs7708392	1.60	Japanese		$2x10^{-3}$
		CCR6	rs3093024	1.18	Chinese		$4x10^{-2}$
		ELF-1	rs7329174	1.27	Chinese		$2x10^{-2}$
		IL-4	rs2243250	0.38	Taiwanese		$4x10^{-2}$
		IL-4	rs2070874	0.31	Taiwanese		$2x10^{-2}$
		IL-4	rs2243291	0.36	Taiwanese		$4x10^{-2}$
		RUNX3	rs4649038	1.16	Han Chinese		$5x10^{-3}$
		CD40	rs3765456	0.47	Korean		$2x10^{-2}$
		Cd11b	rs1143679	N/A	Han Chinese		$5x10^{-2}$ ($P_{corrected}$)
		IL-18	rs360719	2.60	Indian		$2x10^{-2}$ ($P_{corrected}$)
		MCP-1	–2518 A/G	N/A	Indian		$1x10^{-4}$
		TNIP3	rs2230926	1.77	Han Chinese		$5x10^{-5}$
		MFGE8	rs2271715	N/A	Korean		$1x10^{-3}$
		MFGE8	rs3743388	N/A	Korean		$1x10^{-3}$
Musculo skeletal	Inflammatory Arthritis	*RUNX3*	rs4649038	1.13	Han Chinese	[16,17,19,20,26]	$9x10^{-3}$
		TNFSF4	rs1234315	1.37	Han Chinese		$**3x10^{-9}$
		PPP2CA	rs10491322	N/A	Han Chinese		$3x10^{-2}$
		CD40	rs3765456	2.46	Korean		$1x10^{-2}$($P_{corrected}$)
		TNIP3	rs2230926	1.77	Han Chinese		$**7x10^{-8}$
		LUM	c.1567 C/T	2.38	Taiwanese		$6.4x10^{-3}$
Vasculitis	N/A	*UBASH3A*	rs3788013	N/A	Chinese	[9,15]	$1x10^{-2}$
		Intergenic region between *TCF7* and *PPP2CA*	rs7726414 and rs244689	1.26	Han Chinese		$4x10^{-2}$
Hematologic disorder	N/A	*TNFAIP3*	rs2230926	1.57	Han Chinese	[18,25]	$1x10^{-5}$
		CD247	rs704853	0.57	Hong Kong		$3x10^{-2}$

N/A, Not Available
**Genome-wide significant variant P<5x10-8

heterogeneity of SLE in terms of ethnic distribution. However, there is no functional validation to attest the implication of this variant in the pathogenesis of SLE which could serve as a gap for future studies. In addition, rs1234315 C/T predisposed high risk for arthritis in SLE patients ($P=3.35x10^{-9}$, OR=1.37, 95% CI= 1.23–1.51) might be the first demonstrated genotype-phenotype association of SLE in Asia.

Technically, all selected variants were associated with SLE susceptibility and clinical manifestations, regardless of the level of significance of p-value. Besides, genetic heterogeneity of SLE across different populations might give various risk impacts to disease susceptibility.[5] Some of those variants have also been demonstrated in non-Asian population. Other than rs1234315, risk allele A from rs1143679 *(Cd11b)* (OR=3.97) as studied by Li and colleagues had demonstrated to have similar effect sizes ranging from 1.65-1.8 and shared minor allele frequencies from several Non-Asian populations such as Brazilian and Central Mexican.[33,34] Similarly, in rs360719 *(IL-18)* (OR=1.80), the risk allele C has rendered a high risk for SLE with a range of effect sizes (OR=1.18-1.558) in several studies conducted across various European populations such as Spain, Italy, Argentina, and Polish.[35] However, risk allele frequencies of C allele was found higher in Asian SLE patients (the present study which has a frequency of 0.44) compared to the European SLE patients (0.2-0.35). However, all studies have high sample sizes which could indicate that the statistical association might be true according to the allele frequencies. The G allele from rs2230926 (TNFAIP3) (OR=1.65) as studied by Cai and colleagues has been consistently associated with high-risk for SLE in the latest genetics study in European SLE (OR=1.91).[25,36] In fact, a subgroup analysis from a meta-analysis study consisting of thousands of subjects has also demonstrated a similar OR in the minor G allele of rs2230926 between Caucasian (OR=1.675) and African (OR=1.324).[37] For rs1800896 *(IL10)* (OR=1.60), the minor G allele in our synthesis has also been associated in the dominant model of European Population (OR=1.375) but not in the African population.[38] Therefore, Asians have greater impact for SLE compared to Caucasians not just from the prevalence, socioeconomic status and clinical manifestations but also from genetic perspectives.

Another intriguing part of the data synthesis is that these 30 variants were significantly associated (P <0.05) with various clinical manifestations, of which 27 of them contributed to a higher risk (OR>1.00) and 3 of them have lower effects against these manifestations (OR<1.00). In fact, some of these variants such as rs2230926 *(TNFAIP3)*, rs4649038 *(RUNX3)* and rs3765456 *(CD40)* have rendered pleiotropic as they are

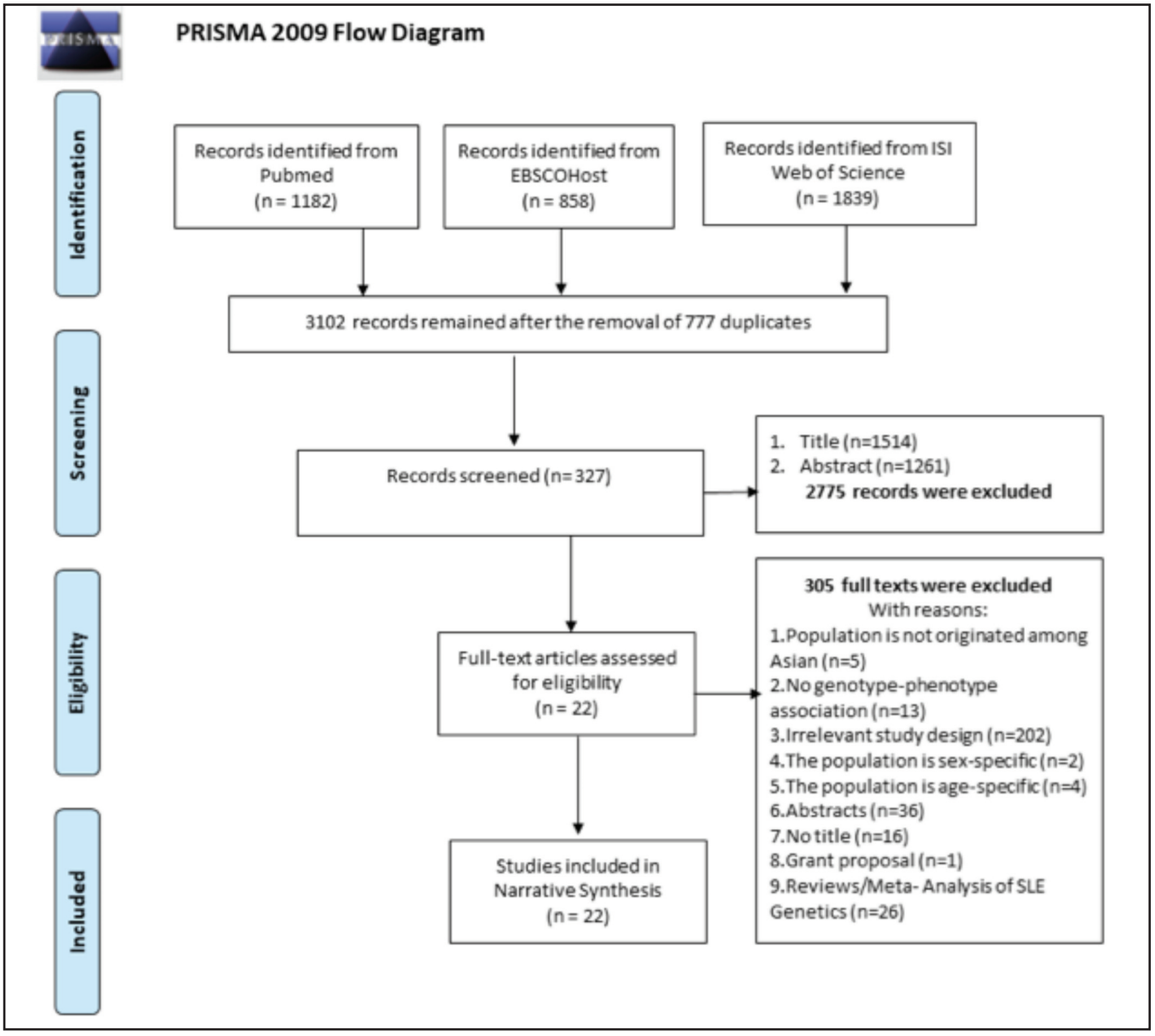

Fig. 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram.

associated with more than a manifestation. The pleiotropy of a variant comes from its ability to regulate the transcription of other genes, which is an important mediator in general biological functions. For example, rs2230926 demonstrated by Cai and colleagues shows higher risk for multiple manifestations including renal, musculoskeletal, malar rash and hematologic disorder.[25] Normally, *TNFAIP3* encoded into an A20 protein which is known as ubiquitin-editing enzyme and a negative regulator of the NF-κB signalling pathway including TNF and Toll-like receptors.[25] However, in SLE, changes in the rs2230926 T>G led to decrease of the ability of *TNFAIP3* to suppress A20 protein expression which results in autoimmunity throughout the constant stimulation of autoantibodies by NF-κB hyperactivation.

The most reported manifestation that was associated with SLE susceptibility genes is lupus nephritis (LN) that affected up to 40% of adults and 80% of children with SLE. LN was shown to be the major cause of morbidity and mortality of every population in the world. Most studies that interrogated SLE/LN associated genes, were also correlated with LN presentations such as high proteinuria in urine and presence of immune complexes upon renal biopsy. In terms of genetic risk of LN by ethnicity, few variants from the present data are in concordance with case-control studies of LN in other populations. For variant rs7708392, the genetic association of the minor allele C with high risk for LN in present data has been simultaneously found in almost every population.[39] In fact, variant rs1143679 in *Cd11b* has also been reported to be associated with high risk for renal disorder from several populations including Asians.[40] Therefore, most SLE-associated genes contributed a pivotal role in LN development, regardless of population types.

Fundamentally, the key pathways related to SLE are the immune system, signal transduction and gene expression.

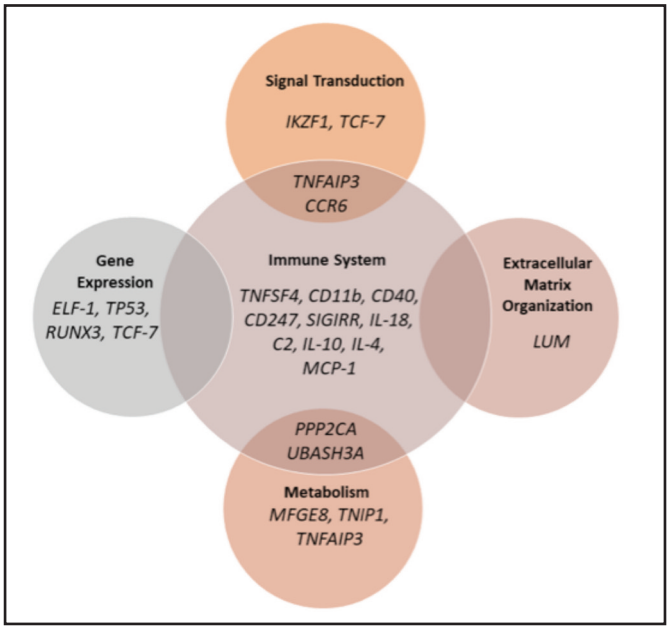

Fig. 2: Biological pathways of genes associated with SLE.

Determination of association between these variants with SLE pathogenesis is crucial to understand the key pathways leading to diversity in the clinical heterogeneity of SLE. The dramatic increase in the genetic information of SLE over the passing years has allowed the depth understanding of SLE related to the pathogenesis stemming from the aberrancies in the downstream signaling pathways which affect the normal immune response. The substantial pathways culminating in several autoimmune events such as continuous production of autoantibodies, higher inflammatory cytokine production, and impaired tolerance has been progressively delineating the mechanistic pathways of SLE pathogenesis in cellular function. In fact, suppression of these pathologic events might be new targets for SLE treatments. However, little or no information of these perspectives has yet to be translated into new therapeutic strategies.

4.3 Limitations of preliminary synthesis

At this point, many studies have identified genetic variants associated with SLE and organ manifestations. However, the association is spurious due to limitations such as lower sample sizes. Smaller sample size would be a major factor of GWAS failure as it would lead to a discovery of false-positive results. In fact, most studies do not apply a multiple testing correction on the statistical value which is extremely important to obtain higher confidence on the statistical outcome as it will eliminate the false discovery rate (FDR). However, most genotype-phenotype associations from the synthesis are inconsistent as some variants fall below genome-wide significance when associated with disease susceptibility, but they reached genome-wide significance when associated with clinical manifestations. Thus, these variants are not reliable as potential biomarkers for disease susceptibility. Furthermore, certain novel variants that were recently discovered, had augmented the difficulty to search for supporting evidence. Many reviews had attempted to conduct a meta-analysis on these novel variants but due to the lack of relevant evidence, it would not be feasible to obtain significant association for these novel variants due to lower sample sizes.

4.4 Strength of Systematic Review

Despite the above limitations, the preliminary synthesis has benefitted the main question in correspondence to the emphasis on associated variants with the disease susceptibility and organ manifestations that reached genome-wide significance threshold ($P<5x10^{-8}$) particularly rs1234315 in *TNFSF4*. Higher genetic risk load of rs1234315 in Asian compared to European has eventually answered why SLE is more prevalent in Asian compared to European despite both continental populations share the same loci across the genome. Although no multiple testing was conducted in this literature search, given the supporting evidences such as meta-analyses and difference allelic distribution between Caucasian and Asian, study by Zhang and colleagues already provided high quality as a potential marker of lupus in Asia.[17] In terms of the effect sizes in study by Zhang and colleagues, rs1234315 has a 1.45 times higher risk to develop SLE and 1.36 times higher risk to form arthritis, which confer modest effect sizes (OR<1.5) and account about 30% of the total genetic susceptibility to the disease.[17] This explains the missing heritability such as gene-gene and gene-environment interaction that might increase the polygenic prediction risk score of rs1234315 in SLE susceptibility, which potentially serves the gap for future study. However, other candidate gene markers may have contributed to a promising genotype-phenotype association of SLE as well, but well-designed parameters such as larger sample sizes and different subgroups should be employed to increase the significance of a study.

CONCLUSION

In summary, we found that *TNFSF4, CD11b, Cd40, CD247, SIGIRR, IL-18, C2, IL-10, IL-4, MCP-1, IKZF-1, TCF-7, PPP2CA,* and *UBASH3A* may contribute to the genotype-phenotype association in Asia, with rs1234315 in TNFSF4 as the highly potential risk biomarker in Asian lupus particularly musculoskeletal involvement. In terms of functional perspective, these genes have been implicated with various roles in the pathogenesis of SLE such as autoimmunity and altered signal transduction and gene expression signature which culminates in loss of tolerance and production of autoantibodies. This might entail an insight on future target therapies which can be tailored to the management of SLE in Asian populations. Our study may suggest that Asians have more severe risk for SLE compared to Caucasians in terms of genetics. However, there are still gaps of ongoing genetic studies of novel variants in Asia that should be replicated in non-Asian populations to ascertain the SLE heterogeneity across different populations. In fact, an effort to define the association of these variants in accordance with their functional implications may be required to propose new therapeutic strategies. Identification of linkage disequilibrium of associated variants that account for gene-gene interaction may as well be necessary to unfold the missing heritability of SLE, especially due to small contribution of risk prediction by certain variants.

ACKNOWLEDGMENT

The authors would like to thank and acknowledge Saravana Kumar for his guidance in the completion of this systematic review. This study was supported by the Fundamental Grant Research Scheme (FRGS), FRGS/1/2018/SKK02/UKM/03/1 from Ministry of Higher Education in Malaysia.

DECLARATION OF INTEREST

The authors declare that there is no competing interest.

AUTHOR CONTRIBUTIONS

Conceptualization, N.A.A.M. and S.C.T.; methodology, A.K.A.A.T. and S.C.T.; formal analysis, A.K.A.A.T.; investigation, A.K.A.A.T., N.A.A.M. and S.C.T.; resources, A.K.A.A.T. and S.C.T.; data curation, N.A.A.M. and S.C.T.; writing original draft preparation, A.K.A.A.T.; writing review and editing, N.A.A.M., E.A.A., S.C.T. and S.S.S.; visualization, A.K.A.A.T.; supervision, N.A.A.M., E.A.A., R.J. and S.S.S.; project administration, N.A.A.M., E.A.A., R.J. and S.S.S.; funding acquisition, S.S.S. All authors have read and agreed to the published version of the manuscript.

ETHICS STATEMENT

Not applicable.

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The need of a system phantom for quantitative hybrid nuclear imaging of PET/CT: A systematic review

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ABSTRACT

Introduction: There has already been a rising demand in utilising phantom for hybrid Positron Emission Tomography/ Computed Tomography (PET/CT) scanner of nuclear imaging. This review further clarifies this topic and investigates how the previous research phantoms operated with the need for quantitative hybrid nuclear imaging of PET/CT while providing a relatively high image quality when it was performed. In this article, the necessity of previous and current phantom studies in hybrid nuclear imaging of PET/CT scanners is reviewed.

Methods: PubMed and Google Scholar were systematically searched for the relevant studies by following the PRISMA 2009 checklist. A past decade literature search was conducted from 2010 until November 2020 to secure the relevance of the phantom study. Databases were recruited using keywords such as phantom, quantification, standardisation, harmonisation, image quality, standardised uptake value and multicentre study. However, all keywords were related to PET/CT. All abstracts and eligible full-text articles were screened independently, and finally, the quality assessments of this review were performed.

Results: From the 200 retrieved articles, 80 were rejected after the screening of the abstracts and 35 after reading the full-text. The 20 accepted articles addressed the distribution of phantom types used in selected articles studies which were NEMA (67%), ACR (8%) and others (25%). The articles showed the various experimental studies, either phantom studies (35%) or phantom plus clinical studies (65%). For clinical studies (n = 829), the distribution of prospective studies was (n = 674) and retrospective studies was (n =155). The distribution of phantom pathway application showed the studies focused on 40% of reconstruction protocol studies, 30% of the multicentre and standardisation of accreditation program studies, and 30% of the quantification of uptake values studies.

Conclusions: According to this review, the phantom study have a pivotal role in hybrid nuclear imaging of PET/CT either in technical aspects of the scanners (such as data acquisition and reconstruction protocol) or clinical characteristics of patients. In addition to this, the necessity to identify the suitable system phantoms to use within PET/CT scans by considering the continuous development of new phantom studies are needed. Researchers are encouraged to adopt efforts on phantom quantitative validation, including verification with clinical data of patients.

KEYWORDS:
PET/CT phantom, quantification, standardisation, harmonisation, image quality

INTRODUCTION

Over the past decade, there has already been a rising demand in utilising phantom for hybrid Positron Emission Tomography/ Computed Tomography (PET/CT) scanner of nuclear imaging. PET/CT scanners perform a significant role in contemporary nuclear imaging as an outcome of their hybrid existence. A Hybrid PET/CT scanner can show the information of the image by merging metabolic imaging (PET) and morphological imaging with computed tomography (CT).[1]

Phantom is commonly used as a PET/CT scanner validation routine in the quality control (QC) process. The quality control process is obligatory to validate quantitative PET/CT imaging in clinical practice. The phantom can be used for acceptance analysis, routine consistency measurement, precision testing of reconstructed image quality, simulated evaluation of whole-body imaging, identification of non-uniform artefacts, and further evaluation testing.[2]

The changing performance caused by different eras of PET/CT scanners like time-of-flight (TOF), two-dimensional (2D) and three-dimensional (3D) acquisitions technology lead to different quantitatively of image quality. Moreover, the problems also include diverse reconstruction technologies such as point spread function (PSF), or Bayesian penalised-likelihood (BPL) and resolution recovery reconstruction. Multicentre standards of PET/CT systems must not be based on the minimum performing scanners. However, they are required to sustain the maximum standard in the performance of the scanners by implementing further evaluation testing parameters using phantom as one of the tools.[3]

This article was accepted: 08 May 2021
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This review further clarifies this topic and investigates on how the previous research phantoms operated with the need for quantitative hybrid nuclear imaging of PET/CT while providing a relatively high image quality when it was performed. Our review is expected to identify the following questions. This purpose of the review is to respond to the following inquiries: (i) What is the particular phantom used in PET/CT? (ii) What are the potential benefits of requiring a phantom study in PET/CT scan? (iii) Is utilising the phantom just for quality control purposes only?

MATERIALS AND METHODS

Search of the past decade literature review was conducted to secure the relevance of the phantom studies of PET/CT by following the checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 (PRISMA 2009).[4]

Eligibility criteria

Our inclusion criteria included all phantoms studies related to hybrid nuclear imaging of PET/CT. The exclusion criteria for this study were:

- The phantoms studies were related to imaging of CT, MRI, SPECT, ultrasound, or other imaging modalities.
- The articles were not related to PET/CT phantom studies.
- The studies were related to animal trials.
- The articles were not a decade published (Articles published before 2010).
- The articles have not been published in peer-reviewed journals.

Search strategies and information sources

We conducted a systematic global analysis of various electronic databases (including PubMed and Google Scholar). Since phantoms studies in PET/CT are comparatively new in imaging applications studies in nuclear imaging, the literature search was organised from 2010 until November 30, 2020. Databases were recruited using keywords phrase searching and Medical Subject Headings (MeSH) methods such as "phantom*", "quantification*", "standardisation*", "harmonisation*", "image quality*", "standardised uptake value*", "multicentre study*". However, all keywords were required to be related to PET/CT or PET. The searches were confined to articles in the English language only. Reference lists of related publications were also identified.

Data extraction for study selection

Search strategies were applied with initial findings imported and integrated into the Mendeley Desktop, the reference management platform (version 1.19.4 ©2008-2018 Mendeley Ltd, Elsevier). After eliminating duplicates, the remaining titles and abstracts were reviewed for inclusion. Full texts were extracted and manually assessed from the relevant articles.

Using structured data extraction techniques, the authors retrieved and compared the data separately. Discrepancies were explored. Data obtained included the published year, type of phantom used, clinical approaches in phantom research, clinical design experiments, phantom pathway study, and outcomes of the studies.

By thoroughly reviewing the aims of the studies, all studies obtained from the search procedure were checked if they were within the scope of the current research or not. The authors of this paper independently reviewed the described and chosen articles. They also reviewed and prepared detailed notes to outline the research purposes, methodology, techniques, significant findings and recommendations and made a definitive decision based on research criteria.

Fifty-five reports were found of articles in full-text. Thirty-five articles were not considered since the papers were not related to phantoms experimental and were excluded for reasons. As a result, the search strategy identified twenty articles according to our study criteria. The review process for related publications using the PRISMA recommendation is shown in Figure 1.

Risk of bias

No qualitative score was applied for the selection of the study. Data obtained from reviewed articles were structured to minimise potential biases using other reviewers only in queries. Data extracted from research that did not follow their possible standardisation requirements were excluded and withdrawn.

Summary data analysis

Descriptive statistics was used to sum up, the information with percentage values for dichotomous variables. Percentages were calculated to determine the per cent of the sample corresponding to the specified frequency. The values are usually presented without decimal points and significant figures (according to American Psychological Association© year 2020 seventh edition standards).

RESULTS

Literature characteristics

There were 20 full articles identified from the year 2010 until 2020 that focused on the experimental phantom studies (Table I). The articles that reviewed the literature were detailed into four information groups (subjects, type of phantom, the aim of the study, and quality of research finding) as demonstrated in Table I.

Distribution of phantom types

This review identified various phantom types used for the PET/CT studies, as presented in Figure 2. First, the phantom used was the NEMA phantom, which was designed according to the endorsement of the National Electrical Manufacturers Association (NEMA). The second was the Jaszczak Deluxe Flangeless PET phantom, which was designed according to the requirement of the American College of Radiology (ACR). Simultaneously, the rest was classified as other phantoms (anthropomorphic, cylindrical and modified micro hollow).

There were 16 articles reported using NEMA phantom as their study in PET/CT. As for ACR phantom, only two phantoms and six papers used other phantoms as their study. The majority used NEMA phantom with 67% in percentage distribution, ACR phantom 8%, and other phantoms were 25%.

Distribution of phantom studies
Table I shows the distribution of PET/CT studies either in the only phantom study or phantom-clinical study approaches. The only phantom study is the research that has been conducted using phantom only and without clinical approaches. For the phantom-clinical study, the research were worked out using phantom and clinical study either retrospectively or prospectively. The only phantom study percentage was 35%, and the phantom-clinical study was 65% from all the reviewed articles. The phantom-clinical study methods were divided into retrospective and prospective studies, with percentages of 20% and 45%, respectively. In the prospective study, the clinical data were directly collected during the period of research study. However, in the retrospective study, the clinical data were usually sampled and collected from the past or previous PET/CT examination.

Distribution of clinical studies in PET/CT
Table I illustrates a more specific distribution of clinical studies, either retrospective or prospective. For retrospective clinical studies, the total number of clinical data was 155. The data was presented by four reviewed articles, they were Devriese J et al. (n=64), Armstrong I et al. (n=68), Wielaard J et al. (n=15), and te Riet et al. (n=8).

In the prospective studies, the total number of clinical data was 674. Nine reviewed articles studied about prospective clinical studies, which were Makris N et al. (n=10), Kelly M & Declerck J (n=10), Quak E et al. (n=517), Texte E et al. (n=20), Hoetjes N et al. (n=25), Lasnon C et al. (n= 52), Kaalep et al. (n=30), Caribe et al. (n=1) and Kero T et al. (n=9).

Result of phantom pathway study in reviewed articles of PET/CT researches
Figure 3 shows the result of phantom pathway studies in PET/CT researches. The pathway was divided into three groups of study approaches, which were a) quantification of uptake values, b) reconstruction protocols, and c) multicentre studies and accreditation programme.

The reconstruction protocols percentage was 40% and the highest of phantom pathway studies with eight reviewed papers. However, the percentage of quantification of uptake values was 30%. The same goes for multicentre studies & accreditation programme, with 30% with six reviewed papers.

DISCUSSION

This review focuses on the need of a system phantom for quantitative hybrid nuclear imaging of PET/CT. The reviewed articles were restricted to a decade publication to highlight contemporary PET/CT studies' outcomes using various phantoms, either study conducted on phantom only or add-on with clinical research. The current review was undertaken and reported using the recommended PRISMA guidelines.

Application of different types of phantoms in PET/CT studies
The reviewed papers highlighted the quantitative studies of PET/CT's hybrid nuclear imaging of PET/CT using various system phantoms. As reported in Figure 1, the reviewed articles reported that the phantoms used were NEMA, ACR and others (anthropomorphic, cylindrical and modified micro hollow). All the phantoms were specific for PET imaging systems and reliable for nuclear imaging studies, as presented in Table II.

From the reviewed papers' extracted information, NEMA phantoms represented the highest number of phantom studies with a total of 16 reviewed articles. Through all that articles, NEMA phantom studies clarified the research pathway of a) multicentre studies and accreditation programme, b) reconstruction protocols and, c) quantification of uptake values.

Data Spectrum explained that the NEMA phantom is fabricated to standardise the evaluation of PET scanner performance according to the standard of the National Electrical Manufacturers Association. The phantom has a part of the body and the lung part attached with six fillable spheres of different sizes. The phantom provides imaging information particularly through PET as the camera-based coincidence imaging techniques. Besides, the phantom helps with system image quality as well as the accuracy of any corrections used.[24]

Many researchers used NEMA phantom due to the specific useful for clinical study, especially for brain and cardiac imaging studies. Biodex Medical System, Inc. informed that this phantom could determine cardiac and brain imaging's synchronise count rate features. Moreover, it complies with NEMA 2012 standard.[25]

However, ACR and other phantoms only showed two common research applications, either in multicentre studies and accreditation programme, or reconstruction protocols. Only two reviewed papers focused on ACR phantom studies and six reviewed articles reported about other phantoms studies.

Biodex Medical System, Inc. and Supertech, Inc. stated that the ACR phantom offers reliable and accurate performance information for any PET systems. From a single scan of the phantom, it can assess various evaluation characteristics of PET systems. The function of the transverse line spread on-axis and off-axis can be easily determined without removing the cover plate. The ACR phantom for PET meets the requirements according to the standard of the ACR.[26,27]

According to the Report of the American Association of Physicists in Medicine Task Group 126: PET/CT Acceptance Testing and Quality Assurance 2019, ACR phantom can evaluate PET image contrast and scatter attenuation correction. The ACR phantom is characterised by four hot vials of varying diameters with a fixed activity concentration relative to the background and three vials of varying material densities.[28]

The SUV ratios will be used in the calculation. The maximum SUV measurements from the four hot vials will be used to measure image contrast. The scatter/attenuation from the Teflon, air, water, and background regions will be calculated using mean and minimum SUV measurements. These values

Table I: Information of each reviewed article regarding the subjects, type of phantom, aim of study and quality of finding

Author	Subjects	Phantom studies	Aim	Quality of finding
Kaalep A et al. [3]	Phantom & patient (n=30)[P]	NEMA	To study the role of EARL-2 revised accreditation guideline on quantitative measurements of clinical PET/CT studies	The updated EARL-2 recommendations resulted in higher SUVs, lower MATV, and similar TLGs.
Makris NE et al. [5]	Phantom & patient (n=10)[P]	NEMA ACR Anthropomorphic	Determine whether the phantoms are ideally suited to detect variations in image quality and quantification, and the methods to identify volumes of interest (VOI) are the least sensitive to these differences.	The three phantoms investigated in this study were suitable for harmonising various scanner quantitative performances, suggesting more potential for harmonising image quality and quantification.
Kelly MD and Declerck JM [6]	Phantom & patient (n=10)[P]	NEMA	They proposed a new approach, reference Standardised Uptake Value (SUVref), to reduce the quantitative variation arising from reconstruction protocol inconsistencies.	This reduction in variance significantly improves clinical image quantitative comparison to assess the disease's treatment response or progression.
Quak E et al. [7]	Phantom & patient (n=517)[P]	NEMA	To validate a specific software tool (EQ.PET) to harmonise SUVs across various PET systems regardless of the reconstruction algorithm used.	This is mostly applicable to multicentre trials and can provide precise quantification for restaging.
Devriese J et al.[8]	Phantom & patient (n=64)[R]	NEMA	To compare lesion SUV values collected via two different reconstruction protocols: a) GE's latest clinical lesion detection protocol (Q.Clear); b) The EARL harmonisation protocol, using the PERCIST protocol	It is advisable to select the EARL protocol for multicentre studies and individual therapy response evaluation to accurately compare the SUL between patients, scanners, and centres.
Rogasch JMM et al. [9]	Phantom	Cylindrical phantom	To investigate the impact of reconstruction integration on various SBRs.	The use of reconstruction for quantitative PET data should be conducted with caution (if SUV of lesions with high contrast compared to low contrast)
Texte E et al. [10]	Phantom & patient (n=20)[P]	ACR	To assess the BPL reconstruction algorithm's effect compared to OSEM on the hypoxia PET/CT images.	The BPL algorithm explicitly raises the quantitative parameters and contrast on PET/CT reconstruction that is consistent with all other papers studying this reconstruction algorithm.
Akerele MI et al. [11]	Phantom	NEMA	To implement the newly proposed background correction and assess its efficiency in lesion quantification accuracy and comparison, using both simulated and actual clinical PET.	Improved quantification and more precise lesions detection were achieved with the newly proposed background correction technique.
Armstrong IS et al. [12]	Phantom & patient (n=68)[R]	NEMA	To study the effect of PSF and TOF simulation on SUVmax	Gains in SNR were seen in both implementations, with the most significant gains seen for matched SUVmax post-filters.
Wielaard J et al. [13]	Phantom & patient (n=15)[R]	NEMA	Determination of minimum 68Ga-injected operation for clinical PSMA imaging studies	Method indicates that a maximum noise level of 25% is sufficient for the proper analysis and quantification of 68Ga-PSMA studies.
te Riet J et al.[14]	Phantom & patient (n=8)[R]	NEMA modified Micro Hollow Sphere (MHS) phantom	To determine the efficiency of BPL compared to OSEM+PSF in 18F-FDG studies acquired under specific clinical conditions using phantom and patient-based studies.	The efficiency of the BPL algorithm is superior to the standard OSEM+PSF algorithm in small lesion detectability.
Hoetjes NJ et al. [15]	Phantom & patient (n=25)[P]	NEMA	To assess the reliability of several PET-based PVC techniques for oncological whole-body 18F-FDG studies	PVC techniques can be used for more accurate, yet equally precise treatment response assessments.

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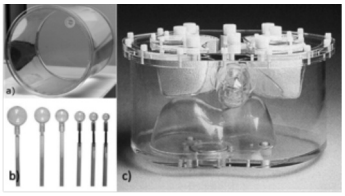
Author	Subjects	Phantom studies	Aim	Quality of finding
Lasnon C et al. [16]	Phantom & patient (n=52)[P]	NEMA	To analyse a strategy in patients imaged on a PET/CT system equipped with reconstruction of PSF.	This can be used in multicentre trials when using SUV for monitoring therapy or as a diagnostic or prognostic tool. This technique validated in NSCLC patients may be extrapolated to other solid tumours.
Karlberg AM et al. [17]	Phantom	NEMA	To conduct a specific quantitative comparison of the performance of PET image quality between PET/CT and PET/MR	The SUV measurements indicate good agreement for both systems.
Kaalep A et al. [18]	Phantom	NEMA	To report the results and impacts of the accreditation programme on the participating PET/CT systems.	Suggested analysis and upgrade to account for developments in acquisition and reconstruction technologies in PET/CT.
Ho Shon I et al. [19]	Phantom	Anthropomorphic Torso Phantom	To determine the minimum CT acquisition parameters required for maintaining the accuracy of AC for PET reconstruction.	The value of SUV COV was equal at higher CT exposures, regardless of reconstruction algorithm.
Boellaard R et al. 20	Phantom	Cylindrical phantom	To present a standardised imaging method for fixed FDG PET/CT data acquisition, QC and QA.	A new version of the guidelines only addresses combined or integrated whole-body 3D PET/CT systems.
Caribé P et al. [21]	Phantom & patient (n=1)[P]	NEMA	To evaluate different β-factors compared to a clinical post-filter kernel by using BSREM instead of OSEM.	The BSREM reconstruction algorithm provided the opportunity to minimise noise by a factor of 2–4 without a loss of contrast compared to OSEM reconstructions for all data evaluated.
Kaalep A et al. [22]	Phantom	NEMA Cylindrical phantom	To investigate the inconsistency of quantitative performance and the viability of quantitative harmonisation in 89Zr PET/CT imaging.	Harmonisation of PET/CT scanners for quantitative 89Zr studies is feasible when adequate cross-calibration scanner-dose calibration and harmonised image reconstruction procedures are followed. The accreditation programme for PET/CT scanners will support multicentre 89Zr quantitative studies.
Kero T et al. [23]	Phantom & patient (n=9)[P]	NEMA	To validate the simplified methods retention index (RI) and standardised uptake value (SUV). For quantification of cardiac 11C-PIB uptake in amyloidosis.	RI and SUV resulted in a high correlation with quantitative results from this kinetic model, using either individual or population average metabolite data.

(n)P: Prospective clinical study, (n)R: Retrospective clinical study, EARL: The EANM accreditation programme Research 4 Life, SUV: standardised uptake values, MATV: metabolically active tumour volume, TLG: Total lesion glycolysis, VOI: Volume of interest, EQ-PET: Siemens new technique of PET/CT filter, GE: General Electric company, SUL: SUV corrected for lean body mass, PERCIST: Positron Emission Tomography Response Criteria in Solid Tumour, SBR: signal-background ratio, BPL: Bayesian penalised-likelihood, OSEM: the ordered subset expectation maximisation, PSF: point-spread-function, TOF: time-of-flight, SNR: signal-to-noise ratio, PSMA: Prostate-specific membrane antigen, 68Ga: Gallium-68, NEMA: National Electrical Manufacturers Association, ACR: American College of Radiology, PET/CT: Positron Emission Tomography - Computed Tomography, PET/MR: : Positron Emission Tomography - Magnetic Resonance, QA: Quality assurance, QC: Quality control, AC: Attenuation-Corrected, NSCLC: Non-small-cell lung carcinoma, BSREM: Block sequential regularised expectation maximisation, 89Zr: zirconium-89, 11C-PIB: Carbon-11-labeled Pittsburgh Compound-B

Table II: The type of PET/CT phantoms used in the reviewed papers

Type of standard PET/CT phantoms	The description of PET/CT phantoms	The phantoms used in the reviewed papers
	**ACR phantom** Name: Esser Flangeless Deluxe PET Phantom™ This phantom meets the ACR requirements, which provide consistent performance information for PET/CT system. [26,27] This phantom is suitable for system performance evaluations such as collimator, artefacts, calibration, and reconstruction parameters, acceptance testing routine, quality assurance and control. [26,27]	Makris NE et al. [5] Texte E et al. [10]
	**NEMA phantom** Name: PET Phantom - NEMA 2012/IEC 2008 2012 NEMA Standards, ideal for whole-body PET. This phantom complies with NEMA 2012 Standard. Generally used to evaluate reconstructed image quality in whole-body PET and camera-based coincidence imaging and used in research. [24,25]	Kaalep A et al. [3] Makris NE et al. [5] Kelly MD and Declerck JM 6 Quak E et al. [7] Devriese J et al. [8] Akerele MI et al. [11] Armstrong IS et al. [12] Wielaard J et al. [13] te Riet J et al.[14] Hoetjes NJ et al. [15] Lasnon C et al. [16] Karlberg AM et al. [17] Kaalep A et al. [18] Caribé P et al. [21] Kaalep A et al. [22] Kero T et al. [23]
	**Other phantoms** Name: a) uniform fillable cylinder phantom, b) Micro Hollow Sphere (MHS) phantom, c) anthropomorphic phantom These phantoms are suitable for evaluating new image fusion software, evaluating new attenuation correction algorithms and particular specific research.	Makris NE et al. [5] Rogasch JMM et al. [9] te Riet J et al.[14] Ho Shon I et al. [19] Boellaard R et al. [20] Kaalep A et al. [22]

are calculated on reconstructed images with all corrections applied (attenuation, scatter, random counts, dead time and others).[28]

The difference between NEMA phantom and ACR phantom is the difference of fillable vials between them. NEMA phantom has six fillable vials with the shape of a sphere and the volume of the sphere is $4/3\pi r^3$. While ACR only has four fillable vials with the shape of a cylinder and the volume of the cylinder is $\pi r^2 h$. However, NEMA can give more information on uptake value since the image slice of the sphere keeps changing due to the difference in diameter. Compared to the ACR phantom with the vials of the cylinder, its diameter is fixed.

The reviewed articles used the anthropomorphic phantom, cylindrical phantom, and micro hollow sphere phantom for other phantoms. The function of the anthropomorphic phantom is utilised in the assessment of non-uniform attenuation and scatter correction techniques. The phantom has a wide body-shaped cylinder including the mimic parts of liver, lung and spine inserts, that is capable of simulating radioactivity distributions' anatomical structures for the upper torso of average to patients.[29]

Next, a micro hollow sphere phantom specialises in simulating small-scale hot or cold spherical vials and presenting a quantitative evaluation of spatial resolution of small object size effects and reconstruction methods. The phantom can also be utilised to evaluate the uniformity.[30] Finally, yet significantly, the cylindrical phantom is a water-filled cylinder phantom containing a uniform injected radioisotope solution like ^{18}F-FDG, ^{68}Ga or the others. This phantom can be used to assess uniformity.

Application of phantoms in PET/CT quantification studies

Quantification of uptake values has numerous clinical applications, including cancer diagnosis and staging. Especially in ^{18}F-FDG of PET/CT quantification, which portrays a crucial function in diagnosing and staging FDG-avid tumours.[31] Hoetjes NJ et al. demonstrated that the partial volume effects, which results in an increased underestimation of standardised uptake value with decreasing tumour volume, affected the quantitative accuracy and precision.[15] This affects the accuracy and precision of quantification of ^{18}F-FDG PET/CT. Therefore, the simulation and phantom experiments were performed to assess PVC's performance accurately corrected SUV of the

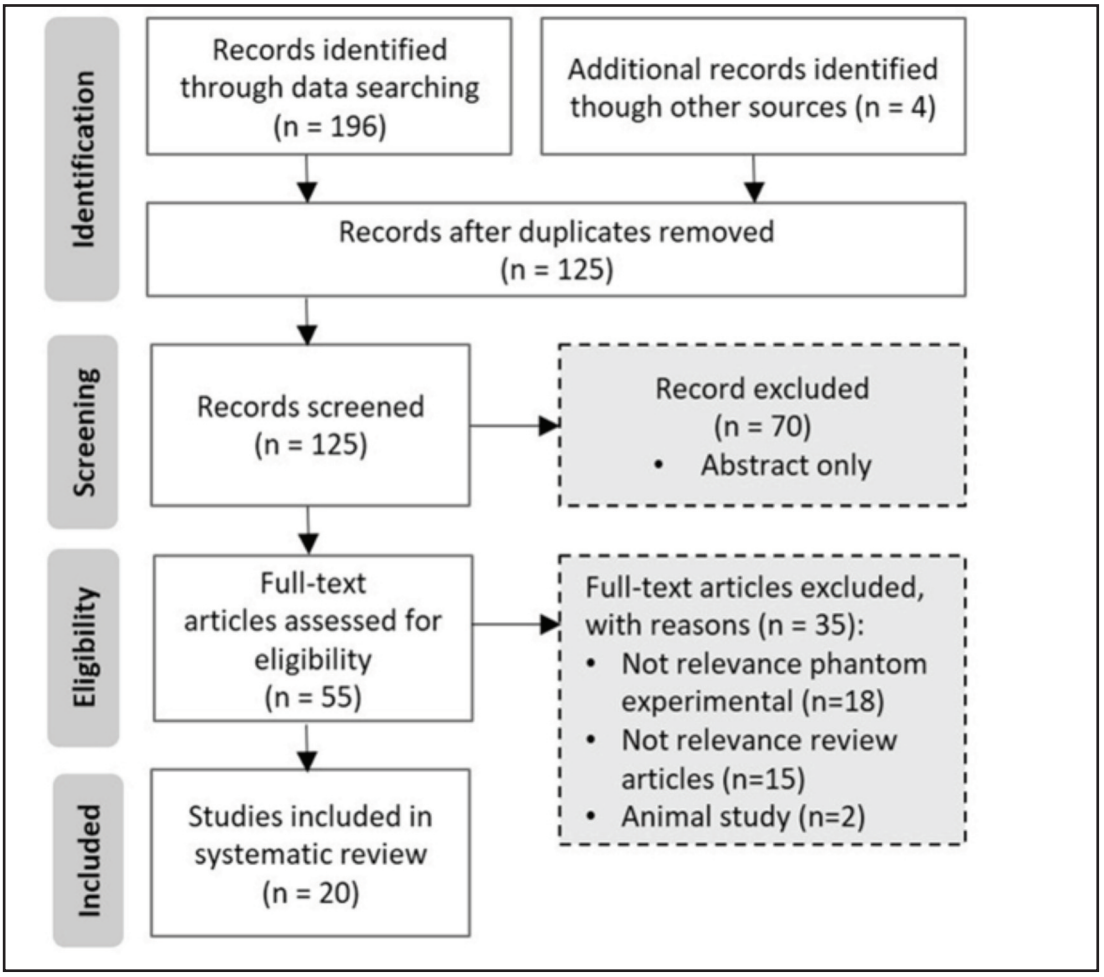


Fig. 1: PRISMA flowchart for PET/CT phantom studies selection process.

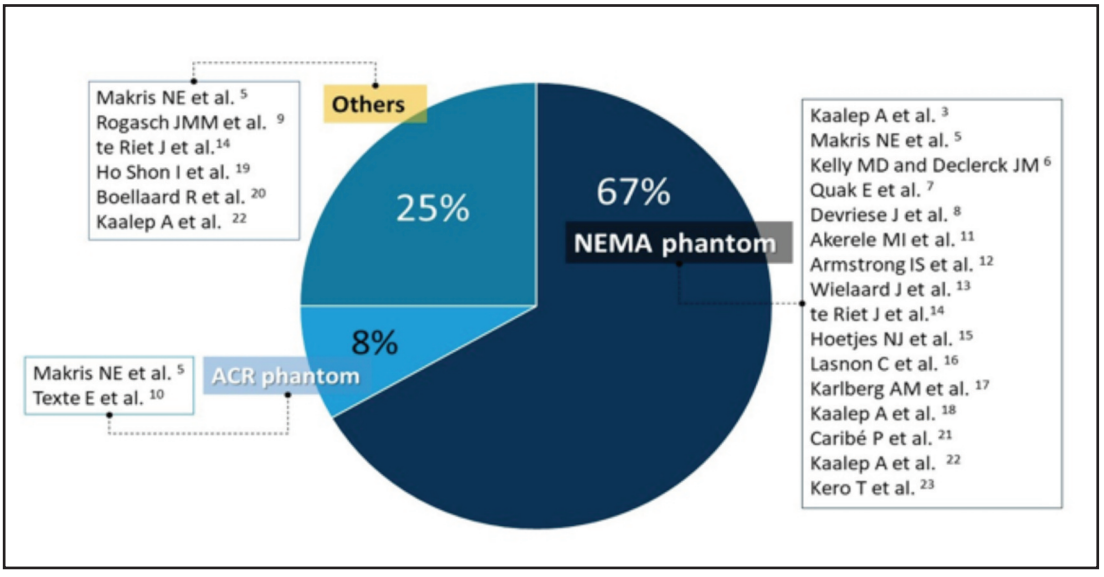


Fig. 2: Distribution of phantoms type used in PET/CT studies in reviewed articles.

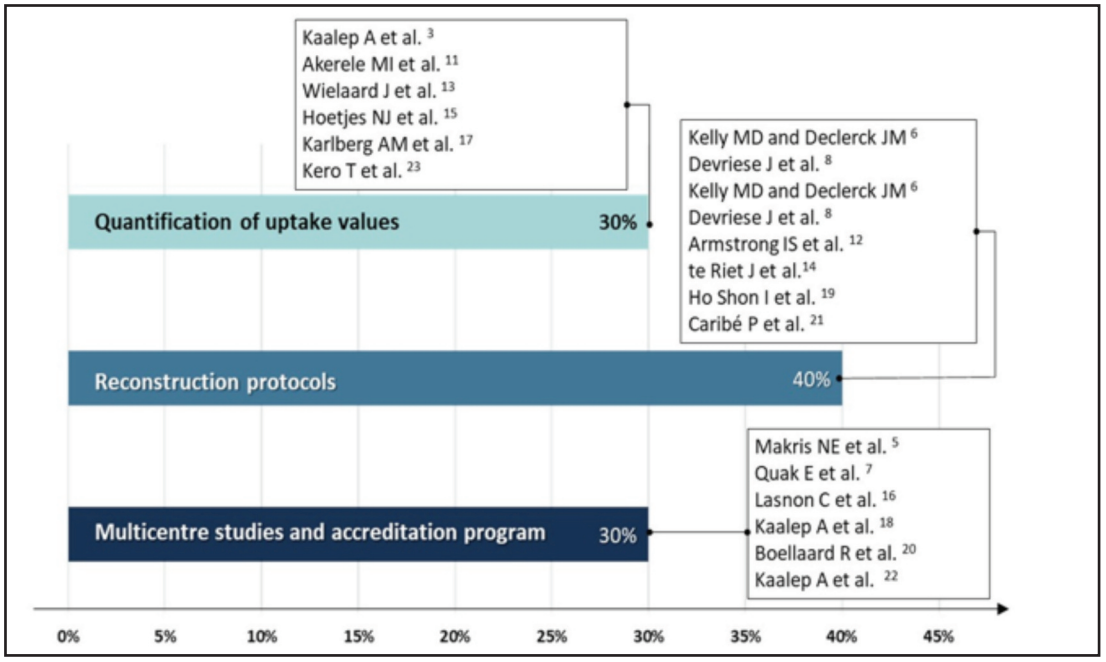


Fig. 3: The result of phantoms application in PET/CT studies.

tumour (sphere of phantom). As the spheres of the phantom are fixed, the results obtained by Hoetjes NJ et al. were consistent during the simulation. This proves that phantoms are acceptable and reliable for image quantification and interpretation.

Besides, Karlberg AM et al. showed the phantom's role in a study of the quantitative comparison of PET system performance between PET/CT scanner and PET/MR scanner.[17] They utilised NEMA phantom to run the performance of PET image quality. They reported that the mean of hot lesions for the systems was relatively similar, and the SUV quantifications showed an acceptable agreement for these two PET systems.[17] The experiment also used the same homogeneous NEMA phantom for the systems to prevent the heterogeneous activity ratios between spheres and background.

Therefore, many clinical researchers used phantoms as a combined experiment since the quantification of the phantoms is consistent. For a new tracer apart of ^{18}F-FDG, the phantom is capable of showing the reliability for image quantification. For example, Kero T et al. used 11C, and Wielaard J et al. used 68Ga in their studies.[13,23] Kero T et al. studied the SUV quantification 11C in cardiac clinical research.[23]

Wielaard J et al. presented the method to ascertain a noise level principle for ^{68}Ga-PSMA PET/CT imaging studies using NEMA phantom. The phantom results validated the significance of the recommended activity procedure on image quantification using 15 retrospective PET/CT patient scans.[13] The method determined that the minimum injected dose for clinical ^{68}Ga-PSMA imaging studies was acceptable for quantification and was also reliable for image interpretation of PET/CT. This shows the need for extensive phantom studies since there are no clear guidelines for tracer of ^{68}Ga-PSMA in PET/CT system, unlike the ^{18}F-FDG PET/CT guidelines that were well established. The ^{18}F-FDG PET/CT guideline will be discussed in the subtopic of "application of phantoms in multicentre and accreditation programme ".

Application of phantoms in multicentre studies and accreditation programme

Phantoms are routinely used as the first step of quality control in examining PET/CT systems to test a PET/CT system's performance, directly impacting the clinical outcome. Recently, many researchers put phantoms as the main subject in multicentre studies. The outcomes of their studies were managed to recommend the specific guidelines, standards, and accreditation programmes. Most researchers have growingly conducted multicentre studies of PET image quality of SUVs between phantoms and patient data throughout the past decade.[32]

Makris NE et al. confirmed that PET/CT institutions need to harmonise the scanners among the various institutions when conducting multicentre trials. All three of the different phantoms (NEMA, ACR and Anthropomorphic) tested in their study were suitable for harmonising various PET/CT scanners' quantitative performance in the Netherlands.[5] However, the article did not state any accreditation programme but suggested that PET/CT be harmonised, as the study was a multicentre PET/CT study.

In France, two articles demonstrated the multicentre study in tumour PET imaging. Quak E et al. used NEMA phantom and oncology patients (n=517) to perform optimal lesion detection.[7] They harmonised the quantification of lesion detection from a single PET acquisition and processed the data set. Meanwhile, Lasnon C et al. utilised NEMA phantom to study the harmonising SUVs in multicentre trials.[16] They followed the accreditation programme of the European Association of Nuclear Medicine (EANM) guidelines to harmonise quantitative values.

In addition, EANM proposed a new guideline of harmonisation of PET/CT – Version 2.0 as the "EANM Procedure Guidelines for Tumour Imaging: Version 2.0". This guideline's aim is to update the guideline version 1.0 that published in 2010.[20,33] Accuracy and precision are also crucial as ^{18}F-FDG PET/CT is utilised to assess tumour response and diagnosis, prognosis, and staging either in phantom or clinical purposes.[20] Besides, Kaalep A et al. reported that the EANM Research Ltd. (EARL) had collected more than 2500 phantom datasets from 200 PET/CT scanners and including 150 worldwide imaging institutions under project of PET/CT accreditation programme.[18] Under the EARL initiative, the EANM has been running an ^{18}F-FDG PET/CT accreditation programme to harmonise the quantitative PET/CT performance and assist multicentre nuclear medicine and research.

We find that the guidelines for ^{18}F-FDG tracer of PET/CT tumour imaging are well established. They utilised various phantom studies to establish the guidelines. However, the rest of the tracers, such as ^{68}Ga, ^{11}C and ^{89}Zr, demonstrate multicentre studies but still have not established any recommended guideline.[13,22,23] Kaalep A et al. suggested the immediate action to develop an applicable cross-calibration and accreditation programme to guide multicentre 89Zr quantitative studies.[22] Perhaps we will see the clarity of the accreditation programme in the future for the new PET/CT tracers rather than the ^{18}F-FDG only.

Application of phantoms in Reconstruction Protocol Studies of PET/CT

The reliance of PET/CT accuracy on quantitative uptake values obtained with different reconstruction protocols uses phantoms with uniformed geometry and activity preparation, presenting an acceptable estimation of clinical morphology and activity administration.[33] The phantoms are a beneficial benchmark of PET/CT scanner performance, integrating the effects of detector resolution, scanner sensitivity, the accuracy of the various corrections performed, and the reconstruction parameters used. For example, the number of iterations and subsets and post-filter smoothing reconstruction parameter. Reconstruction set-ups should be determined for PET/CT scanner capable of producing resolution recovery coefficients within the specified bounds to construct the images.[6] Therefore, Kelly M and Declerck J introduced a new reference standardised uptake value (SUVref) procedure in PET/CT reconstruction protocol by experimenting the NEMA phantom to minimise PET/CT scanner hardware variability.[6]

Devriese J et al. also introduced a new reconstruction protocol approach based on Q. Clear reconstruction criteria by utilising the NEMA phantom experiment and according to Belgian law. They are mainly used for the treatment response assessment. The harmonisation reconstruction protocol should be used as the reconstruction protocol for lesion detection using resolution recovery technique. This reconstruction protocol complies with the EARL programme specifications.[8]

Rogasch J et al. and Armstrong I et al. studied the impact of TOF and PSF reconstruction, focusing on phantom and lung lesions, respectively. Rogasch J et al. used cylindrical phantom to study the TOF and PSF reconstruction outcomes of uptake values.[9] While, Armstrong I et al. implemented the TOF and PSF reconstruction of NEMA phantom data with patient data. However, some minor variations in clinical data existed when TOF was implemented, which was not seen in phantom data, which required further study.[12]

Recently, a reconstruction algorithm method of Bayesian penalised-likelihood (BPL) has been established to produce images with enhanced signal-to-noise ratio and minimised noise compared to standard ordered subsets expectation maximisation (OSEM) algorithm.[35] Ishimori T et al. investigated the effect of Bayesian penalised-likelihood (BPL) PET reconstruction condition on quantitative parameters in FDG-PET/CT.[35] Nevertheless, it does not clarify how the condition of BPL reconstruction influences the quantification of clinical PET/CT.

Then, Riet J et al. presented PET/CT performance evaluation using Bayesian penalised-likelihood (BPL) reconstruction to study the realistic clinical conditions using phantoms-patient-based experiments. They used two types of the phantom which are NEMA and a modified micro hollow sphere phantom. They found that the BPL algorithm's performance is remarkable to the common OSEM-PSF algorithm in tiny and small-scale lesion detectability.[14]

Caribé P et al. also focused on the BPL reconstruction study of NEMA phantom and Belgian patient retrospective studies.[21] They found that BPL can minimise the noise compared to the OSEM reconstruction method. In 2020, Texte E et al. used different phantoms such as ACR phantom to evaluate PET/CT BPL reconstruction's effect in small lesion detectability using low contrast. Interestingly, they used ^{18}F-FDG and hypoxia tracers such as ^{18}F-MIZO and ^{18}F-FAZA.10 Interestingly, the result was consistent with all other previous papers studying this reconstruction algorithm.

Next, the reviewed article states the reconstruction protocol related to CT reconstruction instead of PET reconstruction. Ho Shon I et al. demonstrated the effect of CT reconstruction algorithms and acquisition parameters on attenuation correction for PET reconstruction. They undertook an anthropomorphic torso phantom study to assess CT acquisition parameters' impact with the lower dose. CT iterative reconstruction enhances image quality with lower exposures. Very low dose CT exposures are possible for accurate PET attenuation correction. They suggested that the scanner and reconstruction-specific validation should be employed prior very low dose CT for PET.[19]

Limitations and Future Approach

This systematic review has some limitations. One of the drawbacks is the search strategy, which included only original English-language research papers published between 2010 and 2020. As a result, the probability of sample bias exists in this study. We also acknowledge that the data presented was just a small data collection regarding the type of phantoms used for PET/CT imaging studies (n=20). However, this small data enables us to clarify the need of a system phantom for PET/CT imaging.

Furthermore, another factor limiting the efficiency of the systematic review is that it only coveres the homogenous phantoms study rather than the heterogeneous phantoms study. The heterogeneous phantoms can be used to simulate real clinical conditions. This could be the suggestion of improvement for future research.

Overall, the heterogeneity of phantoms in the literature suggests that further approach research is needed to study the recent advances in phantom development, especially in 3D phantom printing. We believe that further investigation will lead to better consistency in quantitative PET/CT hybrid imaging for diagnostic application. Perhaps, this can be implemented for other applications such as theranostics and dosimetry applications. In the future, this could pave the way for modern medical physics and molecular imaging field studies in Malaysia.

CONCLUSION

This review contributes an overview of the need for a system phantom for quantitative hybrid PET/CT scans despite limited guidance and literature about this topic. According to this review, the phantom study has a pivotal role in hybrid nuclear imaging of PET/CT either in technical aspects of the scanners (such as data acquisition and reconstruction protocol) or clinical characteristics of patients. This study identified the need for phantoms used within quantitative hybrid PET/CT scans, especially for quantification, optimisation, harmonisation and standardisation of PET/CT scanners.

Besides, the necessity to identify the suitable system phantoms to utilise within PET/CT scans by considering the continuous research and keeping ongoing to study a new phantom development. Researchers are encouraged to adopt efforts on phantom quantitative validation, including verification with clinical data of patients. Perhaps, researchers could take into consideration the continuing development of new phantom technologies innovation in the future.

CONFLICT OF INTEREST

We inform that there is no conflict of interest regarding the publication of this paper. We reported that all articles met the stated relevant requirements, but if some papers are missing, this was not intended and we would like to apologise to any authors.

ACKNOWLEDGEMENTS

We acknowledged the Ministry of Higher Education Malaysia via the Fundamental Research Grant Scheme (FRGS/1/2018/STG02/UPM/02/7) for support of publication expenses.

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SHORT COMMUNICATION

Geriatric Telemedicine: Ensuring continuity of healthcare services to the older patients in Kedah, Malaysia during the COVID-19 pandemic

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SUMMARY

Geriatric medicine practice requires a multidimensional and multidisciplinary assessment to provide a holistic overview of the older patients. During the current COVID-19 pandemic time, it becomes more critical to ensure that the elderly patients continue to receive regular geriatric care for their pre-existing chronic illness and at the same time avoid unnecessary exposure to COVID-19 virus. Geriatric telemedicine clinic provides a convenient solution to ensure continuity of care for the older patients. Careful patient selection, technical requirement, geriatric assessment via audio-visual communication, and caretaker involvement were among the important issues discussed in this article.

INTRODUCTION

The demand for geriatric medicine service has risen over the years, partly contributed by rapid development of healthcare-related technology that actualize longevity of human life. Older population is known to have multiple morbidity[1] with complex psychosocial issues. This requires a more comprehensive assessment and management to ensure their quality of life compared with the usual standard care.

The challenges of providing care to meet the complex needs of older patients enter a new chapter with the arrival of the novel coronavirus disease SARS-COV-2 (COVID-19) that originated from Wuhan, China that spread rapidly throughout the world.[2,3] Although the first wave of this deadly outbreak was handled successfully in Malaysia,[4] the second wave of COVID-19, which hit Malaysia in early March 2020, marked a bigger threat and changed the healthcare landscape of the country.[5] Following the implementation of Movement Control Order, Malaysians were advised to stay at home and avoid mass movements and gatherings.[6] Healthcare services have also been affected, including the disruption of regular clinic visits and limited services for non-emergency cases.

In response to the above situation, the geriatric team of Hospital Sultanah Bahiyah (HSB), Kedah state has initiated a Geriatric Telemedicine (GT) Clinic as an alternative to deliver the geriatric care for our patients. HSB is a government-funded tertiary centre situated at northern region of Peninsula Malaysia. This centre provides multidiscipline specialist services to the population of Kedah and nearby northern states. Telemedicine is defined as remote use of communication technology in exchange of medical information from one site to another with the goal of improving patient health.[7] The application of telemedicine in healthcare delivery has been long discussed but was hindered by several shortcomings such as internet connectivity particularly in suburban and rural areas. However, this COVID-19 pandemic has thrust the need for implementation of telemedicine in an accelerated way. The telemedicine service for geriatric patient in HSB was initiated in June 2020. Until the end of April 2021, 40 patients had enrolled into this service with majority were males (57.5%) and in the age group of 80-89 years (52.5%). The demographic and clinical characteristics of the patients are summarized in Table I. We would like to share our experience in setting up the GT service in HSB and simple solution to problem during the virtual consultation.

Patient selection and technical requirement

Careful case selection is the most crucial step in establishing a successful GT service.[8] There are two main aspects to be considered before offering GT service to the patients:

(I) Patient related factor – The patient should be an existing patient who has been under geriatric clinic follow up with stable chronic illness(es). They should not have vision or hearing impairment that is severe enough to interfere with the quality of communication during telemedicine session. Cognitively intact patients can be opted to join the telemedicine session alone or with the presence of their family member(s). Whereas cognitively impaired patients must be accompanied by their main care giver(s) during the telemedicine session.

(II) Availability of telecommunication device and internet connection – The patient or their care giver must have access to appropriate telecommunication device and stable internet connection at home, and they should have some degree of familiarity with the device's operation.

Verbal consent patients and caregivers to participate was obtained before enrolment. Appointment date and reminder for telemedicine session was then given to the enrolled patient and their caregiver through messaging platform application. The technical setup of the telemedicine is made to be reasonably simple. National language *(Bahasa Malaysia)* was used to communicate during GT session. Using their own devices (e.g. smartphone, tablet, computer),

This article was accepted: 26 May 2021
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Table I: Demographic and clinical characteristics of patients receiving geriatric teleconsultation between June 2020 till April 2021 at Hospital Sultanah Bahiyah

Characteristic	n	(%)
Age group		
60-69	7	(17.5)
70-79	10	(25.0)
80-89	21	(52.5)
90+	2	(5.0)
Gender		
Male	23	(57.5)
Female	17	(42.5)
Ethnicity		
Malay	22	(55.0)
Chinese	17	(42.5)
Indian	1	(2.5)
Main diagnosis		
Alzheimer's Disease	12	(30.0)
Vascular Dementia	6	(15.0)
Mixed Dementia	5	(12.5)
Advanced Dementia with Parkinsonism	4	(10.0)
Lewy's Body Dementia	3	(7.5)
Frontotemporal Dementia	1	(2.5)
Pseudodementia	1	(2.5)
Ischaemic Stroke with Unilateral Hemiparesis	2	(5.0)
Non-Traumatic Spinal Cord Injury	1	(2.5)
Cortical Basal Degeneration	1	(2.5)
Depression	1	(2.5)
Depressive Anxiety Disorder	1	(2.5)
Hypoactive Delirium	1	(2.5)
Lacunar Cerebral Infarct with Unilateral Hemiparesis	1	(2.5)
Number of telemedicine session attended by patient.		
1	17	(42.5)
2 - 3	17	(42.5)
4 - 5	6	(15.0)

patients and caregivers in their own homes are connected to the team in HSB via video conferencing platform (Figure 1) with only a click to a link without any need to download additional software. The link to the video conferencing is provided prior to the scheduled appointment. The video conferencing platform utilized provides highly secured video connection to ensure the privacy of the patients and protection of personal data.

Essential elements in geriatric telemedicine

During designing of the working frame for GT, three essential elements were adapted from normal clinic consultation: (I) involvement of multidisciplinary team, (II) administration of comprehensive geriatric assessment, and (III) engagement of patient's family member or caregiver.

(I) Involvement of multidisciplinary team

The involvement of multidisciplinary team in geriatric management have been recommended to ensure a holistic approach to the complex care needs for elderly persons.[9] Core team members for our GT clinic consist of a geriatrician, a trained geriatric nurse and a pharmacist. The presence of other allied health care professionals is optional depending on the need of the patients. Each team member can opt to meet in the same room during the session or join from their respective working station in the hospital.

(II) Performing comprehensive geriatric assessment

Comprehensive geriatric assessment is one of the hallmarks that differentiate geriatric consultation from other specialty, and this should be adopted and maintained as much as possible in GT service. The geriatric team will go through the past medical record of patients prior to the scheduled appointment to maximize the work efficiency during telemedicine clinic session. After confirming identities of the patients and caregivers, the team members will take turn to perform the assessment related to their roles which cover all

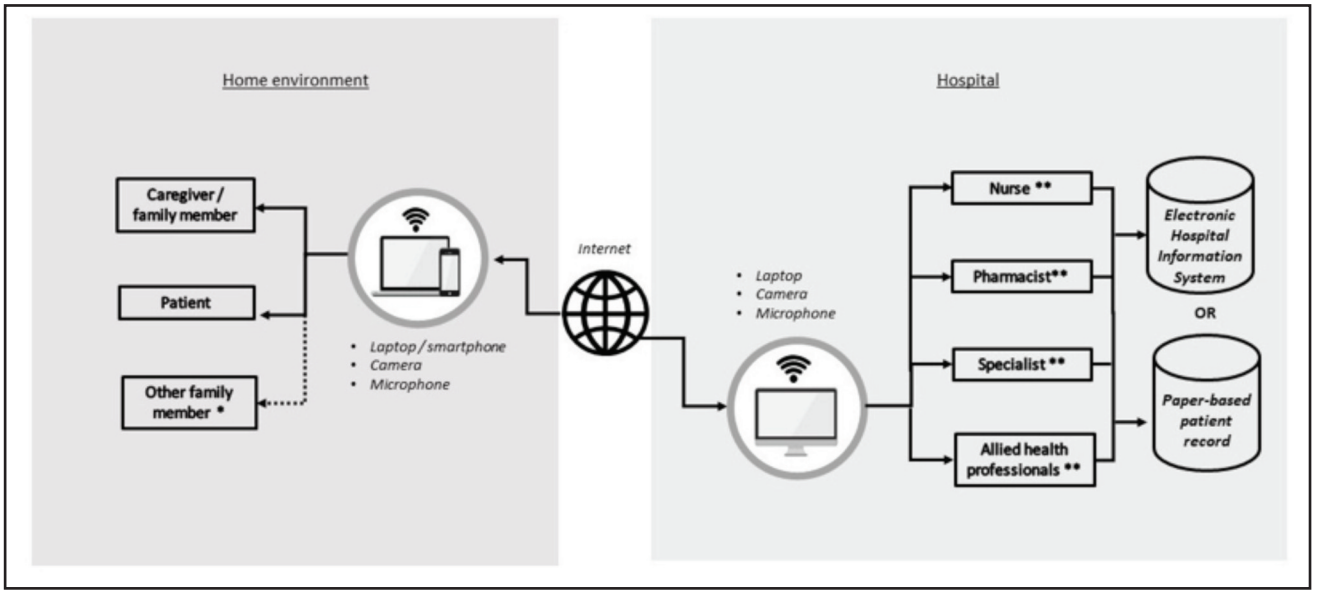

Fig. 1: The components and framework of geriatric telemedicine service in Hospital Sultanah Bahiyah, Kedah. * Patient family member other than caregiver residing in other location. ** Each team member can be in the same room or separate location during video conference.

aspects of care include medical, physical, functional and psychosocial. There was evidence to show that cognitive assessment and mood assessment done by audio-visual telecommunication on elderly were actually quite reliable and not much difference from face-to-face interview.[10]

The quality of the communication during telemedicine is heavily influenced by the device that were used by the patients despite stability of internet connection. There might be variations on what the patients saw and heard during telemedicine session depend on the resolution of the devices they used. Hence, patients were encouraged to wear their hearing aids and spectacles if needed to optimize their engagement during telemedicine session. To adapt to the absence of physical presence for assessment, flashcards were used where some phrases and pictures for cognitive assessment had been reprinted in larger size to ensure all patients are able to view it clearly for assessment. Additionally, caregivers were told to ensure patients are in a conducive and suitable environment to minimize distractions (e.g., turn off television), and maximize sound quality to smoothen the conduct of assessments.

(III) Engaging patient's relatives or caregiver

Input from the caregivers or family members who look after the geriatric patients is important, especially for those patients with cognitive impairment. The caregivers are encouraged to perform self-home monitoring such as blood pressure and capillary blood sugar. This record of home monitoring can be sent to the geriatric team via messaging platform application on the scheduled appointment date. Moreover, the caregivers can also send the photos of lab test results, wound or rash if there is any. All the photos sent were transferred and saved in HSB electronic medical record of the patients to keep it private and confidential.

Apart from main caregivers of the patients, other family members were invited to join remotely from a separate location with the consent of the patients. Treatment plan will be formulated according to the needs and conditions and informed to the caregivers and family members at the end of the session. The prescribed medication is later arranged to be collected by several convenient method of choice by patients such as drive-through or by postage to houses.

In a nutshell, the GT service is not difficult with minimal technical requirement, proper patient selection, committed caregivers and teamwork from multidisciplinary health care professionals. This service is a good kick start to provide continuation of care, reduce patients load in usual clinic and avoid unnecessary exposure to COVID-19 infection among the older patients.

This service has the prospect and potential to be adopted by other medical specialties to cater for patients who have difficulties to commute and attend hospital appointments. The virtual conduct of telemedicine also allows for easier access of family members to the clinical team that would benefit the wellbeing and satisfaction of the patients towards medical care services.

ACKNOWLEDGEMENTS

The authors would like to thank the Director General of Health Malaysia for his permission to publish this article. We also thank Rosnah Ahmad and Khor Lian Fen for their input on telemedicine clinic set-up.

FINANCIAL DISCLOSURE

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. None of the authors had any financial conflicts of interest.

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Letter to Editor

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Dear Editor,

Application of smartphone electrocardiogram (ECG) is gaining momentum worldwide. Its utility in a clinical setting was demonstrated by Ko and colleagues in their article published in the Medical Journal of Malaysia recently.[1] Monitoring patients at risk of prolonged QTc interval, which could increase risk of sudden cardiac death from malignant arrhythmias, is an important and relevant measure. Patients may be able to perform self-acquisition of a single-lead ECG using an easy-to-use smartphone ECG device, that is, by placing their fingers on the touchpad of the device.

The authors have justified the use of smartphone ECG for remote assessment of patients with COVID-19. I would like to add to the discussion: this approach of remote assessment of patients using smartphone ECG can be extended to monitor patients with infectious diseases other than COVID-19. In addition, the approach can be utilised by patients with non-communicable illnesses such as atrial fibrillation (AF) - an illness that affects 59.7 million people worldwide and confers a 5-fold increase in risk of stroke. Patients with AF who take antiarrhythmic medication to control their heart rhythm face the potential risk of QTc prolongation particularly during the initiation of antiarrhythmic drug therapy.[2] The smartphone ECG approach may be scaled up to reach larger population such as this group of patients with AF if the QTc interval could be computed by the smartphone ECG device, validated against a conventional 12-lead ECG device, and the clinicians and patients adopt the utility.

It is noteworthy that QTc interval varies with change in the body position of the user during ECG acquisition and the variation could potentially affect clinical decision and management.[3] The authors of the current study[1] reported that the attending physician and nurses were given the options to acquire ECG using a standard 12-lead ECG device or the handheld single-lead smartphone ECG device. However, the authors did not report the following information: (1) the number of ECGs acquired using each device, (2) the body position of the patients during each ECG acquisition, (3) subgroup analysis to examine variations in QTc measurements due to change in body position, and (4) which lead in the 12-lead ECG tracing was used to compute the QTc interval. The information is relevant and important. This study[1] involved 30 patients and it can contribute to larger case series analysis and systematic review in the future, which can inform relevant authorities in establishing or revising guidelines on QTc monitoring.

Thank you.

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CASE SERIES

Cardiac tamponade from peripherally-inserted central venous catheters in neonates: Three case reports

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SUMMARY

Pericardial effusion (PCE) and cardiac tamponade (CT) are rare but life-threatening complications of percutaneously-inserted central catheter (PICC) use in neonates. There is often a lack in index of suspicion in a neonate with sudden deterioration, resulting in high mortality. We describe a series of three cases of PICC-related PCE/CT in low birth weight infants whose timely diagnosis with echocardiography and pericardiocentesis led to successful resuscitation and survival. We suggest that echocardiographic skills to determine tip position and pericardiocentesis be taught in neonatal resuscitation programs to ensure good outcomes of this otherwise fatal complication.

INTRODUCTION

Peripherally-inserted central venous catheters (PICC) are routinely inserted in preterm infants for administration of total parenteral nutrition (TPN). Common complications include line-related sepsis, extravasation, migration of catheter and blocked lumen. Rarer complications include cardiac arrhythmias, pericardial effusion (PCE) and cardiac tamponade (CT). Incidence of CT associated with PICC is between 0.76 to 3.0% and results in high mortality of up to 50%.[1-3] From July 2017 to March 2020, there were three preterm neonates with PICC-related PCE/CT at the Department of Paediatrics, University Malaya Medical Centre (UMMC), Kuala Lumpur with no resulting mortality. All these three cases used the PICC from Vygon (Premicath size 1). We emphasize here on the importance of the position of the catheter tip and also explore ways to ensure its ideal placement. In low birth weight infants with PICC who present with sudden collapse, a high index of suspicion, early diagnosis of CT and prompt tapping can reduce mortality.

CASE REPORT

Case No. 1

A female infant was born at 30 weeks' gestation with a birth weight of 1120g. She was antenatally diagnosed with duodenal atresia. Amniocentesis was performed and karyotyping was normal. She was delivered preterm due to fetal distress and was stable at birth. To establish weight gain in preparation for reparative surgery, a PICC was inserted through the right basilic vein at day one of life. The catheter tip was reported to be at the cava-atrial junction from plain chest radiograph. The catheter had been in place for 13 days when the infant suddenly deteriorated with bradycardia and desaturation. Cardiopulmonary resuscitation was performed for one hour. Bedside echocardiography showed the presence of cardiac tamponade. Pericutaneous needle pericardiocentesis was performed in between chest compressions and a total of 26 ml of milky fluid was aspirated. The patient improved after pericardiocentesis. The PICC was immediately removed. Biochemical analysis of the fluid was consistent with TPN solution (Table I). Echocardiography done by the paediatric cardiologist the following day showed pericardial effusion mainly anterior overlying right ventricle around 5mm in deepest depth. Minimal effusion at the apex and posterior aspects was seen. No paradoxical right atrium or right ventricle collapse occurred. Poor left ventricular contractility was noted. A tiny patent foramen ovale was seen. A repeat echocardiography five days later showed resolution of pericardial effusion with normal ejection fraction of 78%. At eight weeks of life, the infant underwent duodenostomy and was discharged well at 12 weeks of life. The infant developed acute kidney injury associated with hypoxia due to cardiopulmonary collapse. She has chronic kidney disease and is under the monitoring of pediatric nephrology. The general physical and neurodevelopmental examination remained appropriate at three years corrected age.

Case No. 2

A male neonate was born at 31 weeks weighing 1560g. His mother presented in preterm labour and had a history of vaginal candidiasis two weeks earlier. He was stable at birth and required non-invasive ventilation support. The neonate developed necrotizing enterocolitis at day five of life and was kept nil by mouth. PICC was inserted for nutritional support. The PICC was sited at the left anterior cubital fossa and tip position was confirmed by chest X-ray. Five days later, the condition of the infant unexpectedly deteriorated. He was intubated and bedside echocardiogram performed showed cardiac tamponade. The infant collapsed during preparation for pericardial tapping and cardiopulmonary resuscitation was commenced. Return of spontaneous circulation was achieved after 30 minutes of cardiopulmonary resuscitation. Percutaneous needle pericardiocentesis was performed and 11ml of cloudy fluid was aspirated. The PICC was removed immediately. The fluid from the pericardial sac appeared turbid with fluid biochemistry consistent with TPN components (Table I). Echocardiography was repeated the following day showing normal heart structures with good biventricular function. Tiny pericardial effusion was seen next to the right ventricle. The infant was discharged well at day 33 of life and remained well at 12 months corrected age.

This article was accepted: 08 May 2021
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Table II: Score summary of MBI, IADL, EVS & O&M assessment at baseline and at 3 months visit

Case	Duration of onset of PCE	Observed PICC Tip position on chest x-ray	Type of Infusate through PICC	Pericardial Fluid Biochemistry				
				Trigly-ceride (mmol/L)	RBCs (uL)	WBCs (uL)	Glucose (mmol/L)	Protein (g/L)
1	14 days	Cavo-atrial junction	TPN, lipid	6.2	410	80	73.7	3.03
2	5 days	Right atrium	TPN, lipid, Cloxacillin, Amikacin	5.7	10	0	84.1	<0.01
3	2 days	Right atrium and adjusted to cavo-atrial junction	TPN, lipid, Penicillin, Gentamicin	3.3	39	3	45.4	3.3

PICC- peripherally-inserted central venous catheters; PCE- pericardial effusion; TPN- total parenteral nutrition

Case No. 3

A male infant was born at 30 weeks' gestation with a birth weight of 1090g. He was delivered premature due to maternal pre-eclampsia, intra-uterine growth restriction and abnormal Doppler. At day four of life, PICC was inserted at the right anterior cubital fossa. Chest radiograph post insertion showed the tip of PICC in the right atrium. The line was therefore re-sited to the cava-atrial junction. The infant developed recurrent apnoea requiring intubation by 48 hours post procedure. Antibiotics were started to cover for sepsis. Persistent tachycardia with muffled heart sounds heralded the suspicion of pericardial effusion, confirmed via bedside echocardiography. An ultrasound-guided percutaneous needle pericardiocentesis was immediately performed and a total of 6ml of serous fluid was aspirated. The PICC was removed immediately. Biochemistry findings was consistent with TPN fluid. Ten days later, echocardiography showed resolution of pericardial effusion. Patent foramen ovale was seen. The patient was discharged well at day 53 of life, with good neurodevelopmental outcomes during subsequent follow-up assessments.

DISCUSSION

The incidence of PICC-related PCE/CT were reported to be between 0.4 to 3%.[1,3] The incidence at UMMC was 1.5%. Although rare, early suspicion and detection are crucial due to its high mortality rate of up to 50%.1 Our case series demonstrated expeditious diagnosis of PCE/CT and rapid therapeutic intervention, resulting in good outcome of survival and good prognosis in all three cases. Having immediate access to an ultrasound machine where echocardiography could be performed quickly also aided in establishing the diagnosis early.

In preventing PICC-related PCE/CT, position of the tip of catheter is of utmost importance. It is recommended for the tip of catheter to be placed outside the cardiac chambers, at the junction of superior or inferior vena cava and right atrium, by 0.5-1cm for premature infants, and by 1-2cm in term infants on the chest radiograph.[4-6] Studies have shown that the catheter tip can migrate towards the heart with any movement of the limb and the risk for pericardial effusion is up to 80 to 90% if the tip is within the pericardial reflections on the chest radiograph.[2,3,6-8] Due to frequent catheter migration, Nadroo et. al. recommended serial radiographs twice a week as long as a PICC is in use.[2] In UMMC, plain AP radiograph is routinely used to confirm the position of PICC tip. Acceptable positions of tip of catheter were the cava-atrial junction or the right atrium. The first two cases had the tip of catheter within the cardiac silhouette and in the third case the tip was at the cava-atrial junction.

However, AP chest radiograph was found to have low sensitivity and specificity, at 32% and 89% respectively with significant inter-observer variability.[6,9] In case 1, the tip of catheter was reported by to be at the cava-atrial junction but was found to be within the cardiac silhouette upon review after the incident. A study found that of all lines interpreted to be in the right atrium or atrial/inferior vena cava junction using AP chest radiograph, 60% were found to be in the left atrium by echocardiography.[9] Echocardiography has been recommended as the best modality as it provides precise information regarding the tip position.[6,9,10] However, it is technician dependent and difficult to perform due to small body size of premature infants,[10] and an experienced neonatologist may not be present at the time of emergency.

In conclusion, any preterm infant with PICC who presents with unexplained sudden deterioration should have an echocardiogram performed by an experienced clinician to diagnose PCE/CT. Expeditious pericardiocentesis will avoid sudden death. Conversely, as the condition is rare, sufficient skills in determining PCE/CT and performing pericardiocentesis may not have been acquired. Therefore, patient safety demands for the following essential measures:

(1) Reinforcement of echocardiographic skills to detect pericardial effusion and to determine PICC tip positions.
(2) The integration of pericardiocentesis skills be taught in simulation modules in neonatal resuscitation programs.

ACKNOWLEDGEMENTS

No funding was received in the completion of this case report.

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Ocular leptospirosis in four patients: A diagnostic dilemma

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SUMMARY

Leptospirosis is a zoonotic disease that is caused by the pathogenic spirochetes of the genus *Leptospira*. The infection occurs worldwide and is particularly more common in the tropics. However, it is becoming a neglected re-emerging global health disease due to rapid urbanisation. This disease has a wide range of clinical manifestations from flu-like illness to pneumonia, acute kidney injury, etc. But many uncommon clinical findings are being reported as well. In this paper, we report four patients who presented initially with uveitic features who turned out serologically positive for *Leptospira* after extensive investigations.

INTRODUCTION

Leptospirosis is a zoonotic disease that is caused by the pathogenic spirochetes of the genus *Leptospira*.[1,2] Human infection with *Leptospira* occurs worldwide, and is particularly frequent in tropical areas where the climate is warm and humid.[3] The main animal reservoirs are rodents, livestock and dogs.[3] The disease can be transmitted to humans by direct or indirect contact with the urine of an infected animal through cuts or abraded skin, mucous membranes of mouth, ear, nose, or conjunctivae.[1] The clinical course of leptospirosis is an acute biphasic febrile illness with or without jaundice.4 In the acute leptospiraemic febrile phase, clinical features such as fever, chills, rigors, arthralgia, myalgia, pharyngitis, cough, headache, conjunctival suffusion and non-pruritic rash may be present.[5] The severity of illness varies from asymptomatic presentation to mild, moderate or severe. However, only a minor percentage are symptomatic therefore making the disease not adequately characteristic for an early diagnosis.[4] Resolution of the febrile phase occurs after four to seven days of the initial bacteraemia with rapid clearance of Leptospira from bloodstream by the immune system from all host tissues except immunologically privileged organs like the brain and eyes.[4] This results in immunological diseases like uveitis, which may be evident after two days and up to four years after the initial systemic febrile phase.[4] In this article, we report four patients who presented initially with uveitic features who turned out serologically positive for *Leptospira* after extensive investigations. The patients were all seen at the ophthalmology department of Hospital Raja Permaisuri Bainun, Ipoh.

CASE REPORT

Case 1

A 12-year-old boy presented with a week history of right eye redness with mild blurring of vision. He was systemically well previously. He gave a history of rodent infestations at home. Visual acuity was 6/9 over both eyes. Examination of the right eye revealed injected conjunctiva with streak of hypopyon with anterior chamber cells of four plus. Fundus examination was normal with no vitritis or retinitis. The left eye was normal. A working diagnosis of severe non-granulomatous anterior uveitis of the right eye was given. Steroid challenge with topical corticosteroids to the affected eye was administered and patient responded well. A series of investigations were done to look for the cause; which include infective and inflammatory factors (Table I). Serum for *Leptospira* Immunoglobulin M (IgM) antibody via latex agglutination was positive and further sent for microagglutination test (MAT) which showed a significant dilution at 1:400. The patient was treated with oral doxycycline 100 milligram (mg) twice daily for 14 days, topical cycloplegics and corticosteroids. The uveitis resolved and visual acuity returned to 6/6 at three weeks follow up.

Case 2

A 34-year-old gentleman complained of one week history of right blurring of vision. He was systemically well prior to the ocular complaint. He had a pet cat but denied rodent infestations at home. Right eye visual acuity was 1/60 while the left eye was 6/9. Relative afferent pupillary defect was present over the right eye. Examination of the right eye revealed mildly injected conjunctiva, anterior chamber cells of three plus, and anterior vitreous cells of two plus. Posterior segment examination revealed presence of vitritis, snow banking inferiorly, inferior blurred disc margin, retinitis and choroiditis at posterior pole with surrounding macula oedema (Figure 1a, 1b). The fellow eye examination was normal. Patient was investigated for causes of panuveitis with high suspicion of ocular toxoplasmosis due to having a pet cat (Table I). He was empirically treated with oral bactrim 960 mg twice daily, topical cycloplegics and corticosteroids while awaiting blood results. His blood results revealed positive *Toxoplasma* IgG and *Leptospira* IgM. MAT for *Leptospira* revealed a significant dilution of 1:400. Oral doxycycline 100 mg twice daily for two weeks and oral steroid 0.5 mg/kg/day in tapering fashion for six weeks were commenced. At six weeks' follow-up, there was resolution of panuveitis however the right visual acuity only improved to 6/60 due to central macula scar (Figure 1c, 1d).

Case 3

A 12-year-old boy was referred from the primary care centre for non-resolving right eye redness. He was systemically well prior to presentation. He has a pet cat at home with household rodent infestations. His visual acuity was 6/9 over

This article was accepted: 17 June 2021
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Table I: Investigations and results

Cases number	Case 1	Case 2	Case 3	Case 4
Full blood count	Unremarkable	Unremarkable	Unremarkable	Unremarkable
White cell count (per microlitre)	5,500	7,900	6,500	8,500
Erythrocyte sedimentation rate (mm/hr)	34	45	80	49
Renal profile	Normal	Normal	Normal	Normal
Liver function test	Normal	Normal	Normal	Normal
Anti-nuclear antigen (ANA)	Negative	Negative	Negative	Negative
Rheumatoid factor	Negative	Negative	Negative	Negative
Treponema pallidum hemagglutination (TPHA)	Negative	Negative	Negative	Negative
Toxoplasma gondii	Negative	IgG*: positive	Negative	IgG: positive
Bartonella henselae	Negative	Negative	Negative	IgM*: 1:24 (by IFA*)
Leptospira (MAT*)	1:400	1:400	1:800	1:4000
Mantoux test (cm)	0	0	0	0
Chest X-ray	Unremarkable	Unremarkable	Unremarkable	Unremarkable

*IgG: Immunoglobulin G, IgM: Immunoglobulin M, IFA: Immunofluorescence assay, MAT: Microscopic Agglutination Test;

both eyes. He had right eye circumcorneal pattern injection over the conjunctiva, moderate to severe cells in the anterior chamber, fine white keratic precipitates at the inferior half of the corneal endothelium with posterior synechiae at 12 and two o'clock hours' position. The fundus examination was unremarkable; there was no disc swelling, retinitis, choroiditis or vitritis. The contralateral eye examination was normal. A provisional diagnosis of right severe non-granulomatous anterior uveitis was given. Blood for infective markers and routine screening for connective tissue diseases were taken (Table I). He was started on topical corticosteroids and cycloplegics. Serum for *Leptospira* Ig M antibody via latex agglutination was positive and MAT showed positive titre of 1:800. Patient was planned for oral doxycycline commencement; however, he defaulted follow-up.

Case 4

A 26-year-old gentleman presented with left central visual field defect which was preceeded by 10 day history of fever. He had significant weight loss of two kilograms within one week during the ailment. He has a domestic cat at home, however he denied being scratched. Right eye visual acuity was 6/9 while the left eye visual acuity was 2/60. Relative afferent pupillary defect was present over the left eye. Anterior segment of both eyes were normal. The posterior segment examination of the right eye revealed choroiditis proximal to the superior and inferior arcades while on the left eye there was a swollen optic disc with a partial macula star and choroiditis at the posterior pole (Figure 2a, 2b). A working diagnosis of bilateral eye posterior uveitis with left neuroretinitis was given. Patient was treated along the line of cat scratch disease. While waiting for the results of the blood investigations (Table I), patient was empirically treated with intravenous ceftazidime for 10 days. There was improvement in vision and reduction of disc swelling and macula oedema after antibiotic commencement. Subsequently, *Leptospira* IgM came back positive with a very significant MAT dilution of 1:4000. Oral doxycycline 100 mg twice daily for 14 days was started. At one-month follow-up, visual acuity improved to 6/9 over left eye with resolution of central scotoma. Right eye vision remained at 6/9. Clinical findings showed resolved left optic disc swelling with residual hard exudates over the macula and a reduction in choroiditis lesion over the right eye (Figure 2c, 2d).

DISCUSSION

Ocular involvement of leptospirosis is observed in both the systemic bacteraemic and immunological phase. The incidence of ocular manifestations during acute leptospiraemic phase varies from 2% to 90%.[2] The ocular signs may be subtle and therefore overlooked. Leptospiral uveitis was first reported by Weil in 1866 in his original article and subsequently, several authors found its varying presentations.[2] The features of leptospiral uveitis is typically of an acute and non-granulomatous, and tends to be either mild and anterior or severe and diffuse.[4] Leptospiral uveitis can present with a broad spectrum of clinical manifestations which includes iritis, iridocyclitis, papillitis, membranous vitreous opacities, vasculitis and panuveitis.[2] It may occur as a single self-limiting episode or recurrent episodes and as a unilateral or bilateral presentation.[2]

The patient in case 4 presented with the classical biphasic illness of leptospiral infection; where he was initially in a febrile phase and subsequently went into immunological phase 10 days later with bilateral eye posterior uveitis and left eye neuroretinitis. Patients in cases 1, 2 and 3 presented with uveitis without prominent systemic manifestation. It is possible patients in this group had a mild febrile illness which they did not realise. This is consistent with previous studies who mentioned that most cases of leptospirosis are mild or subclinical and are usually self-limiting.[1,2]

The disease courses of cases 1, 2, and 3, however, posed a diagnostic challenge to the clinicians as the aetiologies of uveitis are very wide including inflammatory, infective or masquerade. Therefore, a thorough history taking with age of patients taken into consideration will narrow down the working diagnosis. As Malaysia is a tropical country, Leptospirosis, Toxoplasmosis or cat scratch disease is considered as one of the differentials that must not be missed in infective uveitis.

Since the clinical signs are not pathognomonic of leptospirosis, laboratory testing is indicated for confirmation of diagnosis. Presence of Leptospira IgM antibodies in blood serum is not useful to suggest an acute infection as the IgM antibodies may remain detectable for several years after the first inoculation. Positive results should be referred for confirmatory testing. The 'gold standard' diagnostic test is

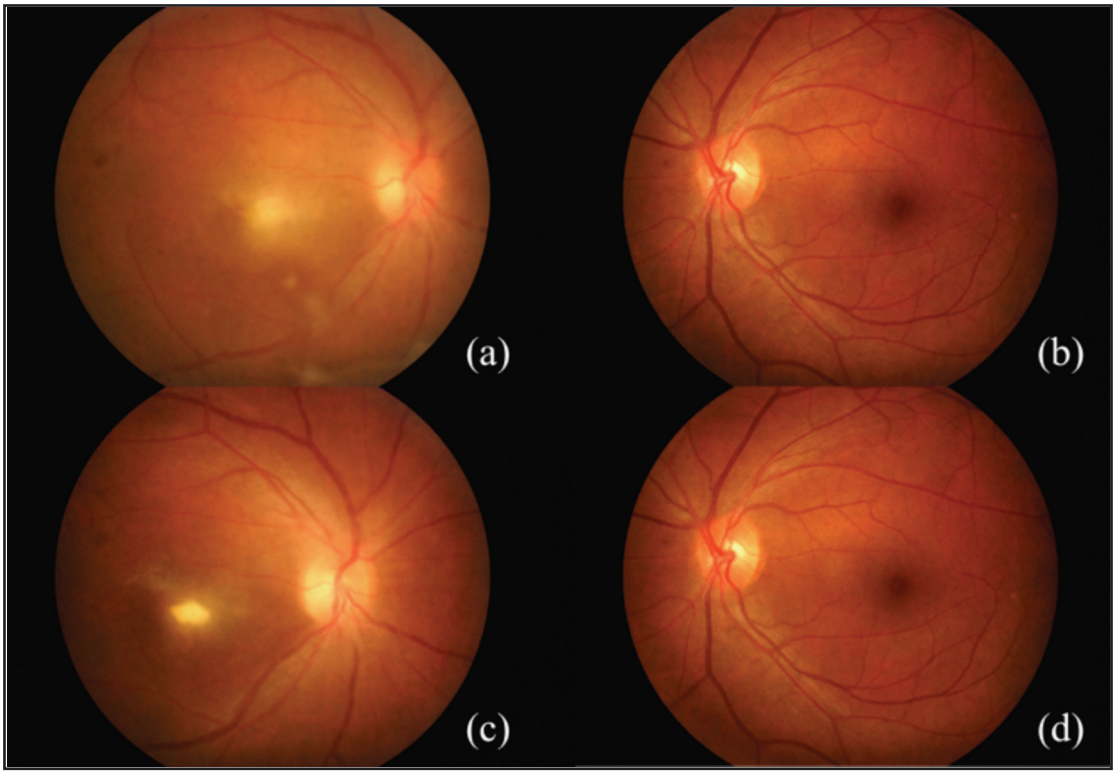

Fig. 1: Fundus photo of right eye at presentation (a) when media is hazy due to vitritis (arrows point to areas of retinitis and choroiditis). Normal fundus photo of left eye at presentation (b). Fundus photo of right eye at six weeks (c) when media is clearer than at presentation due to resolution of vitritis (arrow points to central macular scar). Normal fundus photo of left eye at six weeks (d).

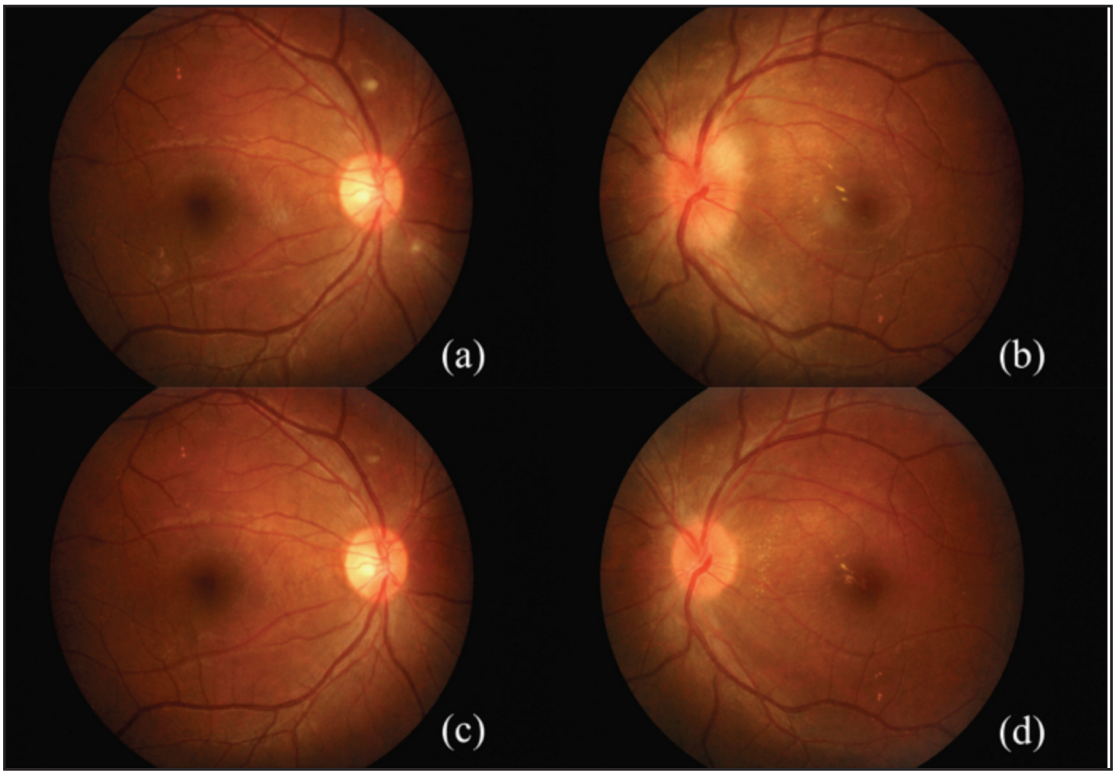

Fig. 2: Fundus photo of right eye at presentation (a) with arrows indicating choroiditis. Fundus photo of left eye at presentation (b) with oblique arrow points to swollen optic disc, vertical arrow points to partial macular star with macular oedema and horizontal arrow point to choroiditis. Fundus photo of right eye at six weeks (c) with resolving choroiditis at the superotemporal arcade (arrow) and resolution of choroiditis at inferonasal arcade. Fundus photo of left eye at six weeks (d) with resolution of optic disc swelling and macular star.

MAT which uses a battery of antigens taken from common (frequently locally endemic) Leptospira serovars.[3,5] MAT titre of ≥400 in single sample, or a four-fold rise in paired samples (between acute and convalescent period) are considered positive for MAT.[5]

Antimicrobial therapy is indicated for severe leptospirosis, but its usage is controversial for mild leptospirosis.[5] The majority of leptospirosis infections are self-limiting in the absence of antimicrobials. Antimicrobial therapy shortens the duration of illness and reduces shedding of the organism.[5] Doxycycline, ampicillin, or amoxicillin has been regarded as the treatment for mild to moderate leptospirosis.[3] For severe leptospirosis, treatment of choice include intravenous penicillin G or third-generation cephalosporins such as cefotaxime and ceftriaxone.[1,3,5] As for immune-related ocular complications such as uveitis, corticosteroids are the basis of treatment.[4] Corticosteroids may be administered in the form of topical, periocular, or systemic and is supplemented by topical cycloplegics.[4]

The diagnosis of leptospirosis may be missed due to its non-characteristic clinical presentation in majority of cases. However, as leptospirosis is a disease of the tropics, it is important this diagnosis be considered in patients presenting with uveitis from this region.

ACKNOWLEDGEMENT

The authors would like to thank the Director General of Health Malaysia for the permission to publish this case report.

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Selective use of Peptide Receptor Radionuclide Therapy following comparative imaging of Ga-68 DOTATATE PET/CT against I-131 MIBG scintigraphy in a small Asian cohort of Adult Neuroblastoma

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SUMMARY

Adult neuroblastoma (AN) is rare with an extremely poor prognosis. No standard therapy exists for this entity and treatment options are limited in recurrent or refractory disease. ^{131}I-MIBG has been used in combination with myeloablative therapy before autologous bone marrow transplantation or in a salvage therapy setting. However, myelotoxicity is a dose-limiting factor in heavily pre-treated patients and response is not always sustained. Somatostatin receptor scintigraphy and theranostics with radiolabelled somatostatin receptor analogues are becoming more commonplace with the recognition of these receptors in over 90% of neuroblastoma cells. We describe three AN patients assessed for somatostatin receptor status and the novel use of ^{177}Lu-based peptide recep-tor radionuclide therapy (PRRT) in two of them and a literature review.

INTRODUCTION

We describe the use of ^{68}Ga-DOTATATE PET/CT to evaluate disease in three adults with histologically-proven neuroblastoma, in a prospective trial approved by the SingHealth Central Institutional Review Board (CIRB 2016/DNMP/001). Written consent was obtained from all patients. Scans were read by two blinded Nuclear Medicine Physicians independently and findings graded on a visual scale and analyzed on a per lesion basis. Consensus agreement was reached whenever discrepancies arose. On the basis of scan findings, two patients subsequently underwent treatment with PRRT on a compassionate basis with tumour board approval.

CASE REPORT

Patient 1

The first patient was an 18-year-old female with high-risk metastatic retroperitoneal neuroblastoma. Staging [^{18}F]FDG PET/CT and ^{131}I-MIBG scans showed a large hypermetabolic retroperitoneal mass, left supraclavicular and retroperitoneal adenopathy with bony metastases. Histology of abdominal tumour showed poorly differentiated MYCN non-amplified neuroblastoma, with 11q deletion and *ATRX* loss. Bone marrow biopsy showed 80% involvement. ^{68}Ga-DOTATATE PET/CT showed more lesions than ^{131}I-MIBG scan (Figure 1). She received standard induction chemotherapy. MIBG scan showed partial response (Curie score from 26 to 20), and bone marrow involvement <5%. She continued with chemotherapy and high dose ^{131}I-MIBG therapy (15mCi/kg bw) followed by consolidation with autologous stem cell rescue and radiotherapy, then post-consolidation immunotherapy (dinutuximab beta) and isotretinoin. She had stable disease after ^{131}I-MIBG therapy (Curie score 20), and partial response after the consolidation and post-consolidation phase (Curie score reduced to 10). However, one month later, she developed new abdominal tumours. She underwent resection and salvage chemo-immunotherapy. Unfortunately she had further disease progression in the marrow. She underwent a second round of MIBG therapy (15mCi/kg bw) followed by haploidentical stem cell transplant and immunotherapy. Repeat ^{131}I-MIBG scan (Curie score 18) showed increased bone metastases and no tracer uptake on ^{68}Ga-DOTATATE PET/CT scan. Her performance status deteriorated, and she succumbed to disease 35 months from initial diagnosis.

Patient 2

The second patient was a 32-year-old male with high-risk metastatic retroperitoneal neuroblastoma. [^{18}F]FDG PET/CT scan showed hypermetabolic retroperitoneal tumour, lymphadenopathy and liver metastases. Histology confirmed *MYCN* amplified, ALK-positive neuroblastoma. Bone marrow showed 30-40% involvement. He received chemotherapy and [^{18}F]FDG PET/CT showed partial response. Bone marrow involvement improved to 5-10%. ^{131}I-MIBG scan showed uptake in abdominopelvic, left supraclavicular lymphadenopathy and hepatic metastases, but failed to show extensive bony metastases seen on ^{68}Ga-DOTATATE PET/CT. He underwent salvage high dose ^{131}I-MIBG (12mCi/kg bw) followed by autologous stem cell rescue. Post-treatment 131I-MIBG and [^{18}F]FDG PET/CT scans showed decreased size of adenopathy, while hepatic metastases remained MIBG-avid (Curie score remained 2). In addition to

This article was accepted: 20 June 2021
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Table I: Patient age, stage of disease, tumour characteristics, ^{68}Ga-DOTATATE PET/CT and ^{131}I-MIBG scan differences, and survival outcomes

Patient No.	Age at diagnosis (yrs)	INRGSS Stage of disease at diagnosis	Tumour *MYCN* amplification	Tumour ALK positivity	Resection of primary tumour	Number of lesions on ^{68}Ga-DOTATATE PET vs ^{131}I-MIBG scan			^{68}Ga-DOTATATE PET Krenning score	^{131}I-MIBG scan Curie score	SUV$_{max}$ of primary lesion	SUVmax of most DOTATATE-avid metastatic lesion	% Bone marrow involvement peri-scan	Survival since diagnosis
						Scan time point	^{68}Ga-DOTATATE PET scan	^{131}I-MIBG scan						
1	18	M	No	No	Gross total resection	Staging	111	30	2	26	11.6	15.6	80	
						Post-induction	33	22	1	20	Resected	4.0	< 5	
						No paired ^{68}Ga-DOTA-TATE PET scan performed with Post-consolidation ^{131}I-MIBG scan								35
						Disease progression	0	N.A.*	0	18	Resected	None	Unknown	
2	32	M	Yes	Yes	Not performed	Staging	25	5	2	2	15.6	17.0	30-40	18
						Post-consolidation	29	3	3	2	20.6	15.9	5-10	
3	37	M	No	Yes	Gross total resection	Staging	41	1	3	0	11.7	15.3	60-70	19
						Post-consolidation	26	4	3	4	Resected	20.3	20-30	

INRGSS = International Neuroblastoma Risk Group Staging System
*Diffuse bone metastases which were not quantifiable as discrete lesions; better assessed with Curie score as a measure of proportion involvement.

these, ^{68}Ga-DOTATATE PET/CT also showed extensive bony disease. After extensive consultation and in view of limited stem cell support, he received PRRT (183.6 mCi ^{177}Lu-DOTATATE). However, five weeks after PRRT, [^{18}F]FDG PET/CT scan showed disease progression, with new intracranial metastases. He developed neutropenia and pneumonia, and died 2 weeks later.

Patient 3

This patient was a 37-year-old male with high-risk metastatic mediastinal neuroblasto-ma. [^{18}F]FDG PET/CT showed hypermetabolic right posterior mediastinal mass, supraclavicular adenopathy and bone metastases. Mediastinal mass biopsy revealed *MYCN* non-amplified ALK-positive neuroblastoma and bone marrow biopsy showed 60-70% involvement. ^{131}I-MIBG scan showed only faint uptake in the primary tumour. ^{68}Ga-DOTATATE PET showed tracer-avidity in all sites and more bony lesions than ^{131}I-MIBG scan (Figure 2). He underwent chemotherapy and resection of the primary tumour, followed by high dose chemotherapy with stem cell transplant and radiotherapy. Bone marrow involvement reduced to 20-30%. However, a few months later, there were new [^{18}F]FDG-avid bone lesions. Again, the ^{68}Ga-DOTATATE PET/CT detected more bone lesions than [^{18}F]FDG and ^{131}I-MIBG scans. Bone marrow biopsy showed 90% involvement. He received PRRT (163.7mCi of 177Lu-DOTATATE) and developed pancyt-openia 3 weeks later. [^{18}F]FDG PET/CT showed mixed response. Multidisciplinary consensus was that the cytopenias were more likely due to disease progression in the marrow. Salvage Alectinib therapy was given, but his pancytopenia worsened. Repeat [^{18}F]FDG PET/CT showed disease progression in liver and bone. He died a month later.

DISCUSSION

Adult neuroblastoma (AN) is exceedingly rare and carries an extremely poor prognosis. No standard therapy protocol exists for adults with neuroblastoma and treatment options for recurrent or refractory multifocal high-risk neuroblastoma are limited. Radionuclide therapy using ^{131}I-MIBG has been used in the salvage setting, either as a single modality or in combination with myeloablative stem cell transplantation. Upfront incorporation of ^{131}I-MIBG therapy into the high-risk neuroblastoma induction backbone is currently being studied by the Children's Oncology Group, as it was observed to be effective as neoadjuvant treatment in advanced neuroblastoma[1,2].

However, myelotoxicity is often dose-limiting, especially in heavily pretreated patients, and response often not sustained. There is therefore a need for development of other therapeutic options, particularly for those who have either failed ^{131}I-MIBG therapy or with low uptake of ^{131}I-MIBG. Somatostatin receptors (SSTRs), particularly subtype 2, found richly expressed in most neuroblastoma cells, raise the possibility of using radio-labelled somatostatin analogs for diagnostic imaging (^{68}Ga-DOTATATE PET/CT) and radionuclide therapy (PRRT) in neuroblastoma.

Although ^{123}I-MIBG remains recommended for imaging norepinephrine uptake, due to its unavailability, ^{131}I-MIBG was used instead. Patients 1 and 2 showed high uptake in DOTATATE and MIBG scans, hence both opted for MIBG therapy initially as this is the more established treatment. Patient 1 then had minimal somatostatin receptor uptake on re-staging scan and became ineligible for PRRT, highlighting a possible "flip-flop" phenomenon, while Patients 2 and 3 underwent PRRT later.

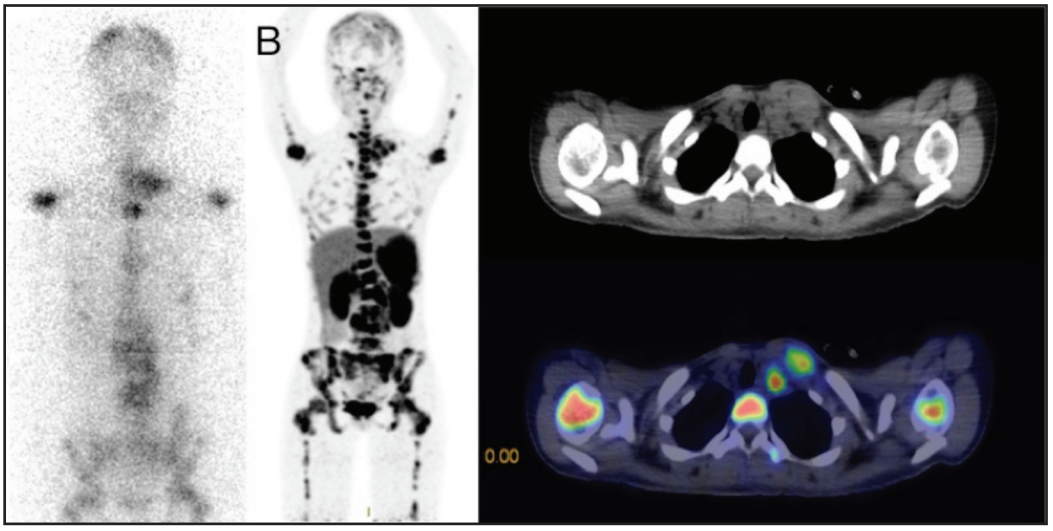

Fig. 1: Comparative imaging evaluation of extent of disease of Patient 1 at initial diagnosis. Anterior planar image of staging ^{131}I-MIBG scan (A), showing fewer lesions compared to maximal intensity projection image of ^{68}Ga-DOTATATE PET/CT (B); representative axial ^{68}Ga-DOTATATE PET/CT images of tracer-avid left supraclavicular adenopathy and bony lesions (C).

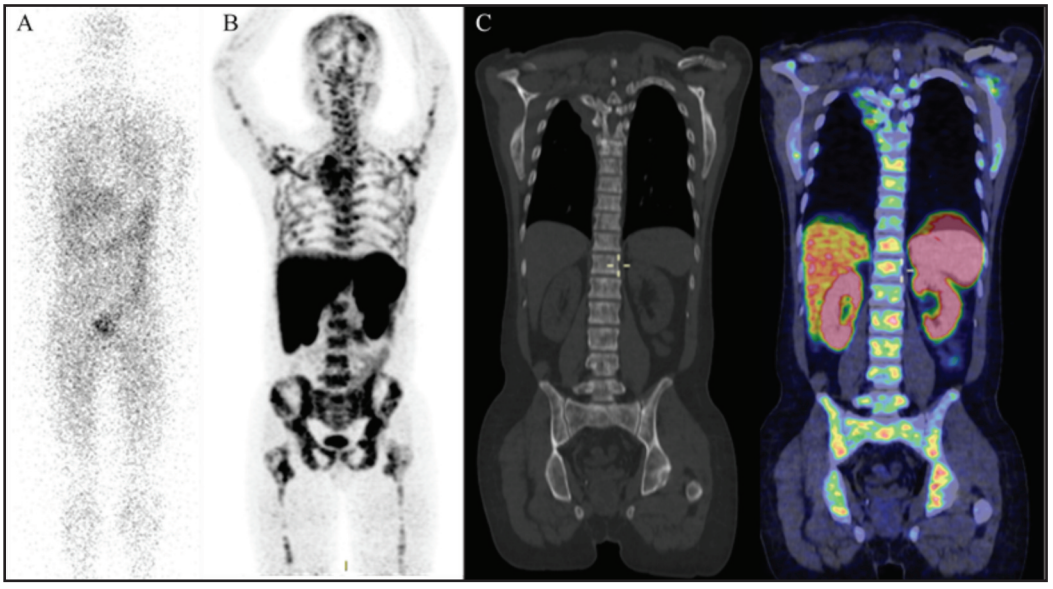

Fig. 2: Comparative imaging evaluation of extent of disease of Patient 3 at initial diagnosis. Anterior planar image of staging ^{131}I-MIBG scan (A), showing fewer lesions compared to maximal intensity projection image of ^{68}Ga-DOTATATE PET/CT (B); representative coronal ^{68}Ga-DOTATATE PET/CT images of tracer-avid bony lesions (C).

Patient 2 received ^{131}I-MIBG therapy initially with good effect. He opted for PRRT sub-sequently as bridging treatment before another ^{131}I-MIBG therapy due to limited autologous stem cell support. The basis for this approach was that PRRT may cause less myelotoxicity than ^{131}I-MIBG. This concept may suggest a new indication for PRRT in future: as an alternative or combinational therapy, reserving more myelotoxic MIBG therapy for later as salvage therapy.

Patient 3 had fewer lesions and faint uptake in MIBG compared with DOTATATE scan. Thus, after high dose chemotherapy and stem cell transplant, he received PRRT instead of ^{131}I-MIBG. The patients, stage of disease and tumour characteristics are shown in Table I.

The sensitivity of ^{68}Ga-DOTATATE PET/CT appeared superior to ^{131}I-MIBG scan on a per lesion basis in our series. This is attributable to PET's superior resolution over gamma imaging and the inferiority of iodine-131 compared to iodine-123.

Of our two PRRT patients, both developed pancytopenia within 6 weeks. While the temporal relation suggests PRRT-related myelotoxicity, both patients developed leukoerythroblastic picture and repeat imaging showed disease progression, suggesting the myelosuppression was in larger part due to disease than PRRT. However, we acknowledge the definite risk of myelotoxicity post-PRRT and long-term risks of mye-lodysplastic syndrome and acute

leukemia. Risk factors such as baseline cytopenia, bone metastases, multiple prior therapies, prior alkylating agents (e.g. Busulfan and Melphalan which our patients received) and radiotherapy increase risk and severity of post-PRRT myelotoxicity.[3] Dosimetry-based individualization of PRRT should continue to be explored, to achieve tumoricidal radiation dose to lesions without substantially increasing toxicity to healthy tissue.

One possible confounder for the poor survival of our 2 patients was the severity of their disease when given PRRT. Before PRRT, Patient 3 already had 90% bone marrow involvement while patient 2 had extensive liver and osseous disease. Moreover, these 2 patients already had high risk metastatic disease according to the International Neuroblastoma Risk Group Staging System, with additional poor prognostic factor of ALK positivity, and *MYCN* amplification.

Studies of ^{68}Ga-DOTA-conjugate imaging and PRRT in neuroblastoma

There are limited reports of somatostatin receptor imaging, and none of PRRT, in AN.

A case series comparing the ^{123}I-MIBG and ^{68}Ga-DOTATOC imaging in the diagnosis and staging of metastatic pheochromocytoma and neuroblastoma showed that amongst neuroblastoma patients (n=5), the sensitivities of ^{68}Ga-DOTATOC and ^{123}I- MIBG on a per-lesion basis was 97.2% and 90.7%, respectively.[4]

Two other case series successfully demonstrated that ^{68}Ga-DOTATATE can be used to image pediatric neuroblastoma and identify suitability for ^{177}Lu-DOTATATE PRRT, yielding response without significant toxicity.[5,6] Gains et al found that amongst 8 children with relapsed or refractory high-risk neuroblastoma, 6 had uptake on ^{68}Ga-DOTATATE PET/CT equal to or greater than the liver and received several administrations of ^{177}Lu-DOTATATE PRRT.[5] Kong et al compared ^{68}Ga-DOTATATE scans of 8 children with refractory neuroblastoma with their MIBG imaging. ^{68}Ga-DOTATATE PET showed additional disease in 3 of the 8 patients, and upstaged 1 patient by detecting marrow involvement. 5 patients had tissue samples available, and immunohistochemistry showed moderate or strong SSTR2 expression with an intensity score 3-4 on the ^{68}Ga-DOTATATE PET/CT. In 6 patients, ^{68}Ga-DOTATATE uptake was higher than background liver, 4 of whom were given PRRT on the grounds of progressive, symptomatic disease.[6]

In these studies, some ^{68}Ga-DOTATATE scans identified additional sites of disease not seen on MIBG imaging, suggesting ^{68}Ga-DOTATATE PET/CT may be more sensitive, and there might be an admixture of tumour cell populations expressing both norepinephrine transporters and somatostatin receptors. PRRT can potentially be used in combination with MIBG therapy to concomitantly target both types of neuroblastoma cells.

Role of ^{68}Ga-DOTATATE for prognostication

Despite differences between somatostatin receptor imaging and MIBG scans, there remains a potential prognosticating role for radiolabelled somatostatin analogs.

A clinicopathologic study showed that favorable histology neuroblastoma had significant positivity for SSTR1, SSTR2 and SSTR4, and expression of SSTR1 and SSTR4 was significantly higher in the surviving cases.[7] ^{68}Ga-DOTATATE radiopeptide has a predilection for SSTR2 receptors, hence its uptake implies higher SSTR2 density on neuroblastoma cells while no uptake may suggest other SSTR subtypes. It was previously shown that SSTR expression correlates well with survival, and neuroblastomas with unfavourable stage showed positive somatostatin receptor scans less frequently than tumours of more favourable stages, and *MYCN* amplification (associated with poorer prognosis) correlated with absent somatostatin receptor expression.[6,8-10]

Unexpectedly, our Patient 2 had unfavourable metastatic stage and *MYCN* amplification, yet positive somatostatin receptor scans. If larger studies find correlations between individual SSTR subtypes and survival, 68Ga-DOTATATE uptake can potentially be a novel prognostic marker for neuroblastoma.

Advantages of ^{68}Ga-DOTATATE imaging

Radiolabelled somatostatin analogue imaging has practical advantages over MIBG imaging as discussed by Alexander et al.[11] Firstly, plasma clearance is quicker with SSTR analogues (^{68}Ga-DOTATATE 2 hours, ^{123}I-MIBG 2 days), allowing injection and imaging to be done within 1 day rather than 2 days required for MIBG. Half-life of ^{68}Ga-DOTATATE is shorter than both ^{123}I-MIBG and ^{131}I-MIBG, time required for ^{68}Ga-DOTATATE PET/CT is about half that of MIBG scan. There is less patient preparation for DOTA-conjugated PET/CT than for MIBG scan (Lugol's solution to block free iodide uptake and avoidance of diet and medications that interfere with MIBG uptake). ^{68}Ga-DOTATATE also exposes patients to less radiation than ^{123}I-MIBG and [^{18}F]FDG PET.

CONCLUSION

Outcomes of AN are dismal. Treatment response to radionuclide therapies has been shown superior in older, compared to younger, neuroblastoma patients.[12] There are fewer systemic toxicities compared with conventional chemotherapy. While it is challenging to conduct randomized controlled trials on radionuclide therapies in high-risk neuroblastoma, more research is necessary to investigate: (i) the sensitivity and specificity of ^{68}Ga-DOTATATE PET/CT for staging, (ii) the potential use of PRRT earlier before multiple treatments compromise critical organ reserves, and (iii) combination therapy with MIBG, especially in patients where an admixture of tumour cells exists expressing either one of these receptors. Meanwhile, PRRT will remain at best an investigational or compassionate use salvage therapy option.

ACKNOWLEDGEMENTS

Funding: SingHealth Foundation (Grant no. SHF/FG652S/2015)

The authors would like to thank the study team clinical research coordinators, radiography staff of the Department of Nuclear Medicine and Molecular Imaging, Singapore General Hospital, and the SingHealth Foundation for their support.

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CASE REPORT

Improving management of visually impaired patients from occupational therapy perspective: A case report

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SUMMARY

The ability to detect and recognise visual deficits among visually impaired patients can improve the management of daily living skills and activities of these patients. In this report, the importance of using objective and subjective visual performance measures by occupational therapists in managing visually impaired patients is discussed. We describe a case of a 17-year-old Malay female who had vision impairment due to a cataract, a secondary complication from diabetes mellitus (DM). The Brain Injury Visual Assessment Battery for Adult (biVABA) can provide occupational therapists with additional visual performance information and a better understanding of managing visually impaired patients. The biVABA was used in conjunction with other activities of daily living skills tools such as Modified Barthel Index (MBI), Lawton Instrumental Activities of Daily Living Scale (IADL) and EVS Orientation and Mobility Screening (EVS-O&M) for a more holistic assessment. This approach provides more relevant and essential information in managing visually impaired patient rehabilitation from the occupational therapy perspective.

INTRODUCTION

Visual impairment affects all aspects of daily activities, from the simplest self-care tasks, to the ability to continue to drive safely and return to work.[1] Managing daily life in people with visual impairment can be challenging. Therefore, it is critical to recognise the changes that require visual skills to manage their daily activities. Deficits in visual processing are generally not significant as long as they do not affect occupational performance. Treatment of patients with visual impairment should focus not only on maximizing residual vision but also on improving functional abilities to perform daily activities. Therefore, a comprehensive occupational therapy assessment is essential and must be integrated into rehabilitating patients with visual impairment.[2] There are many objective measurement tools to assess visually impaired patients such as Modified Barthel Index (MBI), Lawton Instrumental Activities of Daily Living Scale (IADL) and EVS Orientation & Mobility Screening (EVS-O&M). However, most tools did not provide holistic visual information especially visual functional abilities. Specific visual performance such as visual acuity, visual field, reading ability, contrast sensitivity function, oculomotor function and visual attention could be measured using the Brain Injury Visual Assessment Battery for Adults (biVABA).[3] This paper will discuss the use of biVABA and how it can assist in managing visually impaired patient using a case study.

CASE REPORT

A 17-year-old Malay girl was referred to the Occupational Therapy Clinic, Universiti Kebangsaan Malaysia (UKM), for rehabilitation. She was diagnosed with diabetes mellitus (DM) type-1 for five years and suffered from dilated cardiomyopathy (DCM). She had cataract secondary to DM and underwent crystalline lens aspiration of the right eye (RE) at 14 years old and later developed blindness due to the surgery complications. She had high myopia in the left eye (LE). She was prescribed insulin twice daily. There was no family history of other medical conditions except DM. She is currently on regular follow-up for her DM. Her main complaints at the occupational therapy session were 1) blurred vision at distance and near, but she had never used or was prescribed any visual aids, 2) disorganisation in managing personal items, and 3) difficulty with orientation and mobility. Her academic performance has deteriorated since Form 2, and currently attending Form 5 in a residential special school for the blind.

During examination with the biVABA, the Clinical Observation Indicating Visual Impairment component showed her LE pupillary responsiveness to light stimulation and accommodation was constricted plus sluggish. Her unaided distance vision for RE was light perception (LP), while for LE was 6/48, and no improvement with pinhole. Vision for both eyes was 6/48. With the addition of +10.00 Ds, she was able to read N26 at 10 cm. On functional contrast sensitivity testing, she recognised target numbers only at the 25% level. Visual field assessment with the two-person kinetic confrontation test was measured, and the peripheral visual field in the LE appeared to be impaired (Figure 1).

The general result of her basic visual function tests from biVABA indicated that her pupillary response was affected. This resulted in her eyes being slow in adapting to changes in illumination. In addition, reduced visual acuity, visual field extend and contrast sensitivity function resulted in difficulty to identify visual details. This led to below average reading

This article was accepted: 24 April 2021
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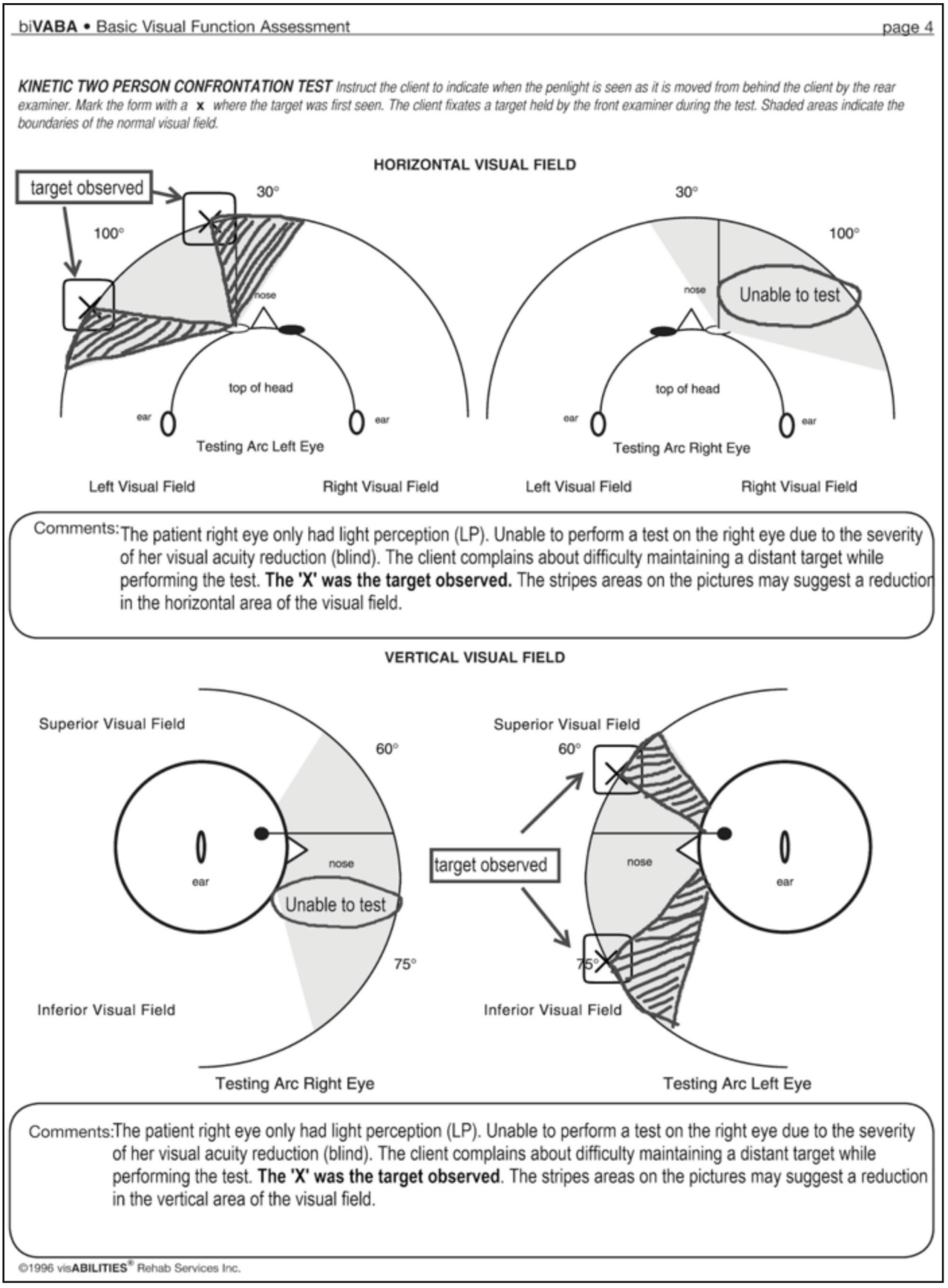

Fig. 1: Visual Field - Kinetic Two Person Confrontation Test

Table I: Summary performance for Visual Attention Assessment of the biVABA

Categories		Search pattern	Time (Norm Average in seconds)	Correct Response (Norm Average in %)	Functional Effect
I. Search strategies for Near Space:					
i) Single Letter Search	Simple	Symmetrical horizontal left to right pattern [1]	288[2] (82)	50[3] (97)	May indicate of difficulty in reading and writing skills
	Crowded		300[2] (112)	40[3] (97)	
ii) Word Search			358[2] (88)	27[3] (98)	
iii) Random Plain Circles	Simple		78[2] (23)	90[3] (100)	
	Crowded		105[2] (49)	85[3] (100)	
iv) Structured Complex Circles Search		Random, no predictable pattern [1]	143[2] (52)	50[3] (99)	
II. Attention to Visual Detail: Design Copy					
House Flower Clock		Using ineffective search strategy for this test	78 (27)[4] 62 (27)[4] 67(27)[4]	1 detail is missing from each drawing[5]	May indicate of presence with inattention and difficulty in reading and writing
III. Search Strategies for Extra Personal Space					
Scan board[6]		Randomly & unpredictable. Initiated from left to the right side.	N/A	All targets are located but had one number was being repeated.	May indicate of memory deficits, difficulty in reading and writing

[1] Using effective and systematic searching strategies for all subtests in near space except for the structured complex circles search.
[2] Overall times performances were impaired.
[3] Overall correct response performances were below average.
[4] Overall times performances were impaired.
[5] Analysis data for correct response of the design copy using norm cut off % (1 error). If more than 1 error is indicating of low performance.
[6] The target number was bold to increase visibility.

Table II: Score summary of MBI, IADL, EVS & O&M assessment at baseline and at 3 months visit

Assessments Tools	Total marks	Baseline 1st assessment mark (%)	3 months 2nd assessment mark (%)	Percentage of Improvement (%)
Modified Barthel Index (MBI)	100	96 (96)	96 (96)	0
Lawton Instrumental Activities of Daily Living Scale (IADL)	8	3 (37.5)	5 (62.5)	25
EVS Orientation & Mobility Screening (EVS O&M)	25	15 (60)	17 (68)	8

speed performance. Furthermore, a significant mobility problem was observed as she could not see overhead signs and floor paths to navigate safely. She was referred to low vision clinic and was prescribed a pair of spectacle magnifiers with +10.00 Ds for near work and a monocular 3x telescope for distance usage.

The eye movement test showed unequal corneal reflections when the eyes moved. She could not fixate on a target or object at 40 cm but able to do so at 25 cm. The RE was always in an upward position, and the LE did not follow the pen torch smoothly. In addition, an unequal ratio or proportion of sclera to iris was observed in each gaze. All findings in the Oculomotor Function Assessment of the biVABA indicated restricted movement of both eyes in all directions of gaze, suggesting paresis or paralysis of the muscle. She also reported difficulty achieving focus during near vision tasks that required her to maintain focus. These findings also suggest possible problem with binocular vision issues. The patient suffered from nausea and blurred vision during head movements suggested visuo-vestibular dysfunction and was referred to the Ear, Nose and Throat Clinic for further investigation and treatment.

In the Visual Attention Assessment of the biVABA, the search strategies for near space, attention to detail and search strategies for the client's additional personal space were measured objectively along with subjective observation. When performing the near-space search strategies, the client was tested using an electronic table magnifier and a closed-circuit television (CCTV) system. Results showed a decrease in reading performance while using both types of equipment and a significantly increased difficulty in maintaining attention. However with effort, she was able to maintain concentration for an extended period. These findings suggest that her attention skills were generally adequate and her difficulties were visual. The search strategies for extra personal space showed that she had a random, slow and unpredictable search pattern, with scanning initiated from left to right. These findings are summarised in Table I. This

deficit in visual tracking makes her community ambulation unsafe, leading to anxiety and restlessness during this activity. Besides, it also affected her in reading and written work. During the rehabilitation session, she was informed and explained about the importance of environmental modifications in reading, optimising ambient lighting, reducing glare, increasing print size and contrast. She was also taught on scanning techniques, using eccentric vision and visual perception activities. The scanning exercise involved in getting her to look frequently and consistently in the direction of her blind right side. Therapy sessions were held twice a week for four weeks.

The MBI score was 96/100, indicated that she could perform all tasks independently but still required some level of supervision, especially in personal hygiene to achieve an adequate level of cleanliness. Using the IADL skills questionnaire, she scored 3/8, able to do her laundry and perform simple household chores. She was able to do some shopping, such as buying groceries at a special school mini-mart and managing her medications with caretaker assistance. She was not confident going up the stairs and sometimes bump into objects in all directions, even in a familiar environment. These findings were consistent with her IADL low scores. Furthermore, she was unable to perform any meal preparation or use public transportation for traveling. Her EVS-O&M score was 15 and she was recommended to undergo orientation and mobility training. She completed the training however, she was unwilling to use the white cane.

After three months, the patient returned for follow-up. A routine functional assessment was performed, MBI, IADL, EVS-O&M screening were repeated. Discussion with the attending optometrist revealed that visual acuity and visual field status for LE was unchanged. The IADL score was 5/8, indicating that her ability to shop and do simple food preparation had improved. However, she required assistance when using public transportation and money management. The MBI score remained the same, while the EVS-O&M score increased to 17/25 (Table II). These findings indicate she was able to avoid moving objects before contact while travelling. She also accepted and used her white cane in her daily activities. The orientation and mobility training enabled the patient to participate more confidently in outdoor activities and travel independently. Follow-up was recommended to the patient six-monthly at the occupational therapy and low vision clinics to monitor her progress.

DISCUSSION

Typically, the visual function status and visual efficiency assessment are not considered in routine occupational therapy assessment[2] or at follow-up occupational therapy clinic sessions in Malaysia. Without acknowledging the importance of visual efficiency, this can reduce responsiveness to rehabilitation programmes and interfere with overall progress.[4] From this case study, using biVABA enables the occupational therapist to identify the difficulties during academic classes the patient experienced such as reading and writing with varying degrees of severity. These findings were in agreement with previous study which recommended that it is vital for the therapist to understand visual acuity, accommodation, binocular vision and ocular motor abilities in a typical elementary school classroom.[5] Previous study also have found that 75% of academically related task time in the classroom is spent on reading, writing at a near distance and on tasks requiring near to distance to near alternate viewing. Children with vision impairment usually performed significantly weaker on educational tests compared to normal children.[6]

Comprehensive occupational therapy assessment on visual function of low vision patients is an essential aspect during rehabilitation because visual impairment can affect the quality of life.[2,3,5] The visual impairment suffered by this patient was blind in RE and mild low vision in LE. Based on the eyes' binocularity, the visual impairment was considered in the range of mild to moderate with loss of depth of perception. However, the impact of the vision impairment on her daily activities was profound. This can be seen where the patient experienced difficulty moving around in a community setting and in daily activities despite only having mild to moderate visual impairment. The low scores of the IADL and the EVS-O&M assessment support these findings.

When the quality of life declines, the patient's motivation to participate in social activities may also reduce. Subsequently, the low vision patient tends to withdraw from families, friends and society which can eventually accelerate further mental health problems.[7] Rehabilitation programmes helped the patient improve her ability to cope with her daily activities. After three months of rehabilitation, her score for MBI, IADL, and EVS-O&M screening showed significant improvement. These achievements motivated the patient to be engaging more with her daily activities and improve her quality of life. Therefore, in order to develop and implement an effective facilitative or rehabilitative programme, therapeutic techniques and functional activities need to be individualised and cater to their visual needs and capabilities of the visually impaired patients.

CONCLUSION

This case study demonstrated that using biVABA during the initial assessment of the low vision patient helped the occupational therapist to be able to identify unrecognised visual deficits which were normally not being access by the occupational therapist. The biVABA also guided all subsequent referrals by the occupational therapist to the relevant clinics. Furthermore, it provides a more holistic understanding of the visually impaired patients' visual status, behaviour and task performance needs. By combining the biVABA, MBI, IADL, and EVM-O&M assessment occupational therapists will be able to provide a more comprehensive and appropriate rehabilitation plan tailored to the visually impaired needs to improve their daily living skills and quality of life. In conclusion, it is recommended that the biVABA assessment to be added during the initial case assessment. The information gathered would enhance the occupational therapists' ability to understand how each visual function affects the patient's daily activities and quality of life. Only then a proper rehabilitation can be prescribed from the perspective of occupational therapists.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

RO designed the construct, rewrote and critically reviewed the manuscript, NR examined the patient, analysed, interpreted investigative data and prepared the manuscript, MW examined and implemented intervention, SK critically reviewed investigative data and manuscript. All authors have read and approved the final manuscript.

ACKNOWLEDGEMENT

The authors would like to thank the Optometry & Vision Science Program and Occupational Therapy Program, Faculty of Health Sciences, UKM, to provide the facilities.

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Lymphocutaneous sporotrichosis of the abdominal wall: A lesson in lymphatic drainage

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SUMMARY

Cutaneous sporotrichosis (CS) presents as asymptomatic lesions of varied morphology. The most common variant is the lymphocutaneous type which typically progresses from a papule to an ulcer and then forms nodules along the superficial lymphatic channels. Diagnosis CS may be challenging when the lesion presents at an uncommon site where the superficial lymphatic drainage is unfamiliar. We present here a case of sporotrichosis of the abdominal wall which was initially misdiagnosed as an abscess but later confirmed by culture and managed successfully.

INTRODUCTION

Sporotrichosis a deep fungal infection secondary to *Sporothrix schenckii* is found in plants, soil or on animals. In contrast to superficial fungal infections caused by the tinea or candida species, this infection affects the subcutaneous tissue, hence present with a different morphology. Lesions develop when the fungus gains entry through cuts, wounds or even microtrauma in the skin, commonly on exposed areas such as the hands, feet and the face.[1]

S. schenkii commonly causes localized infections and occasionally systemic infections especially among immunocompromised individuals. Cutaneous sporotrichosis manifests clinically as lymphocutaneous, fixed and disseminated morphological variants. Lymphocutaneous sporotrichosis is the most common variant, accounting for about 70 to 80% of cases. We report here a case of sporotrichosis presenting at an unusual site challenging the initial clinical diagnosis.

CASE REPORT

A 62-year-old man presented with an asymptomatic ulcer and multiple nodules on the abdominal wall for 2 months. The lesion initially started as a single papule which later developed into a pustule. The lesion gradually enlarged and broke down in the centre forming an ulcer with serous discharge. Later, a few new lesions appeared around the first lesion. The patient denied any animal bite, scratch or injury at the site. He was fond of gardening and frequently worked shirtless in the garden due to the hot climate. He was otherwise well and had no other medical problems. The lesion was initially suspected to be bacterial in origin and he was treated with cap cloxacillin 500mg four times a day for one week. When there was no improvement, he was prescribed Tab Augmentin 500mg twice daily for a week. He was then referred to the dermatologist for second opinion when there was no response to the antibiotics.

On examination, a non-tender oval ulcer measuring 4cm x 2cm x 0.5cm was noted on skin of the abdominal wall at the left hypochondrium. The ulcer margin was indurated, irregular and there was slough at the base. A few dusky nodules were seen radiating from the main lesion towards the left and the right nipple (Figure1).

Axillary and inguinal lymph nodes were not palpable. A presumptive diagnosis of deep fungal infection was made and patient was subjected to skin biopsy and culture. Histopathology of the skin showed, spongiotic dermatitis with superficial, deep and peri-adnexal lymphocytic infiltrations. PAS staining was negative for fungal bodies and the immunofluorescent studies was negative. *S. schenckii* was isolated from tissue culture while bacterial and mycobacterium cultures were negative. The patient was treated with oral Itraconazole 200 mg twice daily for three weeks. The wound healed leaving a small hypertrophic scar and post inflammatory hyperpigmentation macules at the site.

DISCUSSION

Localized sporotrichosis of the abdominal wall is very rare with only a few cases reported.[1,2,3,4] It usually occurs on the limbs and face as these areas are vulnerable to trauma during agricultural activities or by direct inoculation from animal scratch or bite. These lesions are mostly asymptomatic, initially presenting as a papule at the site of inoculation after an incubation period of days to months with an average of 3 weeks.[5] The papule then enlarges and develops into a pustule or nodule which at this stage is often mistaken for a bacterial abscess and treated with antibiotic. The absence of pain, erythema and purulent discharge suggests a non-bacterial etiology.[5] A swab for culture and sensitivity should be performed for infected wounds which are not healing or worsening. This should ideally be done before empirical antibiotic treatment is initiated as antimicrobials may affect culture results. Poor or absence of clinical response to antibiotics requires reassessment of the patient and review the diagnosis.

This article was accepted: 15 May 2021
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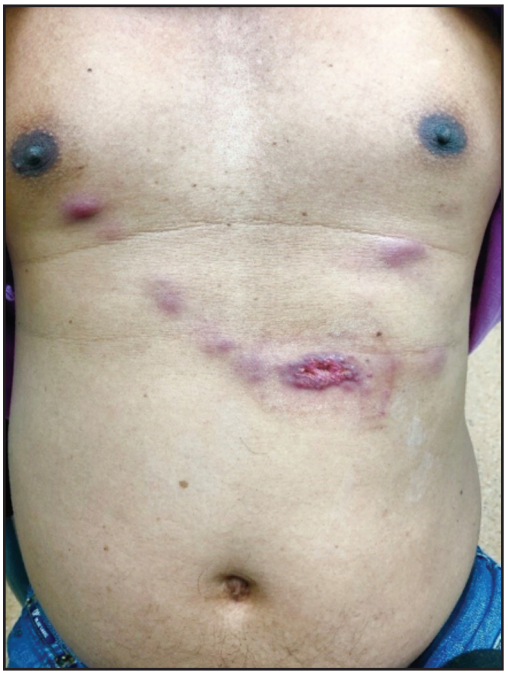

Fig. 1: A large ulcer with irregular margins and slough at the base is seen at the left hypochondrium with a few dusky nodules seen radiating towards the axilla from the lesion (sporotrichoid spread).

If left untreated, the nodule further enlarges and ulcerates forming a sporotrichotic chancre. Characteristic satellite lesions develop along the lymphatic channels draining the affected area described as the "sporotrichoid spread".[5,6] It usually presents along the lymphatic drainage in an ascending manner when inoculation occurs at the distal part of a limb. The superficial lymphatics of the abdominal wall are unique. The area above the umbilicus drains diagonally into the axillary lymph nodes while the area below the umbilicus drains diagonally into the inguinal lymph nodes.[7] In our patient, the inoculation was located above the umbilicus hence the sporotrichoid spread occurred diagonally towards the right and left axillary lymph nodes. This unique appearance, unlike the linear ascending pattern commonly seen on the limbs when the inoculation occurs on the distal part of the limb, casted doubt in the diagnosis during initial clinical assessment. A good knowledge of the superficial lymphatic drainage pattern of the abdominal wall and the typical clinical features of the lesion helped to narrow down the diagnosis. Figure 1, clearly illustrates the superficial lymphatic drainage of the face, upper chest, abdomen and back. The lymphocutaneous sporotrichosis is the most common subtype of cutaneous sporotrichosis seen in Malaysia.[8]

Although *S. schenkii* is the most common cause for the sporotrichoid spread, other pathogens such as *Mycobacterium marinum, Leishmania brasiliensis, Norcardia brasiliensis,* Pasteurellatularensis, Coccidioidomycosis, Cryptocccosis, Blastomycosis, Histoplasmosis may cause a similar presentation.[6,9] The gold standard test for diagnosing *S. schenkeii* is by isolating the fungus by culture.[5] Confirmation should be established before treatment is initiated as the choice of drug, dose and duration of treatment for different pathogens may differ.

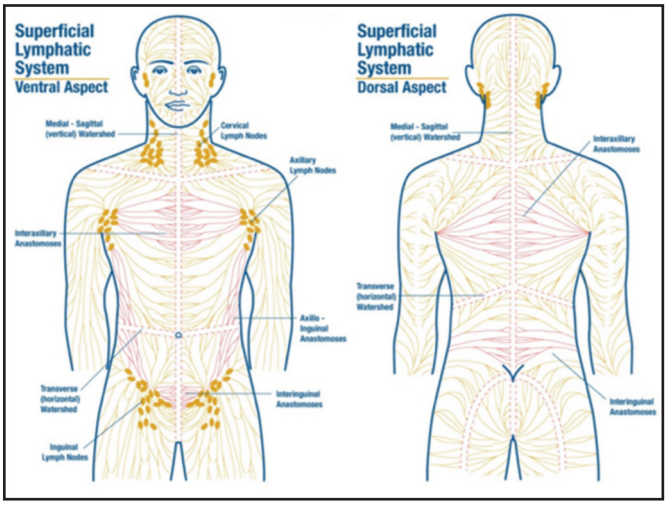

Fig. 2: Superficial lymphatic drainage of the skin on the abdomen showing the region above the level of the umbilicus drains into the axillary lymph nodes while the region below the level of the umbilicus drains into the inguinal lymph nodes (image courtesy of Klose Training and used with permission from Klose Training & Consulting, Colorado).

In summary, subcutaneous fungal infection may be mistaken for bacterial infection as the initial lesions may have similar clinical features. Poor response to antimicrobial therapy and negative bacterial culture should raise the suspicion of an alternative pathogen. Knowledge of the superficial lymphatic drainage pattern is essential to make a clinical diagnosis of sporotrichosis infection in rare sites such as our case. The sporotrichoid spread is not exclusive to *S. schenkeii* hence the causative agent must be confirmed by biopsy and culture for selection of the optimal treatment.

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Combination of hysteroscopic resection of endomyometrium with insertion of Mirena: An alternative treatment for adenomyosis

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SUMMARY

Adenomyosis is a common gynaecological condition encountered in clinical practice. Treatment of adenomyosis can present a great challenge to gynaecologists as women often become resistant to hormonal treatment eventually needing surgical intervention. Hysterectomy has long been the definitive treatment for adenomyosis. However, with women currently being diagnosed at an earlier age and still have not completed their family, there is an increasing demand for effective intervention with uterine conservation. We report here two cases of patients who had undergone a combination of hysteroscopic resection of the endomyometrium combined with Mirena insertion with successful outcome.

INTRODUCTION

Adenomyosis is a common gynaecological condition encountered in clinical practice. It is characterized by endometrial glands and endometrial stroma and a variable degree of smooth muscle hyperplasia within the myometrium.[1] Adenomyosis can be classified based on the degree of invasion of the disease: 1) diffuse adenomyosis, in which the foci of ectopic endometrial mucosa are scattered throughout the uterine musculature, 2) focal adenomyosis, in which the affected area is markedly restricted and embedded within the myometrium, and 3) exomyometrial types, which can take the forms of polypoid adenomyomas, adenomyomas of the endocervical type, and retroperitoneal adenomyomas.[2] Patients can be asymptomatic or present with abnormal uterine bleeding, dysmenorrhoea, chronic pelvic pain and subfertility. Historically, diagnosis of adenomyosis is usually obtained from histological examination of specimens following hysterectomy or excision of the adenomyosis (adenomyomectomy). However, the advancement of transvaginal ultrasound scan (TVS) and magnetic resonance imaging (MRI), has improved its diagnosis pre-operatively.

Treatment of adenomyosis can be challenging especially in patients who wish to preserve their uterus. A step-up strategy is often used, starting with conservative treatment with hormonal or non-hormonal medication followed by uterine-sparing surgical techniques (surgical removal of adenomyotic tissue) and hysterectomy in older women with a resistant disease or those who have completed their family.[2] However, not all women are willing to have hysterectomy despite their older age and having completed their family.

Mirena or levonorgestrel-releasing intrauterine device is an effective treatment for adenomyosis, reducing menstrual bleeding and relieving dysmenorrhoea. Ozdegimenci et al demonstrated significant and comparable improvements in haemoglobin levels in adenomyosis-related menorrhagia and also showed superior effects on patients psychological and social life when comparing Mirena to hysterectomy.[3] Maia et al established that the use of Mirena following endometrial resection in patients with adenomyosis was associated with higher amenorrhoea rates and lower rates of dysmenorrhea than the group of patients who had Mirena inserted alone.[4] We report two cases where the combination of hysteroscopic surgery and insertion of Mirena were used for treatment of adenomyosis successfully.

CASE REPORT

Case 1

A 48-year-old para 2, complained of 3 years' history of worsening prolonged heavy menstrual bleeding of up to 10 days and severe dysmenorrhoea. She took mefenamic acid and tranexamic acid for a year, then continuous Norethisterone for 2 years. Despite the hormonal treatment, she still developed recurrent anaemia requiring prolonged iron supplementation. Bimanual examination revealed a 12-week sized uterus which felt bulky anteriorly. Ultrasound scan (USS) pelvis revealed 4x5cm adenomyosis in the anterior wall of uterus distorting the uterine cavity. Magnetic Resonance Imaging (MRI) of her pelvis confirmed the USS finding. She opted for the insertion of Mirena, which was inserted easily in the outpatient clinic. The Mirena spontaneously expelled a week after. She was not keen on hysterectomy despite completing her family. Decision was made to perform hysteroscopic resection of endometrium with reinsertion of Mirena. The patient was given one dose of Lucrin 3.75mg 1 month before the procedure.

The procedure was carried out using the bipolar resectoscope (Olympus Inc., Germany) equipped with a 3-mm deep and 5-mm wide loop (Olympus Inc., Germany) with isotonic saline as distension media under general anaesthesia. The cervix

This article was accepted: 19 May 2021
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was dilated to 8mm to allow the introduction of the bipolar resectoscope. A large focal adenomyoma was found occupying the entire surface of the anterior uterine wall protruding into the uterine cavity. The endometrium over the posterior uterine wall was normal in appearance, and the uterine cavity length measurement was 10cm. The focal anterior adenomyosis was resected using the loop diathermy. The rest of the endometrium was ablated using rollerball diathermy, and Mirena was inserted. Histopathology result revealed endometrium in the proliferative phase and confirmed the presence of adenomyosis. Six months following the procedure, she reported 5 days of light bleeding during menstruation with no dysmenorrhoea symptoms.

Case 2

A 44-year-old para 4, complained of prolonged heavy menses lasting of up to 14 days with no dysmenorrhea. The patient had no palpable masses per abdomen. Bimanual examination revealed an anteverted uterus at 10 weeks size. The transvaginal scan revealed a retroverted bulky uterus with focal posterior adenomyosis of 2.3 cm x 2.4 cm. Endometrium was not distorted. Pipelle sampling showed a secretory phase. She opted for insertion of Mirena, but it was removed after one week as the Mirena was displaced into the endocervical canal causing discomfort. Outpatient hysteroscopy was performed at the same time which revealed limited uterine distension most likely due to the protrusion of adenomyosis into the cavity. She was given Depo Provera injection temporarily to control her symptoms but started having prolonged heavy menses again following discontinuation of the treatment. As a result, she developed anaemia with haemoglobin of 7.5 g/dl and was given parenteral iron treatment. She was offered the option of hysteroscopic resection of endometrium or total laparoscopic hysterectomy. She opted for the former and was given 1 dose of subcutaneous Lucrin 3.75mg 1 month before the operation.

The procedure was carried out using the bipolar resectoscope (Olympus Inc., Germany) with isotonic saline as distension media under general anaesthesia. The uterine cavity appeared small initially due to mucosal fold elevation/protrusion of the posterior wall into the uterus due to the adenomyosis. During the resection process, there was scattered cluster of glands and locules of bleeding areas seen within the myometrium. The base was ablated with the roller ball to achieve haemostasis. At the end of the procedure, the uterine cavity was restored, and the Mirena was inserted. The procedure was uncomplicated, and she was discharged home the next day. Histopathological findings of the specimen were consistent with adenomyosis. She was very satisfied with the result, and at 6 months follow-up appointment, and she was having light, regular menses lasting for 7 days.

DISCUSSION

Treatment of adenomyosis can present as a significant challenge to gynaecologists. Patients often become resistant to non-hormonal and hormonal medication after a while. Those with resistant adenomyosis will usually end up with hysterectomy once they get older or when they have completed their family.

However, uterine-sparing surgery is becoming more popular as patient demographics are getting younger and with increasing wishes to preserve their uterus. Uterine-sparing surgery aims to control symptoms of adenomyosis and offer an optimal uterine environment for conception and pregnancy.[2] The latter is not really an issue for both our cases as they have long completed their family. However, they still wished to avoid major surgery like hysterectomy unless necessary.

Uterine-sparing surgery includes complete or partial excision of the adenomyotic lesion. Complete excision of adenomyosis or adenomyomectomy is typically performed for focal adenomyosis. Partial excision or cytoreductive surgery is usually associated with diffuse adenomyosis, where attempting to remove all adenomyotic tissue can lead to "functional hysterectomy" and increased complication.[2] A systematic review and meta-analysis by Mikos et al in 2019 found that complete excision of adenomyosis was associated with improvement of pain, menorrhagia, and reduction of uterine volume by a factor of 6.2,3.9, and 2.3 respectively. Partial excision of adenomyosis was associated with improvement in pain, menorrhagia, and uterine volume reduction by a factor of 5.9, 3.0, and 2.9, respectively.[2] Most of the uterine-sparing surgery are performed via laparotomy or laparoscopy. There are very few publications on uterine-sparing surgery by hysteroscopy.

Xia et al in 2017 performed hysteroscopic excision of endomyometrial lesion in 51 women and demonstrated significant improvement in menorrhagia and dysmenorrhoea with low recurrence rate during the 2-year follow-up.[5] Out of 51 women, 7 (14%) required another surgery due to unsatisfactory outcome. All 7 of these patients were diagnosed with diffuse-type adenomyosis involving all layers of the myometrium.[5] Thus a complete resection of the deep ectopic myometrium is difficult without significant risk of perforation or damaging the myometrium integrity. Therefore, hysteroscopic excision of endomyometrial is probably more suitable for focal adenomyosis near the inner muscular layer of the myometrium.

Maia et al performed endometrial resection in 95 women with adenomyosis and randomised the women into two groups, the first group had Mirena inserted immediately following the procedure and the control group received no further treatment.[4] The Mirena group had a significantly higher amenorrhoea and no dysmenorrhoea rates compared to the control group.[4] None of the women in the Mirena group required a second surgical procedure to control persistent uterine bleeding and pain compared to 19% of the women in the control group.[4] This was explained by the possibility of regeneration of the remnants of the deeply embedded glands within myometrium which was not removed during resection. The presence of Mirena within the uterine cavity releases continuous progesterone which suppresses of endometrial proliferation. The other advantage of the combination procedure is that the deeply embedded endometrial glands within the myometrium theoretically are not exposed to high levels of levonorgestrel secreted by the Mirena within the uterine cavity, especially when the endometrium is intact.[4] Resecting the endometrium will

potentially remove the barrier to diffusion of progestin into underlying myometrium. It will deliver higher doses of levonorgestrel directly to the ectopic glands deeply embedded the myometrium.[4] Therefore, combining the endomyometrial resection and Mirena insertion will provide an effective treatment for adenomyosis as demonstrated in both of our cases.

Both our patients opted to have Mirena insertion for their treatment of adenomyosis. Unfortunately, both had problems with expulsion and displacement of the Mirena. For the first case, initial scan at the clinic clearly demonstrated protrusion of the adenomyosis which distorted the uterine cavity. For the second case, initial scan at the clinic demonstrated no distortion of the endometrial cavity by the focal adenomyosis. However, outpatient hysteroscopy performed revealed a smaller uterine cavity which did not distend well possibly due to the mucosal elevation or protrusion from the adenomyosis. Therefore, patients having problem with Mirena expulsion or displacement in the presence of adenomyosis, should have hysteroscopy performed to investigate the uterine cavity. Both our patients were keen to preserve their uterus therefore, hysteroscopic surgery was performed with the aim to reduce the protrusion of adenomyotic tissue into the uterine cavity which will reduce uterine contractility and minimize the risk of Mirena expulsion.

We did not perform the procedures under ultrasound guidance as we were not aiming for complete excision of the adenomyosis. However, for patients refusing to have Mirena insertion following endometrial resection, the procedure can be done under ultrasound guidance to ensure safe removal of as much as adenomyotic tissue as possible. Maia et al reported that all their patients with adenomyosis who received Mirena after endometrial resection developed amenorrhoea.[4] This was not demonstrated in both of our cases as we only resected the affected part of the endomyometrium and not the whole endometrium as was described in their study.

CONCLUSION

Hysteroscopic resection of focal superficial adenomyosis can be offered for cases following Mirena expulsion such as demonstrated in both our cases. Hysteroscopic resection is a much less invasive procedure compared to hysterectomy. Combining hysteroscopic surgery with insertion of Mirena will give significantly better outcomes in terms of reduction of menstrual bleeding, dysmenorrhoea and lower hysterectomy rate. Therefore, it can also be routinely offered to patients with adenomyosis, particularly the diffuse type. Hysteroscopic resection with Mirena insertion should be considered for patients with a strong desire to preserve their uterus.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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CASE REPORT

An infantile late-onset case Group of B *Streptococcus* meningitis diagnosed with a rapid latex kit

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SUMMARY

Globally, vaccination has reduced the prevalence of meningitis caused by *Streptococcus pneumoniae Neisseria meningitidis*, and *Haemophilus influenzae*. However, neonatal Group B *Streptococcus* (GBS) meningitis continues to remain a problematic infection of the central nervous system. Here, we report a case of bacterial meningitis in a 34-day old male baby who presented with fever. A cerebrospinal fluid (CSF) test on the day of admission showed an increase in cell count with decreased glucose level. A rapid latex test of the CSF using a commercial kit diagnosed the causative pathogen as GBS. We administered the antibiotics ampicillin, cefotaxime, gentamicin and panipenem/betamipron to the patient for over 14 days. Partial seizures were frequently observed during the course and were well-controlled with midazolam and phenobarbital. Brain magnetic resonance imaging on day 17 showed subdural hygroma in the frontal region, and 99mTc ethyl-cysteinate dimer-single photon emission computed tomography confirmed a decreased cerebral blood flow predominantly in the left frontal region. After three years of follow-up, the condition of the patient improved without any neurological sequelae. Our report highlights that rapid identification of the causative organism is essential in infantile late-onset meningitis. In addition, we consider that the latex kit-based rapid testing of CSF is beneficial for identifying the causative agent of bacterial meningitis.

INTRODUCTION

Bacterial meningitis in children is one of the most serious central nervous system infections. With respect to neonatal meningitis particularly, prognosis remains poor and mortality rate is high.[1] Therefore, early diagnosis and timely and appropriate antibiotic treatment are important for neonatal meningitis. Cerebrospinal fluid (CSF) examination of newborns is troublesome for two major reasons: (1) small size of their body, and (2) difficulty collecting the fluid. Thus, alternatively a lumbar puncture is used to collect CSF and identify the causative bacterial agent.[2] Culture examination is time-consuming and requires a few days for analysis. In some cases, the causative bacteria cannot be identified by culture testing of fluids from the newborns.[2] Therefore, other methods need to be developed for identifying the causative agent of neonatal meningitis and start antibiotic treatment as early as possible. In this report, we present a late-onset case of neonatal *Streptococcus agalactiae* from Group B *Streptococcus*, (GBS) meningitis wherein the causative agent was identified using a commercial rapid latex kit.

CASE REPORT

A 34-day-old male infant was referred to the Dokkyo Medical University, Tochigi, Japan because of fever and poor feeding. The infant was born by vaginal delivery at 3,500 g at 41 weeks of gestation. He was the first child of his parents. His mother had a negative GBS test during the second trimester of pregnancy. A few days earlier, a one-month medical check-up revealed that the baby had no physical problems. However, the mother had been suffering from mastitis for 6 days.

At the time of admission, the level of consciousness of the baby was sluggish in response to pain stimuli, and he did not cry. Vital sign measurement showed tachypnoea of 70 times/minute; tachycardia of 200 beats/minute; and body temperature of 39.5℃. The anterior fontanelle appeared bulged, but the Kernig sign was negative. Finally, we suspected bacterial meningitis, and the infant was hospitalised after performing routine urine and blood biochemical tests with culture tests.

The blood test findings were as follows: WBC: 2,500/μL, haemoglobin: 11.1 g/dL, platelet: 280,000/mm3, aspartate aminotransferase: 39 U/L, alanine aminotransferase: 20 U/L, lactate dehydrogenase: 339 U/L, Na^+: 135 mEq/L, K^+: 4.2 mEq/L, Cl-: 104 mEq/L, glucose: 115 mg/dL, C-reactive protein: 0.90 mg/dL, IgG: 672 mg/dL, procalcitonin: 37.53 ng/mL, interleukin-2 receptor (IL-2R): 2139 U/mL. Notably, procalcitonin and IL-2R levels were prominently elevated. Brain computed tomography (CT) revealed no abnormalities. CSF from his lumbar puncture showed increased hydropressure and pleocytosis (70 polymorphonuclear cells/mm^3); reduced CSF glucose level (< 5 mg/dL); and increased CSF protein level (343 mg/dL). Due to the increased cell count, we performed a CSF latex kit test (Pastorex™ Meningitis, Bio-Rad Laboratories Co. Ltd., Japan) prior to CSF culture test, and the causative agent of bacterial meningitis was detected as GBS (Figure 1). We also performed a culture test of the vaginal sample of the mother and breast milk and breastfeeding stopped thereafter. Since the baby subsequently had frequent partial seizures, he was intravenously administrated midazolam and phenobarbital as an anti-convulsant. Due to his worsening respiratory status, oxygen administration and nasal directional positive airway pressure

This article was accepted: 26 May 2021
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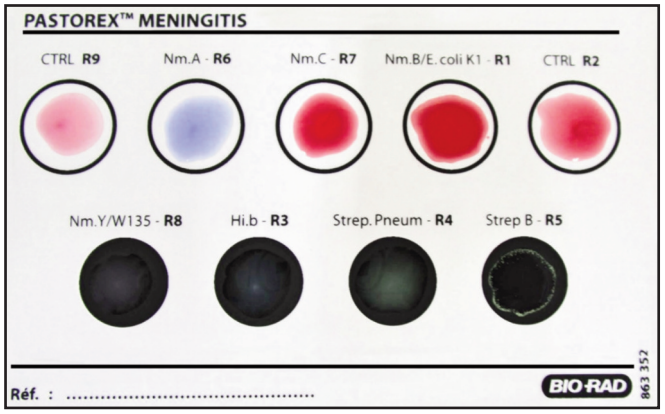

Fig. 1: Diagnosis of neonatal bacterial meningitis using cerebrospinal fluid (CSF) latex kit on admission. A circular latex agglutination reaction is observed on the black circle in the lower right. The causative bacterium is diagnosed as Group B Streptococcus (GBS).

were required. We started antibiotic treatment with 190 mg/kg/day ceftriaxone and 190 mg/kg/day ampicillin (ABPC) immediately. In addition, intravenous immunoglobulin (150 mg/kg/day) was administered for five days. Administration of vitamin K and treatment with disseminated intravascular coagulation were also initiated. On the third day, a second CSF puncture was performed wherein the cell count was found to have increased to 2,121 /mm^3. In addition, both blood and CSF culture tests at admission revealed GBS serotype III. Following this, antibiotic treatment was de-escalated to ABPC, and 5 mg/kg/day gentamicin was added in anticipation of a synergistic effect. On the fourth day, tracheal intubation was started because apnoeic attacks were frequent and the level of consciousness was unstable. Brain CT showed bilateral enlargement of the subdural space and we considered progress of subdural hygroma or subdural abscess. On the fifth day, administration of 100 mg/kg/day panipenem/betamipron (PAPM/BP) was commenced because the CRP levels continued to rise. The second CSF culture was negative on the sixth day of hospitalisation. In addition, the consciousness level of the baby improved. We performed a third CSF puncture; the cell count then decreased to 668/mm^3. Notably, the same serotype (GBS III) was detected in the vaginal culture of the mother. Additionally, another GBS serotype 7271 (GBS VII) was detected in her breast milk culture. Consequently, PAPM/BP treatment was continued for the next 14 days, and the baby's general condition improved.

Brain magnetic resonance imaging (MRI) performed on day 17 demonstrated progressed subdural abscess (Figure 2A), and ^{99m}Tc ethyl-cysteinate dimer-single photon emission CT (ECD-SPECT) showed a considerable decrease in the cerebral blood flow from the left frontal region to the temporal region (Figure 2B). The baby underwent a hearing examination on day 30, and the results were normal. The baby was discharged on the day 32 after admission. Subsequently, the clinical course of the baby was observed in an out-patient department.

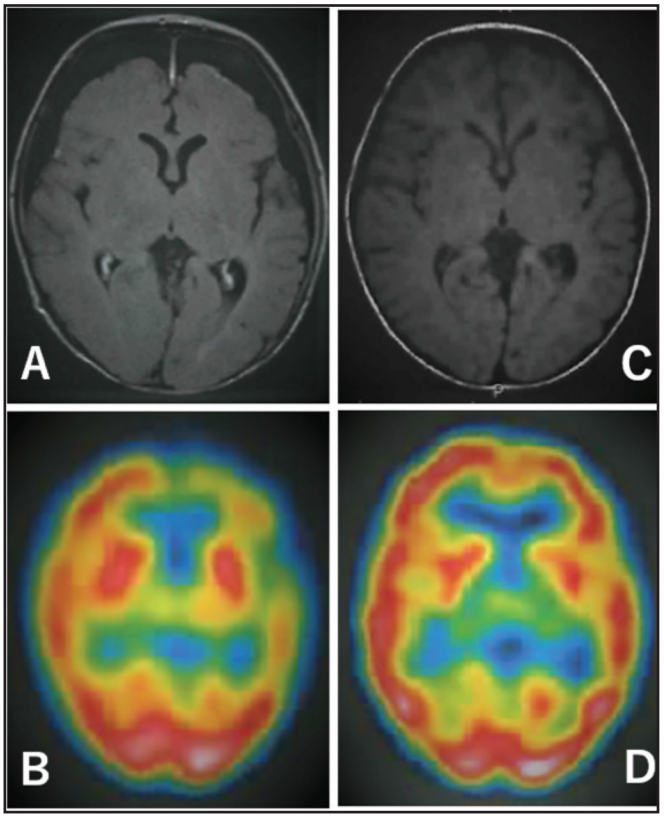

Fig. 2: Magnetic resonance imaging (MRI) and 99mTc ethyl-cysteinate dimer-single photon emission computed tomography (ECD-SPECT) A: Fluid-attenuated inversion recovery brain axial MRI showing subdural abscess of the patient at day 17 of hospitalisation. B: ECD-SPECT showing an area of hypoperfusion that is observed predominantly in the left frontal to temporal region of the patient at day 17 of hospitalisation. C: Brain axial T1-weighted MRI showing improvement of frontal subdural abscess at 3 years of age. D: ECD-SPECT showing improvement in cerebral blood flow at 3 years of age.

At three years of age, the brain MRI of the child showed improvement in the frontal subdural space enlarged with abscess (Figure 2C). ^{99m}Tc ECD-SPECT also showed an improvement in the decreased cerebral blood flow from the left frontal to the temporal region (Figure 2D). No obvious neurological sequelae, such as epilepsy or developmental delay, were observed, and after informed consent with parents, we ended his out-patient follow-up.

DISCUSSION

Bacterial meningitis is one of the most serious bacterial infections. It is characterised by several neurological sequelae and high mortality.[1,3] Worldwide, vaccines have remarkably reduced the incidence of bacterial meningitis caused by S. pneumoniae, H. influenzae, and N. meningitidis. GBS-mediated neonatal bacterial meningitis remains a major health concern not only in developing but also developed countries. GBS disease is classified as early-onset and late-onset if the onset age is 0-6 and 7-89 days after birth, respectively. In Japan, more than 20% of normal pregnant women are GBS-carriers.[4] Therefore, pregnant women

undergo GBS culture tests once or twice during pregnancy and those found GBS-positive are administered ABPC as the delivery progresses. However, the prevalence of late-onset GBS meningitis that develops in week-old newborns is increasing in Japan, and remains an important problem for effective infectious disease control.[5]

It is essential to identify the causative organism when diagnosing bacterial meningitis in newborns via CSF test and eventually start early antibiotic administration. Owing to a few major reasons, CSF testing in newborns is difficult, and in some cases, the causative bacteria cannot be identified by CSF culture testing.[2,3] Therefore, we strongly consider that the blood culture and baby and vaginal smear of the mother, and breast milk culture tests should be conducted along with the CSF culture test of the baby.

CSF and blood culture tests are time-consuming; therefore, alternative methods for identifying the causative bacteria are important. Our case also diagnosed GBS early timing with a latex meningitis kit and we started treatment with ABPC and CTX. However, the patient later developed a subdural abscess. Therefore, we treated patient with PAPM/BP, which has CSF transferability. Taking advantage of the early diagnosis, it may have been possible to prevent the aggravation if higher dose antibiotic treatment was performed from the time of admission. In recent years, polymerase chain reaction (PCR) has been reported to rapidly identify the causative agent of bacterial meningitis, wherein this method overcomes the time-consuming limitation of CSF culture test.[6] However, PCR testing of CSF is not economical, requires technical expertise, and is still not performed extensively across diagnostic laboratories. In this regard, the latex kit used in this report requires less than only a half hour and the diagnosis can be performed the absence of high-end facilities. In a Latex test using specimens of bacteria confirmed by conventional culture identification methods and this product is 100% accurate. However, there is a limitation depending on the condition of the clinically collected specimens. Therefore, bacterial culture remains the gold standard for confirmation of diagnosis. In any event, this kit is a simple, cost-effective, and useful tool for diagnosing bacterial meningitis in suspected/affected individuals of all ages.[7]

CONCLUSIONS

For neonatal bacterial meningitis, it is important to identify the causative organism at an early stage and thereby initiate suitable antibiotic treatment. The rapid latex kit is a useful method for the early identification and selection of antibiotics for subsequent treatment in case of suspected cases of bacterial meningitis.

COMPLIANCE WITH ETHICAL STANDERD AND INSTITUTIONAL APPROVAL

This report was performed with the approval of the Ethical Committee of the Department of Pediatrics, Dokkyo Medical University, Japan.

CONFLICT OF INTEREST

The authors have no conflict of interests concerning in the present study or findings presented in this study.

INFORMED AND CONSENT

Informed consent for publishing this case report was obtained from the patient's parents.

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Hyperglyceridaemia-induced acute pancreatitis in pregnancy: Experience from a tertiary hospital in Singapore

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SUMMARY

Acute pancreatitis (AP) is a serious condition that can occur suddenly in pregnancy. We present a case of sudden onset of epigastric pain with severely deranged serum triglyceride levels in a 32-year-old Vietnamese primigravida with no significant past medical history in the Singapore General Hospital. The patient was managed in the intensive care unit, with plasmapheres and intravenous insulin and was eventually a healthy term foetus was delievered via ceasarian section. This case showcased multidisciplinary co operation between the obstetrics, anaesthetic, endocrinology and intensive care team and serves as a reminder to consider this rare condition for future similar presentations.

INTRODUCTION

Acute pancreatitis (AP) in pregnancy is rare but it is a serious condition with a low incidence of less than 1 in 10000.[1] It usually presents with sudden severe abdominal pain and depending on the severity of the disease and can endanger a pregnancy.[2] AP presents most commonly during the third and post-partum period. AP in pregnancy is usually secondary to biliary obstruction by gallstones. Hypertriglyceridaemia-induced pancreatitis (HLP) which is an extremely rare but important cause of AP and is the main focus of this case report. HLP carries a much higher likelihood of severe AP and is strongly associated with poor fetal outcomes such as fetal distress and stillbirth. We present a case of a woman with this rare entity.

CASE REPORT

The patient, Mdm N is a 32-year-old Vietnamese primigravida with no significant past medical history. The course of her pregnancy was uneventful until 31 weeks of gestation when she presented with constant epigastric pain and dyspnoea. Blood investigations done in the emergency department revealed significantly elevated serum lipase of above 600 U/L and serum amylase of 837 U/L (Table I). An arterial blood gas sample confirmed a compensated metabolic acidosis. The blood samples appeared chylous (Figure 1) and showed a serum triglyceride level of above 50 mmol/L and total cholesterol of 37.36 mmol/L. A provisional diagnosis of hypertriglyceridaemia-induced acute pancreatitis in pregnancy was made and the patient was admitted for further management.

The foetus was appropriately grown on ultrasound with an estimated foetal weight of 2041g and cardiotocography (CTG) was normal. Intramuscular steroid injections in the form of betamethasone were administered to accelerate fetal lung maturity in anticipation of the possible necessity for preterm delivery. She was also started on subcutaneous enoxaparin, a low molecular weight heparin (LMWH) for prophylaxis against venous thromboembolism and also to lower triglyceride levels.

The patient was admitted to the intensive care unit (ICU) for further monitoring. She was started on intravenous insulin with a 10% dextrose infusion to correct her metabolic acidosis.

Despite intravenous insulin, repeat arterial blood gas revealed worsening of the metabolic acidosis. In view of worsening acidosis and extremely high triglyceride levels, she underwent urgent plasmapheresis via a vascular catheter (Figure 2).

The patient's triglyceride levels reduced steadily after 1 cycle of plasmapheresis intravenous insulin, hydration and LMWH.

Subsequently, administration of insulin was converted to daily subcutaneous form and she placed on a low-fat diet. MRI cholangiography was also performed to rule out biliary causes and demonstrated absence of biliary tract stones. the patient was eventually discharged after 10 days of hospitalisation with subcutaneous insulin and oral omega 3 supplements. Her serum triglyceride level at the time of discharge was 8.41mmol/L.

She was followed 2-weekly in our high-risk pregnancy clinic and serial serum triglyceride levels remained stable as shown in table II. Foetal growth parameters were followed up closely with regular ultrasound scans and were deemed within normal range.

In recognition of the risk of relapse, she was electively admitted at 37 weeks of gestation for induction of labour. Despite multiple prostaglandin pessaries, she failed induction of labour and subsequently underwent an uneventful cesarean section. A healthy term foetus was delievered. Mdm N was reviewed by endocrine post operatively and her serum triglycerides remained stable. She was discharged well 3 days' post operation as per routine protocol and started on oral fibrates for long-term control of her hypertriglyceridaemia.

This article was accepted: 26 May 2021
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Table I: Summary of bloods done at admission

Blood results			
Haemoglobin (g/dL)	10.5	Potassium (mmol/L)	3.2
White blood count (x10^9/L)	13.04	Glucose (mmol/L)	5.6
Platelet (x10^9/L)	274	Creatinine (umol/L)	62
Neutrophils absolute (x10^9/L)	11.4	Bicarbonate (mmol/L)	14.1
		Amylase (units/L)	867
pH	7.405	Lipase (units/L)	>600
pCO2 (mmHg)	26.0	Ketones (mmol/L)	3.5
PO2 (mmHg)	98.0	C-reactive protein (mg/L)	128
Base excess (mmol/L)	-8.0	Calcium, serum (mmol/L)	1.87
		Amylase (units/L)	867
Heart rate (bpm)	125	Blood cultures (aerobic)	No bacterial growth
Temperature	38.3 degrees	Blood cultures (anaerobic)	No bacterial growth
Blood pressure	98/59	Cholesterol, total (mmol/L)	37.36
		Cholesterol, HDL (mmol/L)	>6
Urea (mmol/L)	1.5	Triglyceride (mmol/L)	>50.00
Sodium (mmol/L)	117	Cholesterol, total (mmol/L)	37.36

Table II: Trends of triglyceride level following treatment

Triglyceride trend over the next few days after starting treatment								
Triglyceride (mmol/L)	31.29	25.21	17.19	14.09	12.39	10.45	9.56	8.83
Triglyceride trend during her outpatient visits								
Triglyceride (mmol/L)	8.41	7.70	9.12	8.73	8.59			
Triglyceride trend post caesarean section								
Triglyceride (mmol/L)	7.19	7.27						

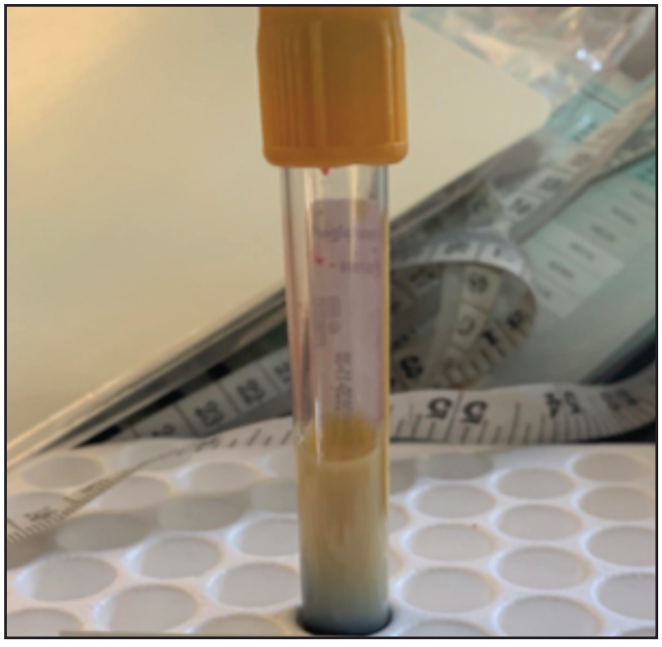

Fig. 1: Lipemic blood sample taken from patient upon admission.

Fig. 2: Plasmapheresis machine demonstrating lipemic plasma extracted from patient.

DISCUSSION

HLP accounts for only 4-6% of cases of AP in pregnancy but is more likely to have severe manifestations and complications as witnessed in our patient. In the third trimester of pregnancy, there is a two to four-fold increase in serum triglycerides level. The significant increase in triglycerides is postulated to be driven by the elevated levels of oestrogen and human placental lactogen (HPL) in the late second to third trimester. HPL stimulate lipolysis in adipocytes while estrogenic state enhances lipogenesis and hepatic VLDL synthesis and decreases hepatic lipase activity, giving rise to increased triglyceride-rich LDL and high-density lipoprotein in the maternal circulation.6 These physiological alterations in lipid metabolism can precipitate an episode of

acute pancreatitis, especially in patients with underlying disorders of lipoprotein metabolism such as those with pre-existing hypertriglyceridaemia.

When evaluating a patient in the secondary or third trimester presenting with abdominal pain, clinicians should maintain a high index of suspicion for HLP and the management requires a multidisciplinary approach. Care of our patient involved obstetricians, neonatologists, endocrinologists, gastroenterologists, nephrologists and radiologists. Initial treatment consists of supportive management with intravenous hydration, bowel rest and a fasting state. This strategy usually results in a drop in serum triglyceride levels after 48 hours. A more aggressive approach was necessary in our patient who was severely ill at presentation. This is especially so since HLP is associated with a maternal mortality rate of up to 9% and a fetal loss rate of 17.5%.[5]

Main treatment modalities are insulin and plasmapheresis, with the aim of lowering triglyceride levels. Insulin lowers serum triglyceride levels by potentiating lipoprotein lipase (LPL) activity and also hormone sensitive lipase in adipocytes. HLP has been proven beneficial in various studies and should ideally be initiated early in cases of severe HLP for rapid removal of plasma lipoproteins and inflammatory cytokines with the aim to reduce serum triglyceride levels and reduce risk of pancreatic necrosis.[6,7] Our patient was also started on heparin in the form of LMWH. Heparin stimulates the release of LPL into the circulation to further reduce triglyceride levels, though the effects are transient as chronic use results in a depletion of LPL. We also used supplementation with omega-3 fatty acids in our patient which is safe in pregnancy and is known to increase LPL activity. Fibrates, the mainstay of pharmacological therapy for hypertriglyceridaemia in non-pregnant individuals, has been used in pregnancy though its safety has not been proven. We decided not to use this drug as our patient remained stable with the other modalities.

Apart from maternal complications such as acute renal failure, sepsis and acute respiratory distress syndrome, there are also potential foetal complications with HLP. Foetal risks from AP in pregnancy include pre-term labour, prematurity, and in-utero foetal death.[6] In a retrospective review between 1996 and 2006, describing 43 pregnant women with acute pancreatitis, there were 6 pre-term delivery and only 2 of these infants survived. An observational study of 54 pregnant women with AP showed that HLP is associated with more intrauterine foetal distress and worse foetal outcomes compared to AP from other aetiologies. Close foetal monitoring with cardiotocography and growth scans should be performed.

We attribute the good obstetric outcome in our patient to the initial aggressive medical treatment to correct maternal acidosis and reduce serum triglyceride levels. This and subsequent close antenatal surveillance allowed our patient to carry her pregnancy to term. The decision to induce labour at 37 weeks, albeit unsuccessful, can be justified on risk-benefit considerations. The physiological changes in pregnancy continue to predispose these women to a relapse of HLP and delivery of the foetus, once it is mature, is beneficial. Delivery also allows for the subsequent use of lipid-lowering drugs which may be contraindicated in pregnancy.

CONCLUSION

HLP is a rare but potentially lethal cause of abdominal pain in pregnancy associated with and is associated with significant maternal and fetal morbidities. Timely diagnosis and multi-disciplinary management of both AP and hypertriglyceridaemia are crucial in order to minimise complications.

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CASE REPORT

Pneumoperitoneum following an Endoscopic Retrograde Cholangiopancreatography (ERCP): A case report

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SUMMARY

Post Endoscopic Retrograde Cholangiopancreatography (ERCP) pneumoperitoneum is commonly associated with perforated viscus but is rarely associated with benign causes. We present a case of 29 years old lady who underwent ERCP, who was found to have benign pneumoperitoneum subsequently. She was treated conservatively and recovered without complication. Although rare, post ERCP pneumoperitoneum of benign causes should be investigated as the course of treatment and outcome differ largely.

INTRODUCTION

Pneumoperitoneum is a radiological finding which indicates a perforated hollow viscus in over 85-90% of patients. On the other hand, there are 10 - 15% pneumoperitoneum cases where the aetiology is due to other causes like post operation, thoracic causes, pneumotosis cystoides intestinalis, endoscopy related, post-partum and the list goes on. These can be termed as "benign pneumoperitoneum" or "non-surgical pneumoperitoneum".[1] We present here a case of post Endoscopic Retrograde Cholangiopancreatography (ERCP) pneumoperitoneum from the latter group.

CASE REPORT

A 29 years old lady, para 4, postpartum 19 days (uneventful assisted breech delivery), presented with epigastric pain for 1 week. The pain radiated to the back, associated with nausea and vomiting. She also noticed yellowish discoloration of her eyes and skin, along with tea coloured urine and pale stool.
On examinations, she was jaundiced, per abdomen tender over right hypochondrium and epigastric region, no mass palpable. Liver function test showed increased total bilirubin with predominantly direct bilirubin, significantly increased ALP, mildly increased AST and ALT.

Ultrasound hepatobiliary system showed dilated intrahepatic ducts over bilateral lobe. Common bile duct (CBD) was dilated with measurement of 1.1cm with a large hyperechoic lesion with posterior shadowing measuring 1.5cm in diameter suggestive of calculus.

Thus, ERCP was proceeded on the next available elective date which showed normal part 1 and 2 of duodenum, slit like ampulla of Vater. CBD was cannulated (no sphincterotomy done). Cholangiogram showed multiple distal CBD stones with large common hepatic duct stones. The CBD was stented, with good flow of bile after that.

Almost immediately post ERCP, the patient developed severe epigastric pain which radiated to the tip of right shoulder. Pain was adequately controlled with IV Tramadol. On examinations, per abdomen showed tenderness over right hypochondrium and epigastrium region, no guarding. Amylase was 254. Chest x-ray erect was done, which showed air under diaphragm bilaterally (Figure 1).

A contrast enhanced Computed Tomography (CECT) Abdomen was carried out to investigate further. Mild pneumoperitoneum was noted at perihepatic region, falciform ligament, left subphrenic, and left hypochondriac regions. There were dilated bilateral intrahepatic ducts with aerobilia, more affecting the left intrahepatic ducts. No evidence of bowel perforation, biloma or intra-abdominal collection was observed (Figure 2).

She was treated with antibiotics, adequate analgesia, and hydration. Pain subsided after a few days in the ward, and she was discharged subsequently.

DISCUSSION

Post ERCP pneumoperitoneum is a rare complication. It is most associated with a perforation, especially in the duodenum. Depending on the severity, this perforation will usually warrant an emergency surgery to repair it to prevent a catastrophic consequence.[2] However, there is a group of "benign pneumoperitoneum" where perforation does not occur and can be managed conservatively. One of the explanations for this pneumoperitoneum without perforation is the high pressure of compressed air used during ERCP to maintain the patency of the lumen, creating a pressure valve from a site of low resistance, causing air to leak into the intraperitoneal space. This can happen in the retroperitoneal space as well, which causes pneumoretroperitoneum.[2,3] In our patient, as evidenced in the CECT abdomen, aerobilia is noted in bilateral intrahepatic ducts, more affecting the left side. This may have been due to excessive air insufflation used during ERCP, and leakage of air through the mechanism as mentioned above.

Another cause regarding post ERCP benign pneumoperitoneum is the rupture of intrahepatic bile ducts

This article was accepted: 01 June 2021
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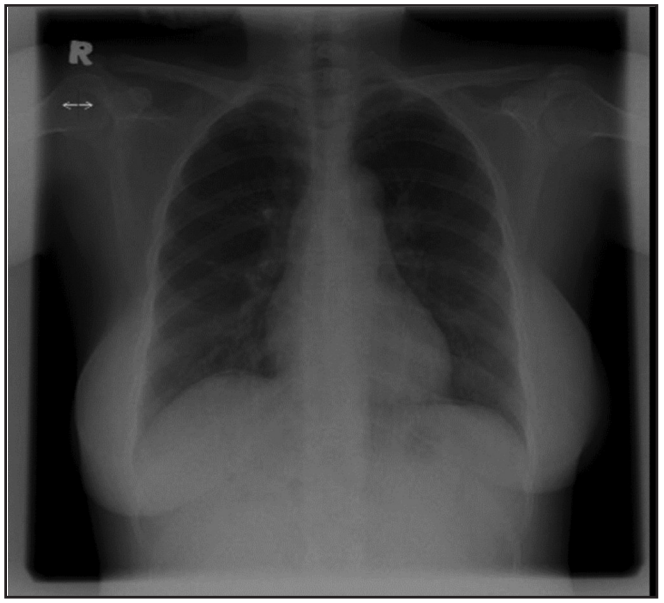

Fig. 1: Chest x-ray erect after ERCP which showed bilateral pneumoperitoneum.

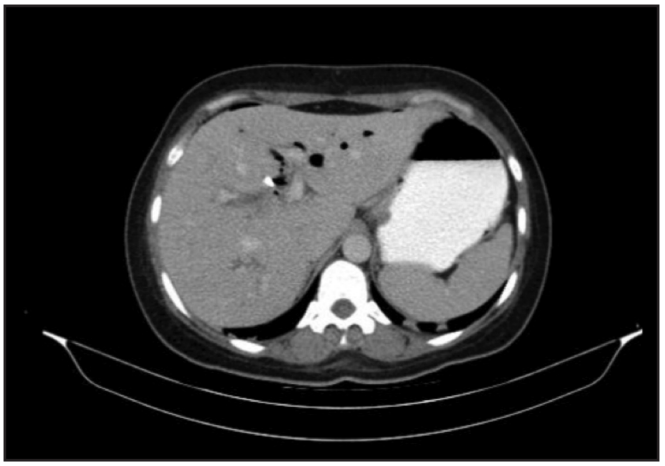

Fig. 2: Axial view of the CECT Abdomen – evidence of mild pneumoperitoneum and dilated bilateral intrahepatic ducts with aerobilia.

and Glisson's capsule in a peripheral hepatic lesion. This is more common in cancer patients who have liver metastasis, owing to neoplastic tissue friability. However, benign disease such as hepatic abscess has been described as well. The explanation for this is air sufflation during ERCP causes retrograde airflow through the patent biliary tract into the diseased intrahepatic duct or Glisson's capsule, causing rupture and subsequently air leakage into the intraperitoneal cavity.[4,5]

Other than ERCP related causes, gynecological cause is another possibility, as in our case. Since 1953, multiple gynecology related causes have been described, such as frequent vaginal douching, rough sexual intercourse, oral-vaginal insufflation, pelvic examination, postpartum or even an accidental fall in a jetted bathtub causing insufflation of the vagina.[6]

Previous publications have theorized two potential paths of air entering the peritoneal cavity through vagina.

1) Air enters through vagina, uterus, fallopian tube and into the peritoneal cavity. This usually happens in oro-vaginal insufflation, rough sexual intercourse, and vaginal douching.
2) Through opening at the vaginal stump post hysterectomy.

For postpartum patients, the first pathway is the underlying mechanism. It was suggested that the more patent post-partum female genital tract allows air to pass into the abdomen more easily through the vagina. This patency exists up to the involution of the uterus at 1-month post-partum.

On the other hand, generally, the commonest cause of benign pneumoperitoneum is post operation, when the air is trapped in the peritoneum from the established wound. Resolution of the air is expected with time. Two-thirds of cases resolve within 2 days and 97% of the cases resolve within 5 days.[7] However, some of the post-operative pneumoperitoneum may persist up to 8 – 10 days or even longer, depending on the nature of surgery.

Benign peritoneum post colonoscopy has been reported as well, although rare with an incidence at 0 to 3%. It was thought that microperforation or inflation of the bowel can cause transmural passage of air.[8]

Thoracic causes are common too, which can be due to mechanical ventilation, cardiopulmonary resuscitation, and tracheal ruptures due to endotracheal intubation.[9]

If diagnosis is in doubt, CT scan with contrast can be used. The high clinical efficacy of CT scan for diagnosis of perforated viscus is well established.[10] In cases when the patient is not suitable for CECT scan or in a situation where CECT scan is not available, upper gastrointestinal Gastrografin study under fluoroscopy is another option. If no extravasation is demonstrated, a benign pneumoperitoneum can be diagnosed.

CONCLUSION

Majority of post ERCP patients who have abdominal pain and pneumoperitoneum will raise suspicion of perforated viscus and will require emergency laparotomy. However, other benign aetiology will need to be considered, especially when there is no clinical abdominal tenderness or peritonism, and when laboratory findings are less suggestive. CT scan is a reliable investigation to rule out perforated viscus. If it is deemed to be benign pneumoperitoneum, patients can be managed conservatively with intravenous antibiotics and bowel rest. Thorough history taking including gynecological or obstetrical system is a valuable adjunct in identifying the cause of pneumoperitoneum.

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Giant epithelial nonparasitic splenic cyst a pre-operative diagnosis dilemma: A case report

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SUMMARY

Giant splenic cyst is rare disorder affecting the spleen. As the occurrence is so in-frequent that the diagnosis preoperatively remains a challenge. We report a 12-year-old boy who presented to Sarawak General Hospital, Malaysia with left upper abdominal pain initially mistaken as a complex left liver cyst. He underwent surgery which turned out to be a giant splenic cyst and underwent laparotomy and total splenectomy. He was discharged well and remains asymptomatic after 6 months postoperative follow up.

INTRODUCTION

True splenic cyst is a rare clinical entity and is classified into parasitic and nonparasitic cyst.[1] Nonparasitic splenic cyst (NPSC) comprises of less than one third of all splenic cyst while true NPSC only makes up 10% of all benign splenic cysts.[1] Giant splenic cyst is defined as a cyst with a diameter greater than 15cm.[2] As parasitic splenic cyst is rare in Malaysia and NPSC occurrence is infrequent the diagnosis preoperatively remains a challenge. We report a case of a 12-year-old boy with a giant epithelial NPSC. To the best of our knowledge, this is the first giant epithelial NPSC to be reported in Malaysia.

CASE REPORT

A 12-year-old boy presented to a district hospital in Sarawak with left upper abdominal pain and distention for 1 month. Physical examination revealed a huge palpable left upper quadrant mass extending to the umbilicus. Contrast-enhanced computerized tomography scan (CECT) of the abdomen showed a large, well demarcated, cystic lesion at the left hypochondrium measuring 17cm x 15cm x 15cm inseparable from left lobe of liver and spleen with no associated calcification (Figure 1A). The rest of the cyst was homogeneously hypo-dense with attenuation suggestive of proteinaceous content (Hounsfield Unit 20) with a septum in between and irregular margins (Figure 1B). Serology for *Echinococcus granulosus*, Meliodosis, biohazard screening and tumour markers were all negative. The patient never had fever and other blood parameters were normal. Pre-operative diagnosis of an exophytic, complex liver cyst arising from segment II of liver was made. As our centre is a *Hepato-Pancreatico-Biliary center*, the child was referred to us and laparotomy and removal of cyst were discussed with the parents of the boy with possible left hemihepatectomy or splenectomy. The child was vaccinated prior to surgery with 3 intramuscular vaccines. The vaccines were the Pneumovax 23 a polyvalent pneumococcal vaccine (Merck Sharp & Dohme Corp, Sumneytown Pike, USA), Hiberix a polysaccharide conjugate *Haemophilus influenzae* type b vaccine (GlaxoSmithKline, Rixensart, Belgium) and Menactra a polysaccharide Diphtheria Toxoid conjugate vaccine (Groups A, C, Y and W-135) (Sanofi Pasteur, Swiftwater, USA). Intra-operatively, however the cyst was found to arise from the medial aspect of the spleen occupying almost the entire spleen while the liver was normal (Figure 2A). Total splenectomy was performed due to the large size of the cyst occupying the entire spleen (Figure 2B) The post-operative course was uneventful and he was discharged 5 days later. Pathological examination showed a unilocular epithelial splenic cyst with fibrous cyst wall (Figure 2C) lined by cuboidal cells (Figure 2D). At a follow-up review of 6 months, he was well.

DISCUSSION

Splenic cyst was first reported by Andral in 1929. The incidence was 0.07% in a large case series of 42327 autopsies over a 25-year period.[3] NPSC are mostly seen in children particularly females. NPSC is common in Europe and North America, while parasitic cyst is common in Africa and Central America.

The 2 main principal classifications by Fowler and Martin are based on the presence of cyst lining.[1,4] Type I cysts are primary (True) cyst with epithelial lining while Type II (False) cyst is without epithelial lining. True cysts can be further classified into parasitic and non-parasitic. In 2002, Morgenstern subdivides NPSC into congenital, neoplastic, traumatic and degenerative.[5] 80% of NPSC typically originates from trauma and degeneration while only 10% are congenital.

The pathogenesis is uncertain but there are 3 postulated theories. The first theory is the invasion of mesothelial lining after the rupture of the splenic capsule during development. This lining is pluripotent in nature and can undergo metaplasia with secretion of fluid leading to cyst formation.

This article was accepted: 08 June 2021
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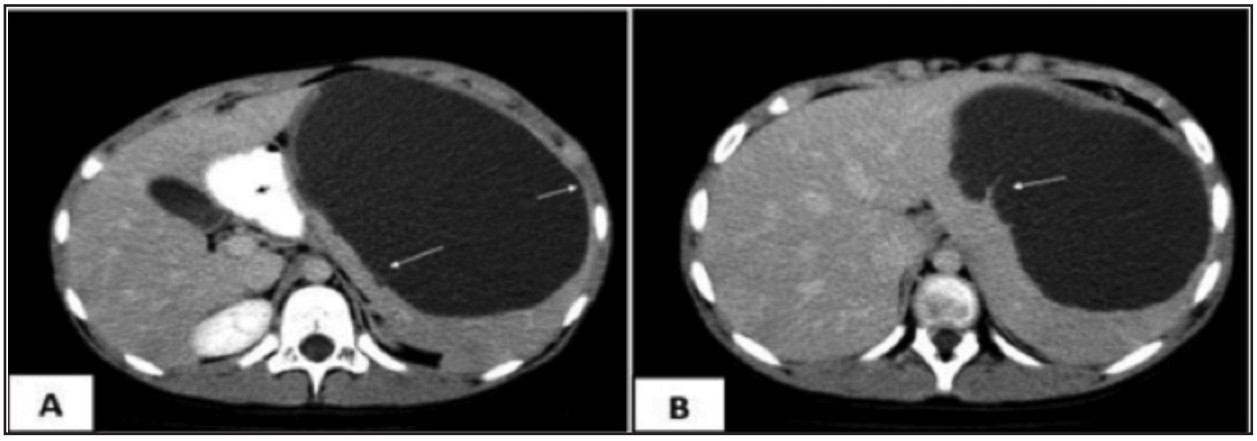

Fig. 1: (A) CECT showing large splenic cyst surrounded by splenic parenchyma posteriorly and anterolaterally (white arrow). Stomach is being pushed to the right (black arrowhead). (B) CECT scan showing thick septae (white arrow) and mild irregular wall at superomedial aspect of cyst.

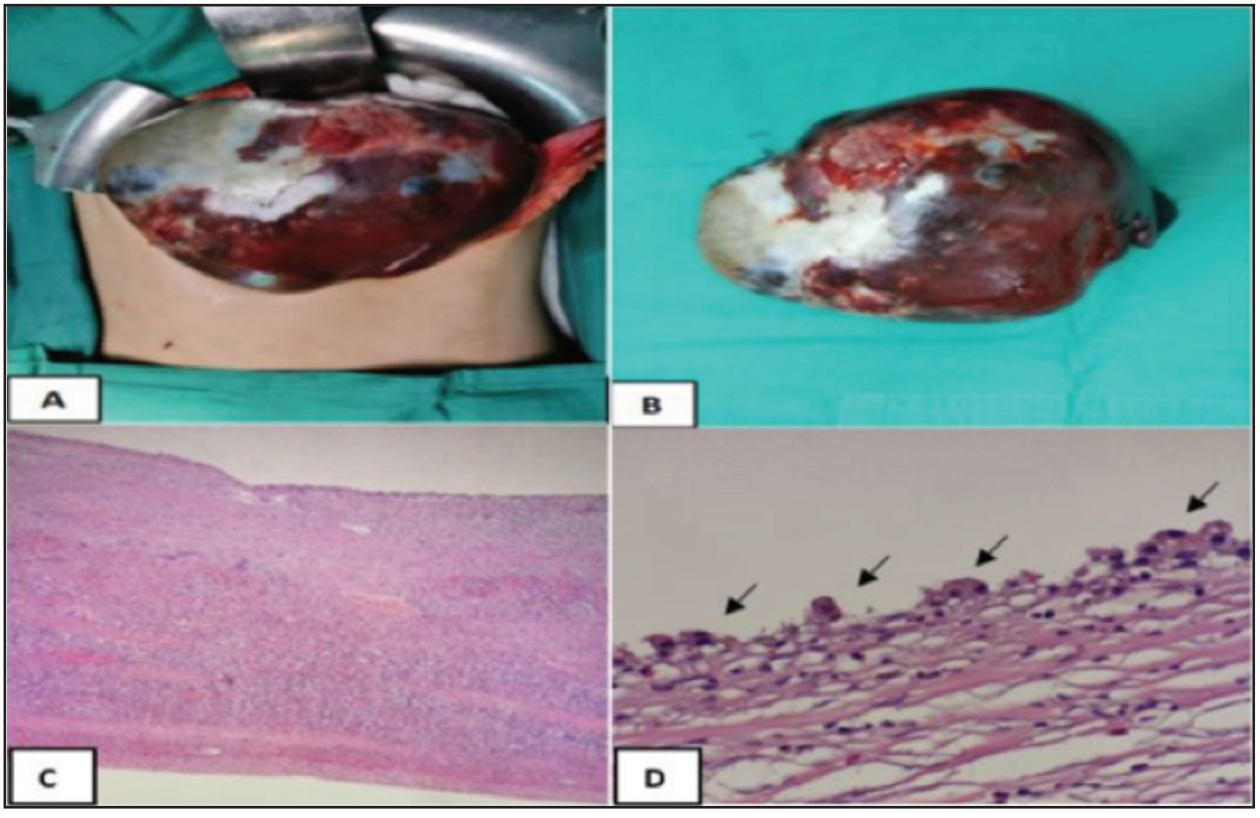

Fig. 2: (A) Giant splenic cyst intra operatively arising from the medial aspect of the spleen occupying the entire parenchyma. (B) Giant splenic cyst measuring 17cm x 15cm x 15cm removed intact together with the spleen. (C) Hematoxylin-Eosin stain: Fibrous wall infiltrated by lymphocytes (4x magnification). (D) Cyst wall lined by cuboidal cells (black arrows) (40x magnification).

The second theory is lymph space theory where the cyst arises from the normal lymph spaces in the spleen. The final theory is endodermal inclusion that proposes that epithelial splenic cyst develops by true metaplasia of the heterotopic endodermal inclusion within the spleen similar to the first theory. But there are studies that report that the epidermoid nature is due to the teratomatous differentiation or inclusion of fetal squamous lining instead of metaplasia.

Splenic cysts are usually diagnosed incidentally unless they are large enough to cause mass effect or complications. Various imaging modalities could be used to diagnose their cystic nature with ultrasound being the initial imaging modality of choice. For large lesion such as our case, cross-sectional imaging such as CECT or magnetic resonance imaging (MRI) is indicated to further characterize the cyst and assess its origin and extension. In this patient, CT scan was done as it was more readily available. Pre-operative

differential diagnosis based on the CT findings included exophytic, complex left liver lobe cyst, pancreatic pseudocyst, or splenic cyst. Pancreatic pseudocyst was considered less likely in the absence of previous trauma or episodes of pancreatitis and a normal looking pancreas. Complex liver cyst was favoured over splenic cyst in view of epidemiological prevalence of liver cyst in our local population and rarity of splenic cyst. Retrospective review of the CT images revealed the enhancing soft tissue at posterior aspect of cyst actually corresponds to the surrounding splenic parenchyma and was misinterpreted as thickened cyst wall. A thin sliver of compressed splenic parenchyma forming sharp interface with the cyst at its anterolateral and inferomedial aspect would further serve as a clue to the origin of the cyst arising from the spleen rather than left lobe of liver.

The definite diagnosis can only be made via histopathology. Most of the primary NPSC are solitary but rarely can be multiple. Histologically, NPSC have an epithelial lining and by using Immunohistochemistry the epithelial cells will be positive for pan cytokeratin and negative for CD 240 (lymphatic marker) and CD34 (an endothelial cell marker). In our case, the final pathological diagnosis was splenic epithelial (Mesothelial) cyst.

Total splenectomy has always been advocated in the treatment of symptomatic large cysts. Recently, spleen preserving surgical approach has been recommended due to the risk of overwhelming post-splenectomy infection (OPSI) (4%) and mortality rate (1.5%). Conservative methods include aspiration, drainage or injecting sclerosing agents but are associated with high recurrence rates and potential risk of bleeding and infection. Moreover, the inflammatory response can lead to dense adhesion and make subsequent surgery difficult. Surgical approach includes partial splenectomy, cystectomy, decapsulation and marsupialization via open or laparoscopic procedure. The preferred surgical method would be laparoscopic partial splenectomy if the cyst is small and done by a highly skilled and experienced laparoscopic surgeon. Cystectomy, decapsulation and marsupialization are simpler with minimal blood loss, but the disadvantaged is a higher recurrence rate. However, total splenectomy is indicated for giant splenic cyst occupying the whole spleen (like our case), or atrophic remnant spleen or splenic cyst involving the hilum.

CONCLUSION

Pre-operative diagnosis of giant NPSC remains a challenge and should be considered a differential diagnosis though rare. Laparoscopic and splenic preserving surgery is the preferred technique of treatment, but it is mainly for relatively small and peripherally located cyst. In our patient, we believe that total splenectomy was the best option and effective method to treat giant epithelial NPSC.

ACKNOWLEDGEMENT

The authors would like to thank the Director General of Health Malaysia to publish this article.

DECLARATIONS

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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CASE REPORT

A rare presentation of ectopic thyroid gland at right axilla

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SUMMARY

The thyroid gland and its hormones play important roles in organ development and in the homeostatic control of physiological mechanisms in human beings. As a result of embryogenic descent of thyroid gland, it commonly resides along the midline – from tongue to mediastinum (90%). Ectopic thyroid gland is a rare occurrence, with extra-lingual ectopic thyroid gland being even rarer. Thus, there is a concern for malignant metastasis. Madam H, a 56-year-old healthy woman presented to the Hospital Sultanah Nora Ismail, Johor, Malaysia in April 2020 with an increasing size of right axilla mass and history of weight loss. She was having right axilla mass for the previous 7 years but only noticed the increase in size about 1 year ago. She has no other constitutional symptoms. A tru-cut biopsy performed demonstrated a benign ectopic thyroid tissue. Thyroid function test showed primary hypothyroidism. Serum Chromogranin A and other thyroid antibodies were within the normal value. Further radiological imaging showed the normal thyroid gland at neck, with no signs of distant malignancy. There was no other axillary, mediastinal or hilar lymph node enlargement. She was started on regular T. L Thyroxine 100mcg daily and given regular follow-up in endocrine clinic. Benign ectopic thyroid gland is an unusual finding. As such, follow up is needed with possibility of carcinomatous transformation such as papillary carcinoma should be considered.

INTRODUCTION

The thyroid gland and its hormones play multifaceted roles in organ development and in the homeostatic control of physiological mechanisms in human beings. During embryogenesis, thyroid gland descends from the floor of the primitive foregut to the final position of the thyroid in the neck. As the result, ectopic thyroid gland can reside anywhere along its embryogenic pathway.

Ectopic thyroid (ET) gland is a rare occurrence. It occurs in 1 per 100,000 to 300,000 individuals.[1] Lingual ectopic thyroid gland accounts for 90% of the reported cases[2] while extra-lingual ectopic thyroid is less frequently encountered. Cases of ectopic thyroid tissue adjacent to the esophagus, heart, aorta and pancreas have also been described. We would like to share a case of rare occurrence of ectopic thyroid gland at the right axilla presented to our center.

CASE REPORT

Madam H, a 56 years old lady presented to the Hospital Sultanah Nora Ismail (HSNI), Johor Malaysia in April 2020 for right axillary mass. She was then referred by the surgical team for optimization of her thyroid function test in September 2020.

On further history, she first noticed the right axilla swelling about 7 years earlier. The size was initially about 4cm X 5cm, non- tender, firm in consistency with no discharges. However, the axilla mass began to increase in size gradually over the previous 1 year for which she sought medical attention in April 2020. During the period of 1 year, she noticed that she had weight loss from 80kg to 60kg. She had loss of appetite as well at the same time. There were no other constitutional symptoms or B-symptoms noted.

She was a school teacher then attached to a local secondary school. She did not have any chronic medical illness prior to presentation to HSNI. She did not drink alcohol beverages nor smoke cigarettes. Madam H was married and blessed with 5 children. There was no family history of thyroid malignancy.

Thyroid function test during initial presentation in May 2020 showed free T4 level at 5.5 mmol and TSH at 0.01 mmol. She was then started on T. L-Thyroxine 100mcg OD (maintenance) in May 2020. The titration of L-thyroxine was done subsequently in visiting endocrine clinic. At the same time, other notable blood investigations like serum T3, thyroid antibodies were sent and described in Table I.

Ultrasonography of the neck showed no significant abnormality of the orthotopic thyroid gland. A tru-cut biopsy was performed on the right axilla mass by the surgical team in April 2020 which was in consistent with benign ectopic thyroid tissue (Figure 1).

After reviewing the histopathology examination result (HPE) of the axilla mass, Madam H underwent computerized tomography scan of neck, thorax and abdomen (CECT TAP) in September 2020 for staging and for further delineation of the axillary mass. CT scan showed an enlarged, heterogeneously mass in the right axillary region with coarse calcification within measuring 7.8cm X 7.0cm X 9.3cm (Figure 2a and 2b). There was no other axillary, mediastinal or hilar lymph node enlargement. The orthotopic thyroid gland was seen at its normal location (midline anterior neck region) and demonstrating homogenous enhancement and normal in size (Figure 2c). Both lung parenchyma were normal.

As Madam H remained clinically euthyroid during the entire period of consultations in HSNI, urgent surgical resection was not performed on her. Her condition was stable on regular T.

This article was accepted: 11 June 2021
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Table I: Results of blood investigations taken during visits to the clinic

Date	Investigation	Result	Normal Range
1/10/2020	Free T3	Low	1.88- 3.18 pg/mL
12/10/2020	Anti- Thyroglobulin	473.0 (High)	< 115 IU/ml
12/10/2020	Anti- Thyroid Specific Peroxidase	19.10	< 34 IU/ml
12/10/2020	Serum Chromogranin A	69	27- 94 ng/ml

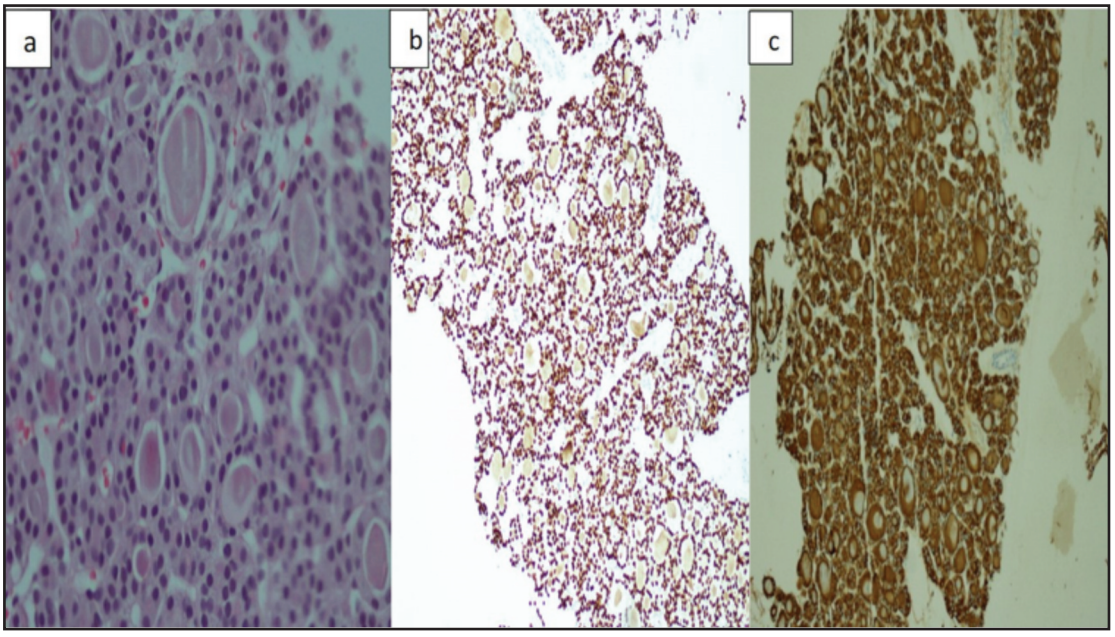

Fig. 1: Histopathological examination shows thyroid follicles of varying sizes (a) with lumen containing colloid. The thyroid follicles are lined by simple cuboidal epithelium having uniform, rounded and basally located nuclei. There are no nuclear features of papillary thyroid carcinoma TTF-1 and thyroglobulin immunoreactivity (b -c) to support thyroidal origin.

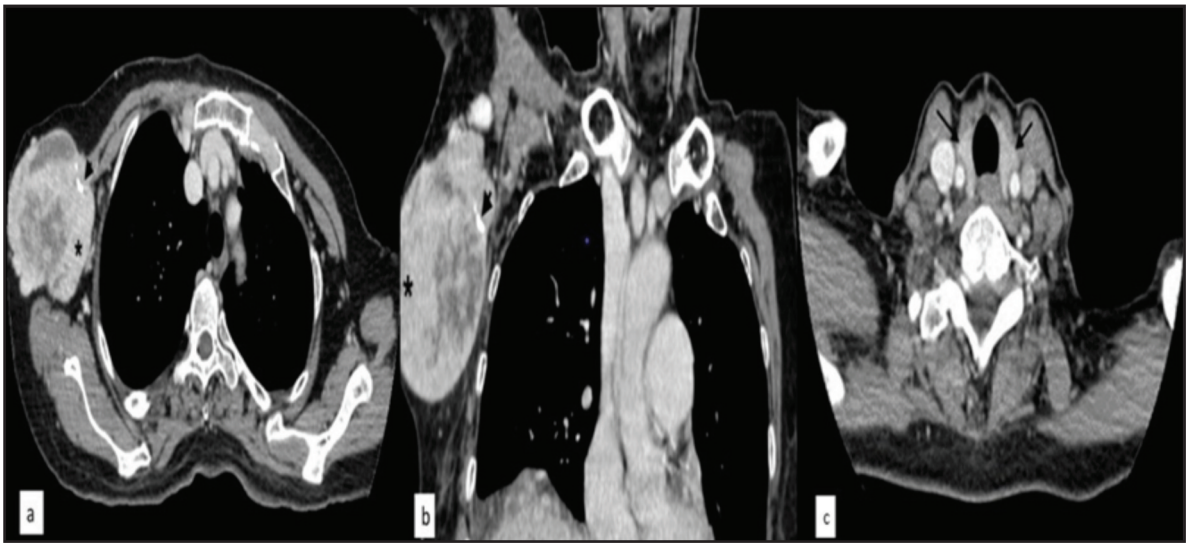

Fig. 2: Axial (a) and coronal (b) contrast-enhanced CT images demonstrating enlarged heterogenous ectopic mass in the right axillary region (asterisk) with coarse calcification within (arrowhead). Contrast-enhanced axial CT (c) demonstrating orthotopic thyroid gland (arrows) with homogenous enhancement, normal in size and at its normal location (midline anterior neck region).

L-Thyroxine 100mcg OD. However, she was later scheduled to undergo wide local resection of the ectopic thyroid gland on her right axilla on an elective operating date.

DISCUSSION

ET is an unusual presentation. The most common sites for an ectopic ET are lingual, thyroglossal and laryngotracheal which corelate with the anatomical descent of thyroid gland during embryogenesis. Only rare case reports exist of ET in other locations, including the chest (heart, trachea), abdomen (liver, gallbladder, pancreas) and pelvis (vagina).[3] The aetiology of this abnormality is not fully understood. However, genetic factors and mutations in the regulatory genes expressed in the developing thyroid gland have been implicated in human thyroid ectopy. ET gland has risk of malignant transformation. The risk involved is less than 1% and almost all are papillary thyroid carcinomas.[4] At the same time, radiation and obesity can increase risk of malignant transformation in ectopic organs including thyroid glands.[5,6] Radiological imaging studies such as ultrasound, CT scan and Magnetic Resonance Imaging (MRI) may be helpful in knowing the extension of ET gland, but the best diagnostic test for the gland is thyroid scanning with technetium-99m.

A thyroid mass usually demonstrates high CT density on plain scan due to the iodine content and homogeneous enhancement after intravenous contrast injection. An ET tissue is typically identical in appearance to orthotopic thyroid tissue, a well-circumscribed homogeneous mass with increased attenuation.[7] However, our patient demonstrated heterogeneous appearance of the right axillary mass, thus malignant transformation or axillary nodal metastasis were suspected initially. This dilemma was solved by tru-cut biopsy HPE reporting as benign thyroid gland. At the same time, serum chromogranin A was in the normal range and this has ruled out possible neuroendocrine tumour involvement.

A case report of benign ET tissue in the left supraclavicular has been reported, having similar CT findings of axillary mass in our patient.[8] CT scans in our case was also vital to provide a detailed picture of masses relation to the other structures of this region to help in pre-operative plan in the future. Scintigraphy offers a useful and effective role to differentiate ET gland from other tumours especially deep-seated tumour such as in the mediastinum[7] where procurement of tissue samples requires deep invasive surgical method. However, Madam H's axilla mass was superficially located and thus superficial percutaneous approach was sufficient to obtain the required biopsy sample.

The treatment of ET tissue depends on factors such as mass size, symptoms, age of the patient, thyroid functional status and histological findings.[9] In symptomatic cases, surgical resection remains the mainstay of treatment. Treatment can also be aided by hormone suppression and radioactive 131-ablation[10] as well. Madam H received hormone replacement therapy in view of her deranged thyroid function test. As she remains euthyroid, wide local resection is being planned later in order to remove the axillary mass mainly because of the compressive symptoms.

CONCLUSION

Benign ET gland is a rare occurrence, more so in the case of lateral aberrant thyroid. Further follow up is needed as possibility of carcinomatous transformation such as papillary carcinoma arising in struma ovarii should be considered.

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Acute compartment syndrome of the forearm: A case report of radius fracture with concomitant brachial artery transaction

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SUMMARY

Acute compartment syndrome (ACS) is a surgical emergency that requires timely recognition and early management for a good outcome. We report a case of a 71-year-old male seen at the Emergency Department of Universiti Sains Malaysia (USM), Malaysia, on anticoagulant therapy for valvular atrial fibrillation, who had sustained a closed fracture of the left distal end radius following a fall. Examination of the left upper limb showed deformity and tenderness over the left wrist, associated with swelling and a tense anterior compartment with blisters formation and rapid expansion of hematoma at the cubital fossa away from the fracture site. Both radial and brachial pulses were absent and confirmed with the absence of a doppler signal over the brachial and radial artery and CT angiography of the left upper limb showed there was a vascular injury of the brachial artery. Fasciotomy of the left upper limb and revascularization of the left brachial artery was done. Intraoperative findings showed a tight anterior compartment with muscle bulging upon compartment release with a complete cut of the left distal brachial artery. The primary end-to-end vascular anastomosis was done and distal circulation was restored. The distal end radius fracture was treated conservatively. The patient underwent split skin grafting of the left forearm after 6 weeks post-injury and went home well. It is critical to recognize a concomitant vascular injury in fracture-related ACS as the clinical feature may overlap. Failure in detection of concomitant vascular injury may lead to emergency fasciotomy without vascular exploration and repair.

INTRODUCTION

Acute compartment syndrome (ACS) is a surgical emergency. Recognizing ACS in a closed distal end fracture of the upper limb with concomitant proximal acute vascular injury may be challenging and easily overlooked. Overlapping of the clinical features between these two conditions in ACS may lead to emergency fasciotomy without a complete vascular assessment and investigations. We report a case of ACS with acute left brachial artery injury in a patient with a closed fracture of the left distal end radius.

CASE REPORT

A 71 years old gentleman with underlying hypertension and chronic rheumatic heart disease with valvular atrial fibrillation (AF), on warfarin therapy was brought to the Emergency Department (ED) of the Universiti Sains Malaysia (USM), Malaysia after sustaining an injury to his left forearm. He fell onto an outstretched hand while herding his cow with a rope. Initially, he sustained swelling and deformity of his left wrist. As time progressed, his entire forearm becomes progressively swollen and painful.

The injury occurred at around 1400H and he arrived at the ED 4 hours later. He was triaged to the Red Zone and was attended to immediately. He was alert, in pain as shown by a constant facial grimace. He was normotensive with good oxygen saturation under room air. His cardiac monitoring showed AF with a rate of 120-130 beats per minute (bpm). His rate slowly improved to 90-100 bpm after the patient was given adequate analgesia. The primary survey was unremarkable. Examination of the left upper limb showed deformity and tenderness over the left wrist, associated with swelling and tense anterior compartment, extending to the elbow joint. There were formation of blisters and rapid expansion of hematoma at the cubital fossa. Both wrist and elbow joints had a restricted range of movement (ROM). The pain was aggravated by the passive stretching of the fingers. The sensation was reduced over the median nerve distribution. The fingers were in dusky coloured and cold (Figure 1A and 1B). The capillary refill time was prolonged. Radial and brachial pulses were absent. Left radius and ulna radiograph showed distal end radius fracture (Figure 2A and 2B). Blood investigations showed a slightly elevated total white cell count of 13.9 x 10^9, haemoglobin of 12.5g/dL, platelet of 253 x 10^9, INR of 2.10, a significant rise in CK level of 12,313 and potassium level of 4.1 mmol/l.

He was subsequently reviewed by the Orthopaedics team. He was clinically diagnosed with ACS even though no intracompartment pressure measurement was done due to the unavailability of the equipment. He also was suspected to have vascular injury due to the absence of doppler signal of brachial and radial arteries based on the bedside handheld Doppler device. Computed tomography angiography (CTA)

This article was accepted: 11 June 2021
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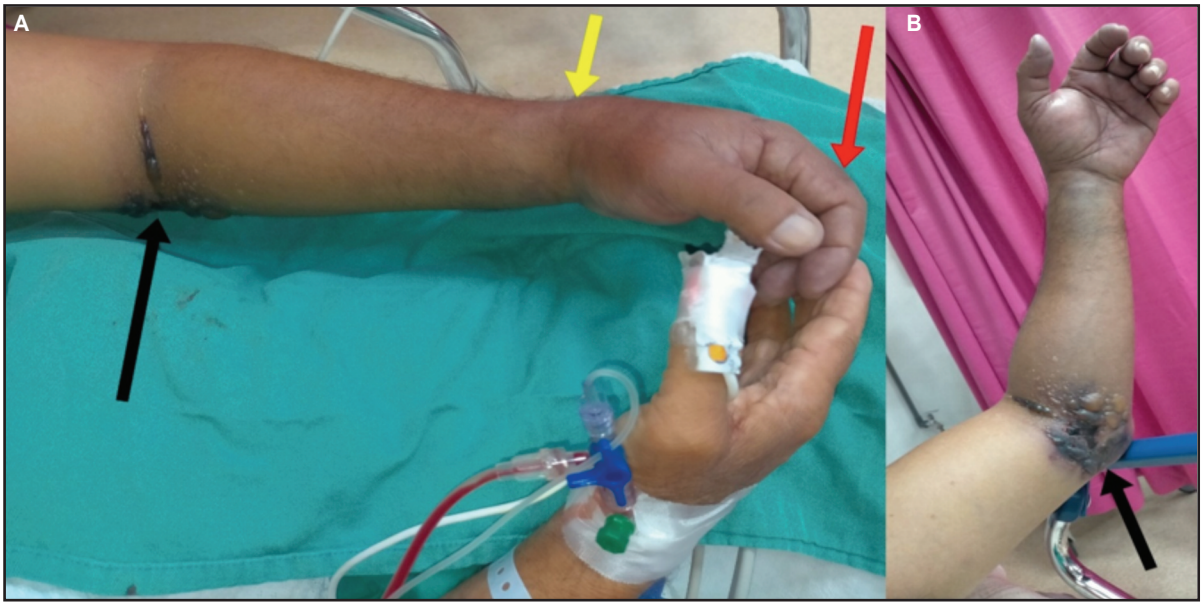

Fig. 1: The red arrow shows the left fingers appear swollen and dusky compared to the right fingers. The yellow arrow shows deformity and swelling over the wrist. The black arrow shows blister and hematoma formation over the medial cubital fossa proximal to the distal end radius fracture.

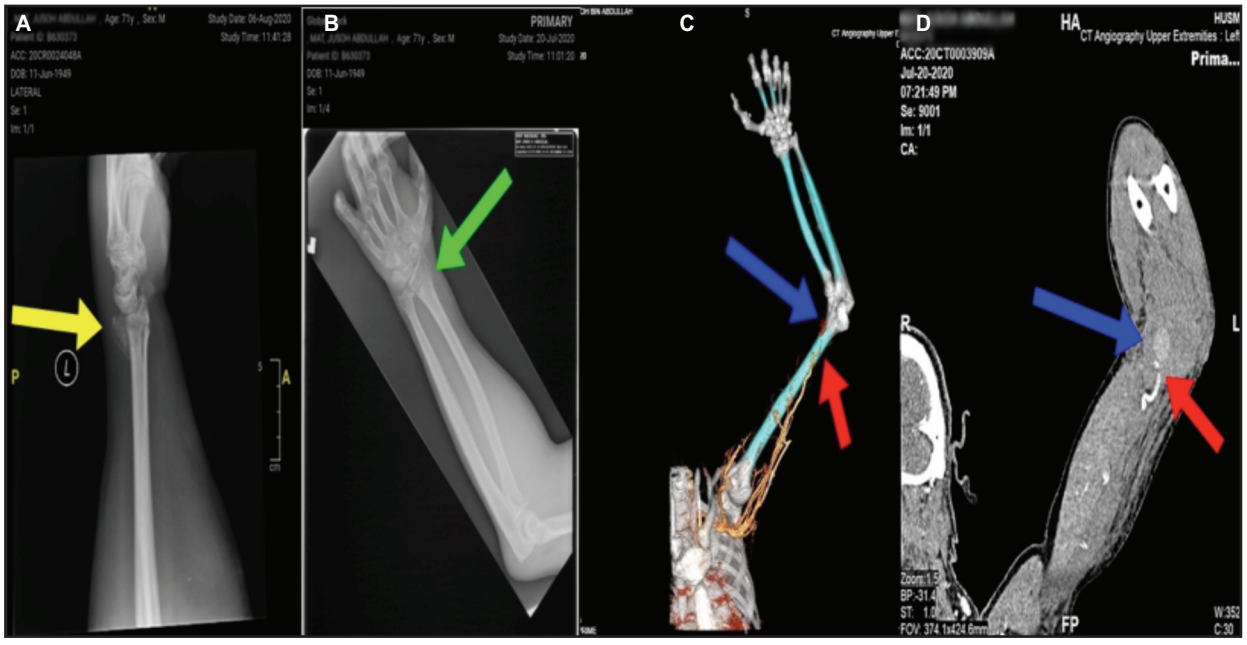

Fig. 2: Yellow arrow shows dorsal angulation of distal end radius on the lateral view of radius-ulna radiograph. The green arrow shows a linear fracture of the distal end radius on the anteroposterior Radius-Ulna radiograph. The red arrow shows abrupt non-opacification to the distal of the left brachial artery, while the blue arrow shows contrast extravasation adjacent to the distal brachial artery which appears to be connected to the injured vessel on the volume rendering technique reconstruction image and coronal reconstruction image of the left upper limb computed tomography angiography.

of the left upper limb was done and the result showed there was an abrupt non-opacification of the distal left brachial artery with contrast extravasation in all phases in keeping with vascular injury (Figure 2C and 2D).

The patient was sent to the Trauma Operation Theatre after 7 hours of the injury for fasciotomy of the left upper limb and revascularization of the left brachial artery. Intraoperative findings showed a tight anterior compartment with muscle bulging upon compartment release. There was a complete cut of the left distal brachial artery before bifurcation to the radial and ulnar artery with surrounding hematoma over the cubital fossa, extending to the proximal forearm. The primary end-to-end vascular anastomosis was done by the

Reconstructive and Plastic Surgery team. Distal circulation was restored as shown by the post-procedural doppler where a triphasic signal was present. The colour of the fingers became pink and there was normal capillary refill time. The distal end radius fracture was treated conservatively.

The raised CK level of 12,313 indicated as a sign of rhabdomyolysis, as a complication of ACS. The patient was put on adequate hydration with a targeted urine output of 3 to 4 ml/kg/h monitoring. The warfarin was temporarily withheld, and he was started on subcutaneous enoxaparin sodium on day one post-operation. The CK value gradually showed downtrend and normalized on day 18 post-injury and no acute kidney injury ensued. 6 weeks post injury, the patient underwent split skin grafting of the left forearm and was discharged home well.

DISCUSSION

ACS occurs when tissue pressure within a closed muscle compartment exceeds the perfusion pressure and results in muscle and nerve ischemia. It is considered a surgical emergency that requires timely recognition and early management for a good outcome. Unrecognised ACS may lead to a non-viable limb. The flexor compartment of the forearm is the commonest site and fracture-related is the most common cause of ACS in the upper limb extremity.[1] Injury to soft tissues without fracture is the second most common cause of ACS and one-tenth of the patients had a bleeding disorder or were taking anticoagulant drugs.[2]

The diagnosis of ACS is always controversial and is based on the clinical hallmark of 5 Ps' - pain, paraesthesia, pallor, paralysis, and pulselessness. However, the most sensitive clinical signs is disproportionate pain and pain on passive muscle stretching (sensitivity 98%, negative predictive value 98%).[3] The remaining 4 P's of ACS are mostly late signs after prolonged ischemia and subsequent neurovascular injury. Pulselessness and paralysis are rare features and usually occur after an arterial injury or after a substantial amount of time has elapsed, particularly in a patient on anticoagulation therapy.[4]

Our patient had all the classic 5 Ps' for ACS during the presentation. It is critical to consider a vascular injury as a cause of ACS if there is a rapid absence of distal pulses and expanding hematoma. In ACS case without vascular injury, the peripheral pulses will be preserved until long after the intra-compartment pressure exceeds the systemic blood pressure and the large arteries are compressed.[5] Pulselessness is considered a late sign. The patient was on anticoagulant (warfarin) therapy for his valvular AF and this should raise the suspicion of haemorrhage that lead to ACS, even though his INR was within the therapeutic range.

The decision either to proceed for operation or perform a CTA of the left upper limb first was crucial in this case. CTA is the gold standard for vascular injury as it provides 100% sensitivity and specificity. Bedside ultrasound doppler did show an absence of radial and brachial pulse. However, this finding was inadequate to distinguish ACS as the sole cause or concurrent presence of vessel injury as one of the causes. Location, nature, and extent of the vascular injury can be objectively identified with CTA and thus guide the approach and type of repair (either end-to-end anastomosis or venous graft). Furthermore, by obtaining CTA, the prognosis and soft tissue viability could be determined via the establishment of collateral circulation.[6]

A CTA of the affected limb must be performed to evaluate the presence, types and level of vascular injury. A volume rendering technique (VRT) and coronal reconstructive CT provide the site and types of vascular injury like spasm, intimal tears, intramural haematoma, pseudoaneurysms, arteriovenous fistula (AVF), vessel transection or avulsion. In this patient, the finding was an abrupt non-opacification to the distal left brachial artery with contrast extravasation in all phases, in keeping with vessel transection. With the imaging, it helps the surgeon to locate the injury and guide the approach and type of vascular repair. Urgent fasciotomy and vascular exploration were required.

CONCLUSIONS

ACS is a clinical diagnosis. ACS caused either by a fracture or vascular injury can manifest as pulselessness on the affected limb. Failure to identify vascular injury may result in only fasciotomy is done without vascular exploration and repair. We recommend that in the setting of minor trauma, past medical history of anticoagulant use with clinical findings of rapid absence of distal pulses and rapid expansion of hematoma away from the fracture site warrant a CTA. Vascular injury must be ruled out prior to fasciotomy and vascular exploration. A VRT reconstruction image and coronal reconstruction image yield an excellent anatomical site, types and the extent of vascular injury.

ACKNOWLEDGEMENTS

The authors would like to thank the staff of the Department of Emergency Medicine, Orthopaedics and Radiology of the HUSM and the patient for his consent to have his case published.

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CASE REPORT

Hypothalamic-pituitary fungal infection causing panhypopituitarism

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SUMMARY

Madam LPS, a 69 years old lady complained of left eye blurring of vision since January 2017. It was associated with left orbital swelling with chemosis, eye redness, epiphora, several episodes of self-limiting epistaxis and bilateral ophthalmoplegia. Other neurological examinations and cerebellar systems were intact. Magnetic Resonance Imaging (MRI) Brain and Orbit were performed, depicting a sellar mass with suprasellar extension with blood investigations results showed panhypopituitarism. She underwent bilateral orbital decompression. Trans-nasal endoscopic biopsy showed suppurative granulomatous lesion, which cultured Candida Albicans and Candida Galbrata. She was started on antifungal and hormonal replacement therapy for panhypopituitarism. Unfortunately, she did not respond well to treatment as repeated MRI Brain on December 2018 showed increase in size of sellar mass causing obstructive hydrocephalus and increasing size of left orbital lesion. She was counselled for another debulking surgery with a ventriculoperitoneal (VP) shunt. HPE taken were reported as chronic inflammatory process in favour to fungal infection. Pituitary infections may mimic pituitary mass. Some may exhibit symptoms of panhypopituitarism as well. Thus, physical examination, MRI brain imaging as well as HPE of biopsy are important aids to achieve diagnosis. Optimal treatment of fungal pituitary abscess includes transsphenoidal surgery combined with antifungal therapy.

INTRODUCTION

The pituitary gland and the sella region are located just below the centre of the brain in the base of the cranium. This central eminence of the middle cranial fossa is specialized as a saddle-like seat for the pituitary gland – known as sella turcica. At the centre of the cranial cavity; lies the pituitary gland. The hypothalamic-pituitary-adrenal axis (HPA axis) is a form of neuroendocrine unit which consists of the hypothalamus, the pituitary gland, and the adrenal glands.[1] The axis plays a major role in basal homeostasis and in body's response to stress.

Any diseases of the hypothalamus or pituitary gland may result in hypopituitarism due to disruption to the hypothalamus pituitary axis. This will cause diminished secretion of hypothalamic-releasing hormones, thereby reducing secretion of the corresponding pituitary hormones. The clinical manifestations of hypopituitarism depend upon the cause of pituitary disease as well as the type and degree of hormonal insufficiency. A person may be asymptomatic or present with symptoms related to hormone deficiency or a mass lesion, or even nonspecific symptoms such as fatigue.

There is currently no information available on hypothyroidism among Malaysian population. The prevalence of hypopituitarism among adults in Northern Spain is 29 - 45 of 100,000 population. Among the causes of hypopituitarism are pituitary tumour (61 %), nonpituitary tumour (9 %), and a nontumor cause (30 %).[2] Pituitary adenomas are the most common cause of sellar masses from the third decade on(clarify age group), accounting for up to 10 % of all intracranial neoplasms.[3] As such, other factor of hypopituitarism due to non-tumour cause like infection to the sella region is often missed. Hypothalamic-pituitary infections are extremely rare lesions which amount to less than 1% of all pituitary lesions.[4]

Here we would like to discuss a rare case of *Candida glabrata* and *Candida Albican* infection masquerading as a sella tumour in a patient seen in Sarawak General Hospital (SGH), Malaysia.

CASE REPORT

Madam LPS was a 69 years old lady with no know medical illness who complained of left eye blurring of vision since January 2017. The onset was sudden and progressively worsened in the next 2 months. It was associated with left orbital swelling with chemosis, eye redness and epiphoria. She also experienced several episodes of epistaxis (moderate amount of fresh blood, resolved with compression). Further history revealed that she began experiencing lethargy, malaise, loss of appetite and loss of weight (70kg to 50kg) for the past 6 months. There was no recent febrile illness, hearing impairment or signs of increase intracranial pressure. She is a housewife with no recent travelling history, bird rearing, and usage of traditional medications / over the counter drugs. She was from a middle-income family with 7 siblings where 1 of her younger brother was diagnosed with lymphoma.

Upon presentation to the SGH l in April 2017, the initial physical assessment revealed worsening bilateral eye ophthalmoplegia with reduced external ocular movement. Right eye showed quadrantanopia and the left eye had complete tunnelling of the visual field. Visual acuity

This article was accepted: 16 June 2021
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Table I: Madam LPS hormonal profile during presentation on April 2017 and other clinic visits in 2018 and 2019

Laboratory Investigation	April 2017	September 2018	September 2019	Normal Range (unit of measurement)
TSH	1.08	0.005	0.005	0.27- 4.2 mU/L
FT4	1.7	23.45	15.40	12-22 pmol/L
Prolactin	6.1			102- 496 uIU/ml
Cortisol	<14	38.2	1646	171 -536 nmol/L
FSH	0.9			26.0 – 135 IU/L
LH	<0.1			15.9 – 54 IU/L
GH	0.3			0.077 – 5 ug/L

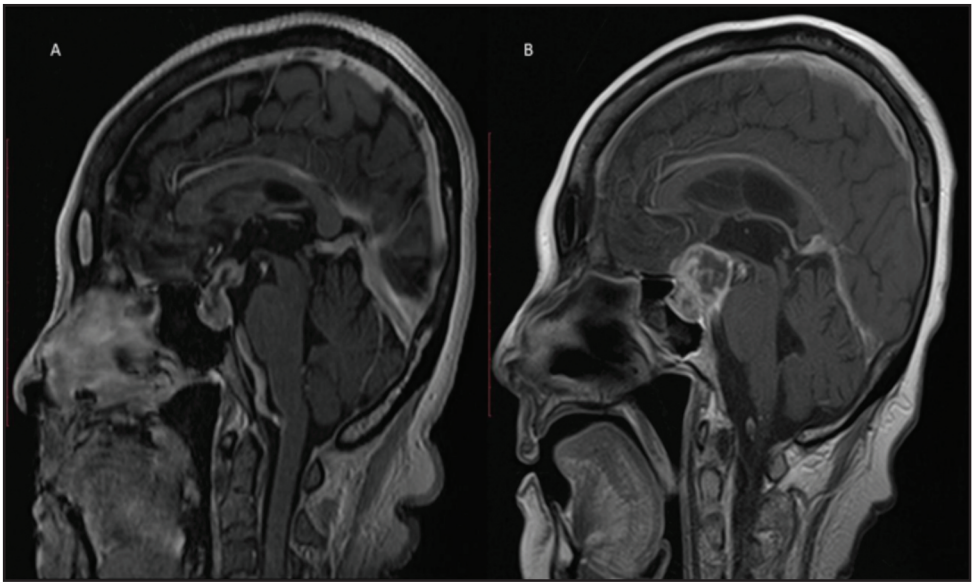

Fig. 1: A) MRI Brain on April 2017 and B) MRI Brain December 2018.

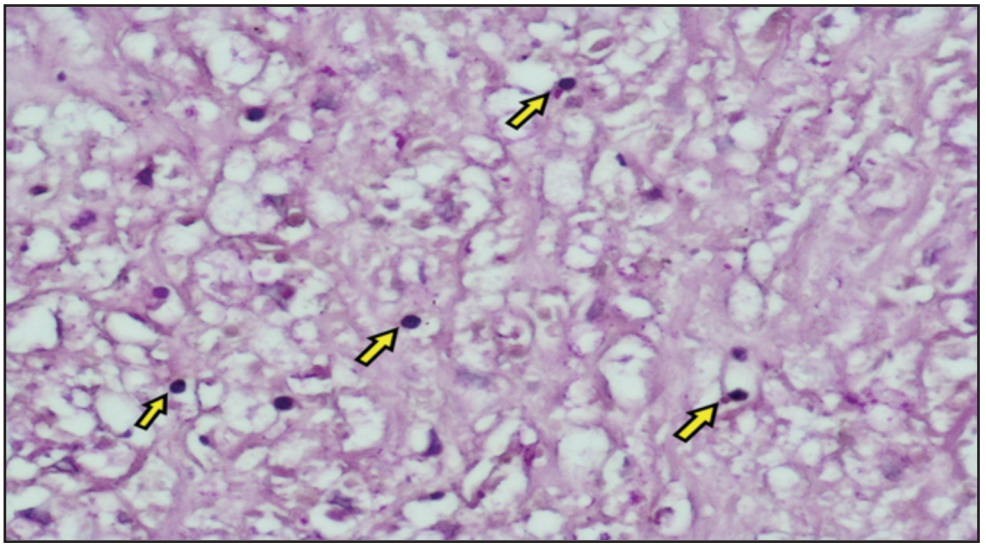

Fig. 2: Periodic acid Schiff stain highlights ovoid yeast cells with no pseudohyphae and characteristic of Candida Galbrata sp at 40x magnification (yellow arrows).

worsened to LE 3/60 and RE 6/45. Other neurological examinations and cerebellar systems were intact. Baseline hormonal profile taken showed panhypopituitarism (Table 1). Biohazards screening for Hepatitis B, Hepatitis C and HIV were negative. Magnetic Resonance Imaging (MRI) Brain and Orbit done was reported as sellar mass with suprasellar extension measuring 1.2x1.3x1.8cm in keeping with pituitary microadenoma or a craniopharyngioma (Figure 1A).

The patient had features that were in keeping with pituitary tumour, she was counselled by the neurosurgical team for a

nasal biopsy to obtain histopathological examination (HPE) samples. Subsequently, she underwent endoscopic nasal biopsy with bilateral orbital decompression in April 2017. Nasal HPE was noted to be suppurative granulomatous inflammation. The nasal fungal culture (C+S) however, grew *Candida albicans* and *Candida galbrata* respectively. Hence, on noticing the positive yield in the fungal culture, she was managed in line for pituitary fungal infection. She was referred to the Infectious Disease team and was started on T. Variconazole 200mg BD for 1-month duration. She was also referred to the endocrinology team for panhypopituitarism. She responded well on maintenance dose of oral Hydrocortisone 10mg/ 5mg/ 5mg, L-thyroxine 50mcg OD and Desmopressin 0.1mg Am/ 0.2m PM. For the treatment of fungal pituitary infection, she was maintained on T. Fluconazole 300mg OD which was planned for 6 months duration. Unfortunately, she developed hepatitis due to oral fluconazole (duration) and her oral anti-fungal medication was stopped.

As she moved into 2018, Madam LPS's condition was regularly monitored in the neurosurgical clinic of SGH. Hormonal profile showed improvement with hormonal replacement and anti- fungal treatment. During her clinic visit in December 2018, she was noted to have on and off fever, lethargy and worsening bilateral lower limb weakness. She was by then continuous bladder drainage (CBD) dependant and had developed sacral sore due to her immobility. A repeated MRI brain on 10/12/18 showed increased in size of sellar mass causing obstructive hydrocephalus and increasing size of left orbital lesion with worsening local involvement (Figure 1B). A ventricular peritoneal shunt (VPS) was inserted by the neurosurgical team to manage the obstructive hydrocephalus and relieved some of Madam LPS symptoms. As her condition was likely due to the resurgence of fungal pituitary infection, Madam LPS was counselled for endoscopic transnasal and transsphenoidal debulking of the lesion with right fascia lata harvest. She agreed for the procedure after being briefed regarding indication and complication of the procedure. At the same time, oral Voriconazole 200mg BD was started as empirical treatment for fungal infection.

After obtaining her consent, the surgery was performed on 24/2/2019. HPE samples were gained and sent for identification and special staining studies. Suprasellar HPE sample were reported as chronic inflammatory process in favour secondary to fungal infection. Special stainings and microscopic examination and stains were performed. Fungal and yeast cell was able to be identified in the microscopic examination (Figure 2). Fungal culture (C+S) however did not yield any growth. She was then allowed home with transfer of care to Hospital Sibu (another tertiary hospital) for regular follow-up to monitor her hormonal profiles and symptoms. Her antifungal (T. Voriconazole 20mg BD) and her hormonal treatment (T. L-Thyroxine 50mcg OD & T. Hydrocortisone 20mg AM, 10mg PM, 10mg ON) were continued and adjusted accordingly by the physician at Hospital Sibu (HS), Sarawak. At HS, she was continued to be monitored by visiting endocrinologist. Hormonal profile taken also showed improvement with hormonal replacements. However, in September 2019, she was admitted to Hospital Sibu for severe sepsis. She succumbed to the illness a few days later.

DISCUSSION

Fungal pituitary abscess is rare as it only amounts to 1% of the pituitary infections.[5] The most common pituitary infections are bacterial in origin namely staphylococci and streptococci. From a review done by Lie et al, most of the fungal pituitary abscess are caused by *Aspergillus* sp. (nine out of ten cases reported).[6] There was one sole case of pituitary abscess which grew Candida sp. In our case, samples taken from Madam LPS's nasal and sellar mass grew *Candida* sp.

The most common presentation of pituitary infections are headache and visual disturbances such as decrease in visual acuity, blurring of vision or loss of vision.[6] Some of the patients may also exhibit symptoms of panhypopituitarism clinically and biochemically. These features may be subtle over months to years and mimic to that in patients with pituitary adenoma. Madam LPS had similar presentation of visual disturbances with panhypopituitarism symptoms such as lethargy, poor oral intake and loss of weight. Her biochemical markers for pituitary function showed adrenal dysfunction which required her to be on hormonal replacement therapy.

Pituitary abscess is most commonly caused by hematogenous seeding of pituitary gland or direct extension of an adjacent infection (meningitis, sphenoid sinusitis, infected cerebrospinal fluid (CSF) fistula).[7] There are several factors involved which may increase the risk of pituitary abscess such as immunocompromised conditions and previous pituitary surgery or irradiation.[8,9] Our patient is an immunocompetent who didn't have any risk factors. Biohazards and diabetes mellitus screening on her were unremarkable. Multiple imaging done on her also showed no concurrent pituitary lesions, like Rathke cleft cysts, pituitary-adenoma or craniopharyngioma which may be a factor that potentiates the risk of infection.

The diagnosis of pituitary infection remains a challenge as relatively few patients present with symptoms of central nervous systems infection. Hence, other modalities of investigations should be utilised to complement the clinical findings. Cultures and swabs from the pituitary lesions via surgical intervention are proven to be beneficial to guide the proper antibiotics treatment. Imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) brain helps to improve the sensitivity with which pituitary lesions are detected and thus, helped to verify the diagnosis of pituitary abscess. Madam LPS's culture grew candida sp. Which lead her to be on antifungal therapy. The repeated fungal culture post transsphenoidal did not yield any growth as she might have been pre-treated earlier on. Nevertheless, the various imaging done on her showed a pituitary mass suggestive on infective in origin. HPE was able to demonstrate presence of fungal/yeast cell by Grocott (methanmine) silver (GMS) stains and Periodic acid Schiff staining as well.

Optimal treatment of fungal pituitary abscess is transsphenoidal surgery combined with antifungal therapy. Surgical option is curative for patients who presented with headache or vision problem as it is directly related to pituitary lesion. Early consultation with infectious disease team is strongly recommended to ensure comprehensive

review and appropriate usage of antifungal therapy. Madam LPS was started on antifungal therapy initially, however her symptoms persisted with increasing size of the pituitary mass leading to removal of it via the transsphenoidal surgery. Post operatively, she was resumed on antifungal Voriconazole as per infectious disease team's suggestions.

CONCLUSION

Fungal pituitary mass is rare and remains a diagnostic challenge. A good clinical history with HPE of tissue obtained will lead us to the correct diagnosis. We need to consider fungal pituitary abscess in the differential diagnosis of pituitary mass as unrecognised pituitary infection will lead to poorer outcome.

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Acknowledgement
July Issue 2021

The Editorial Board of The Medical Journal of Malaysia gratefully acknowledge the following individuals for reviewing the papers submitted for publication:

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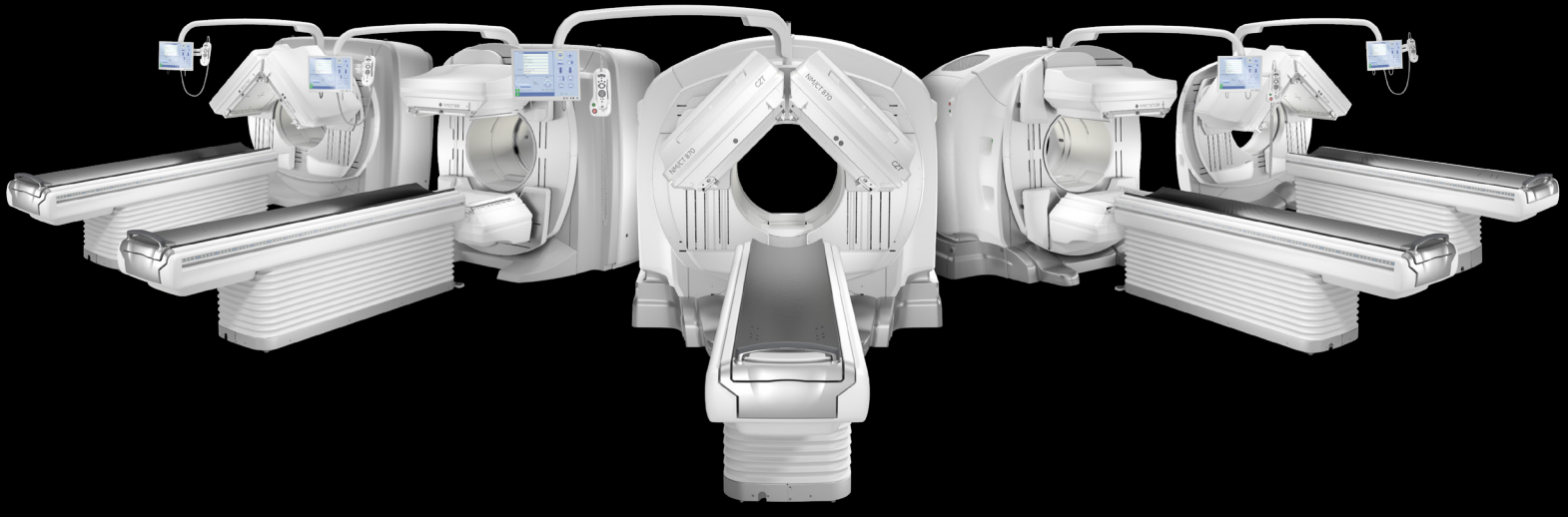

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