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Tel: (03) 4042 0617, 4041 8972, 4041 1375 Fax: (03) 4041 8187
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The Medical Journal of Malaysia

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Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. Med J Malaysia 2020; 75(6): 613-25.

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Books and Other Monographs:
Personal Author(s)
Goodman NW, Edwards MB. 2014. Medical Writing: A Prescription for Clarity. 4 th Edition. Cambridge University Press.

Chapter in Book
McFarland D, Holland JC. Distress, adjustments, and anxiety disorders. In: Watson M, Kissane D, Editors. Management of clinical depression and anxiety. Oxford University Press; 2017: 1-22.

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Comparative analysis of IVF-ICSI outcomes between advanced and early stage of endometriosis stimulated with HMG

Akmal Hisyam Arshad, MBBS[1], Muhammad Azrai Abu, MD[2], Mohd Faizal Ahmad, MD[2], Abdul Kadir Abdul Karim, MD[2]

[1]Department of Obstetrics & Gynaecology, University Institut Teknologi MARA, Sungai Buloh, Selangor, [2]Advanced Reproductive Center, Department of Obstetrics & Gynaecology, Hospital Universiti Kebangsaan Malaysia, Bandar Tun Razak, Cheras, Kuala Lumpur

ABSTRACT

Introduction: Endometriosis is a challenging disease to treat, and patients may eventually need in vitro fertilisation with Intracytoplasmic sperm injection (IVF/ICSI) to conceive after other modalities failed. There are inconsistent outcomes of IVF performance in patients with endometriosis especially with highly purified human menotropin gonadotrophin (hMG). This study was commenced to determine whether the use of hMG affects the IVF outcome in different stage of endometriosis.

Materials and Methods: This is an observational study. Eighty-seven women who had endometriosis confirmed surgically and underwent IVF/ICSI treatment, stimulated with hMG alone were included. Based on the revised American Society for Reproductive Medicine (rASRM), the participants were classified as early endometriosis (I/II) (n=39) or advanced endometriosis (III/IV) (n=35). The main outcome measures used were clinical pregnancy rate.

Results: Women with advanced endometriosis had a lower oocyte yield, less good quality day-3 embryos and lower clinical pregnancy rate compared with the mild endometriosis. However, higher fertilisation rate were recorded in advanced stage endometriosis compared to milder disease.

Conclusions: The rASRM classification of endometriosis is valuable in predicting IVF outcome as advanced endometriosis performs poorly compared to a milder disease. Highly purified hMG could be an alternative as an ovarian stimulation in endometriosis.

INTRODUCTION

Endometriosis is a disease characterised by presence of endometrial glands or stroma in sites other than the uterine cavity. It is considered as one of the challenging gynaecologic diseases in reproductive medicine and it affects 2-10% of women in general population.[1] However, the prevalence of endometriosis in women who seek fertility treatment in much higher at 20.50%.[2]

Various reasons have been attributed to cause reduced spontaneous conception, including altered pelvic anatomy due to formation of fibrosis and adhesion, ovulatory dysfunction following chronic ovarian inflammation,[3] dysregulation of folliculogenesis because of elevated radical oxidative stress and impairment in cytokine, growth factor, and interleukin homeostasis as well as flawed implantation due to alteration in endometrial receptivity.[4] All these conditions may adversely affect the reproductive system of women.

To date, endometriosis is commonly staged using the revised American Society Reproductive Medicine (rASRM) classification, in which stage I and II are considered as early stage or mild endometriosis, and stage III and IV considered as advanced.[5] In women with endometriosis, the European Society of Human Reproduction and Embryology recommends *in vitro* fertilisation and embryo transfer (IVF-ET) as a viable fertility treatment.[6]

However, the outcomes of IVF-ET are not the same in women with endometriosis compared to other patients due to different causes of infertility. In one meta-analysis by Rossi et al., advanced endometriosis had a lower live birth rates following IVF compared with mild disease.[7] In contrast, another meta-analysis in a larger endometriosis population revealed a weak association between successful pregnancy outcomes following IVF according to the stage of endometriosis.[8]

The results of different studies differ, and this could be due to the type of gonadotropin stimulation used. Current evidence is still inconclusive with regards to the types of gonadotropin stimulation and a successful IVF outcome in women with endometriosis. One meta-analysis proved that highly purified human menotropin gonadotropin (hMG) has been shown to achieve similar ovarian stimulation compared with recombinant FSH.[9] But the evidence to support the effect of hMG for different stages of endometriosis is limited.

The present study was undertaken to investigate the outcomes of IVF in ovarian stimulation with human menopausal gonadotropin in patients in different stages of endometriosis in order to form the basis of providing the best advice for patient.

This article was accepted: 10 September 2021
Corresponding Author: Akmal Hisyam Arshad
Email: dr_akmal@yahoo.com

MATERIALS AND METHODS

Study participants

This retrospective observational cohort study was carried out at tertiary teaching hospital in Kuala Lumpur, Malaysia. The study was approved by local research and ethics commission board committee with ethics approval reference code project: FF-2020-375. The data of the participants from January 2016 to June 2020 was retrieved from the Universiti Kebangsaan Malaysia Medical Centre record unit.

The inclusion criteria were women who were surgically diagnosed with endometriosis and have underwent their first attempt *in vitro* fertilisation/intracytoplasmic sperm injection (IVF/ICSI) were identified. The data were retrieved and classified using revised American Society Reproductive Medicine (rASRM) either into early disease (stage I-II) or advanced disease (stage III-IV).

Women who had received recombinant gonadotrophin stimulation, had elevated day-2 FSH level (>15 IU/l), were >40-year-old were excluded. Severe male factors defined as total spermatozoa count of <5 million per ejaculate were also excluded. Figure 1 shows the flow of patient selection and reasons for exclusion.

Ovarian stimulation, oocyte retrieval, and intracytoplasmic sperm injection procedures

All patients had an ovulation stimulation with daily subcutaneous injections of human menopausal gonadotropin (Menopur, Feriing, Germany) at appropriate doses between 225 and 300IU. The ovarian response to treatment was tracked by transvaginal ultrasound. Gonadotrophin releasing hormone (GnRH) antagonist was not used routinely and if was used, it was started once the leading follicle reaches 14mm. Once the dominant follicle reached 18 mm in diameter, 10,000IU human chorionic gonadotropin (Pregnyl®, Merck Sharp & Dohme Limited, UK) were injected to trigger ovulation.

Oocyte retrieval was performed after 34-36 hour under sedation and later fertilised. Intracytoplasmic sperm insemination (ICSI) was implemented for all mature oocytes three hours after retrieval. The oocytes were examined for fertilisation on the following day and cultured in a 20µL of G-TL (Vitrolife, Sweden) enclosed in 3mL of Ovoi (Vitrolife, Sweden) under effect of 5.5% CO_2 and 5.0% O_2.

At day-3, the embryos were evaluated based on the number of the blastomeres, shape and fragmentation. Cultivated embryos were graded and recorded according to their morphology and cleavage stage according to Gardner classification.

Fresh embryo transfer and luteal phase support

A single or double embryo transfer (ET) was performed 3-5 days after oocytes aspiration. The decision was based on the discussion between the clinician and couple, which included previous IVF outcomes, patients age and multiple pregnancy and cost concerns. One or two embryos were immersed in 1mL of embryoglue (Vitrolife, Sweden) and placed for 15 minutes. Later, a transfer catheter (Kitazato, Shizuoka, Japan) which was loaded with the embryos was used under transabdominal ultrasound guidance. All patients received luteal phase support with a combination of oral and vaginal progesterone for at least two weeks.

Assessment of hCG positive, clinical pregnancy and implantation rates

The serum hCG concentrations of patients were recorded 14 days after embryo transfer to confirm pregnancy. Biochemical pregnancy referred to as elevated serum b-HCG levels (>5IU/mL) taken 14 days after ET. Women with positive biochemical pregnancy had a serial ultrasound monitoring, to determine the gestational sac(s) with foetal cardiac activity at four weeks after embryo transfer and considered as clinical pregnancy.

The primary outcome of interest in the study was to determine the clinical pregnancy rate, defined as the presence of gestational sac on vaginal ultrasonography. Secondary outcomes included the number of oocytes obtained, fertilisation rate, number of blastocysts cultured, biochemical pregnancy and ectopic pregnancy, and miscarriage.

The oocytes response, embryo grade and pregnancy outcome, including biochemical pregnancy rate and clinical pregnancy rate, were analysed. Only data from first cycle of fresh transfer were included.

Statistical analysis

Statistical analyses were carried out with SPSS version 26.0 software (SPSS Inc., Chicago, IL, USA). Shapiro-Wilks test was used to evaluate the distribution of the data. The Continuous data were presented as mean±standard deviation (SD). Statistically significant differences in groups were compared with one-way analysis of variance (ANOVA) with Bonferroni adjustment or Kruskal-Wallis test as appropriate. Categorical variables were presented as percentages and numbers. Differences between proportions or rates were evaluated with the chi-square test.

RESULTS

A total of 74 women with endometriosis who fulfilled the inclusion and exclusion criteria were identified. The characteristics of the patients are shown in Table I. Women with advanced endometriosis were younger but had a longer infertility duration than patients with mild endometriosis. The type of subfertility and body mass index (BMI) were comparable between the two groups. In mild endometriosis, two third of subjects had their day-2 basal serum CA-125 elevated more than 35U/mL but majority (97.1%) of advanced endometriosis had an elevated basal CA-125.

In our study, all patients had a fresh embryo transfer, either on day-3 or day-5, and no cancellation of cycle was observed. The IVF laboratory parameters and IVF outcomes are presented in Table II. Patients with mild endometriosis had more oocytes retrieved but had a lower fertilisation rate compared to advanced disease. The quality of the embryo of both groups at day-3 was comparable and statistically significant. In early disease, 22 patients (56.4%) had embryo transfer using day-3 embryo and 17 patients (43.6%) had

Table I: Baseline characteristics of the endometriosis patients who underwent HMG stimulation according to rASRM stages

	ARSM staging		p-value
	I/II (n = 39)	III/IV (n = 35)	
Age (mean±SD)	32.7±3.5	30.2±3.3	p=0.954
Body Mass Index (mean±SD)	22.6±3.1	22.7±3.1	p=0.196
Duration of subfertility (mean years±SD)	3.4±1.3	4.3±4.3	p<0.05a
Subfertility (%)			
Primary	26 (66.6)[b]	31 (68.6)	p<0.001[c]
Secondary	13 (33.4)[b]	4 (31.4)[b]	
Day 2 basal serum CA125 (U/mL) (%)			
≤35	13 (33.3)	1 (2.9)	p=1.000
≥36	26 (66.6)	34 (97.1)	

a<0.05. Data presented in mean±SD and subjected to Mann-Whitney test; b<0.001. Data presented in percentage and subjected to Chi-Square test; c<0.001. Comparison between group using Pearson Chi-Square test.
Note: SD, Standard Deviation

Table II: The overall outcomes of women with mild and advanced endometriosis who underwent IVF-ICSI cycles with hMG stimulation and fresh embryo transfer

	ARSM staging		p-value
	I / II (n=39)	III / IV (n=35)	
No. oocytes retrieved per cycle (mean±SD)	5.3±5.8	4.4±5.9	p=0.554
No. of fertilized (mean±SD)	3.3±2.4	4.3±3.1	p=0.266
Fertilization rate (%)	50.2 %	56.8 %	
Embryo grade on transfer (%)			
I	29 (74.4)	22 (62.9)	p<0.001[c]
II	7 (17.9)[b]	8 (22.9)[b]	
III	3 (7.7)[b]	5 (14.3)[b]	
Day of embryos transferred (%)			
Day 3	22 (56.4)	19 (54.3)[b]	p<0.001d
Day 5	17 (43.6)	16 (45.7)[b]	
Biochemical pregnancy rate (%)	27 / 39 (69.2)	11 / 35 (31.4)	p=0.074
Clinical pregnancy rate (%)	18 / 39 (46.1) (17.1)	6 / 35	p=0.016[c]

Note: SD, Standard Deviaiton
b<0.001. Data presented in percentage and subjected to Chi-Square test; c<0.05. Comparison between group using Pearson Chi-Square test; d<0.001. Data presented in percentage and subjected to Chi-Square test.

embryo transfer with day-5 embryo. Meanwhile, in advanced endometriosis, 19 patients (54.3%) had embryo transfer using day-3 embryo and 16 patients (45.7%) had embryo transfer with day-5 embryo.

Biochemical pregnancy was achieved in 69.2% of women with a mild disease but only 31.4% in advanced disease. Clinical pregnancies were 46.1% and 17.1% for mild and advanced endometriosis, respectively.

DISCUSSION

Among the patients recruited in this study, even though it was not significant difference, we noticed that patients with advanced stages of endometriosis were younger than the ones with mild disease. This is possible because patients with severe endometriosis could have presented earlier for other symptoms like dysmenorrhea, leading to an early laparoscopic diagnosis and IVF treatment. Most of the patients with advanced disease had an elevated basal serum CA-125 compared with those with mild disease. Our finding is consistent with previous studies in which high level of serum CA-125 directly correlates with advanced endometriosis.[10] However, it has limited role in IVF/ICSI as it was considered as nonspecific marker and poor predictor for IVF outcomes.[11]

In our study, it was observed that various aspects of IVF were badly affected by advanced stage endometriosis, especially the number of oocytes obtained, embryo quality, implantation, and clinical pregnancy rate. Sonja et al. (2014) also reported these findings, which showed the success rate for IVF was also reduced as the disease severity progresses.[12] The low response could be due to the nature of the disease or the type of previous ovarian surgery.

Highly purified menotropin gonadotrophin is perceived to perform lower than the recombinant FSH, although a recent meta-analysis proved that hMG achieved a similar result compared with recombinant FSH as an ovarian stimulation.[13] In one study in which recombinant FSH was used for IVF stimulation in endometriosis, the author also showed that advanced endometriosis had a worse prognosis for IVF treatment than mild stage.[14] Similarly, when hMG was used in this study, the findings consistently showed that advanced disease had more unsatisfactory IVF performance than mild disease. This study had shown that severe or advanced endometriosis had a detrimental effect on IVF outcome using HMG. This outcome maybe similar irrespective of the type of gonadotropin used as demonstrated in meta-analysis by Bordewijk EM et al.[13]

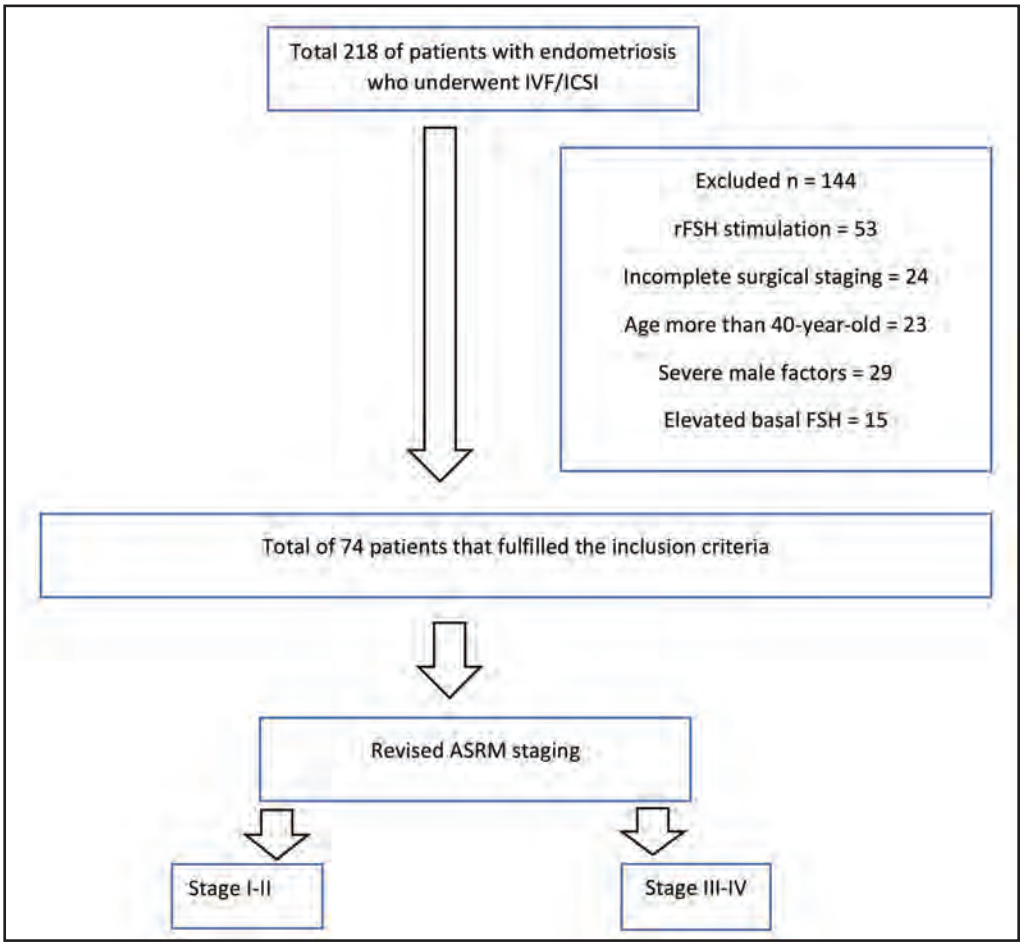

Fig. 1: Flow chart showing participants excluded patients excluded from the study.
Note: rFSH = recombinant FSH

It is also important to note that a lower fertilisation rate was recorded in mild endometriosis in our study. This could have resulted from the ongoing secretions by the active glands seen in the mild group, as a previous study showed that peritoneal fluid of women with active lesions has a higher chemotactic activity.[15] However, 74.4% of the fertilised embryos were of excellent quality at day-3 compared with the advanced disease despite a lower fertilisation rate. This explained the higher rate of both biochemical and clinical pregnancy rates in mild disease than the advanced disease.

The current findings also have several clinical importance. Firstly, the rASRM classification is considered reliable in predicting the IVF outcome of infertility treatment, which can be useful for counselling. Advanced endometriosis translates a worse prognosis for IVF outcomes compared to milder stages. Secondly, the usage of hMG as ovarian stimulation in endometriosis is not inferior compared with recombinant FSH, making it a suitable alternative medication. Lastly, it can be concluded that fertilisation rates are not impaired in all endometriosis stages.

It is important to note that there was no cycle cancellation in our study and only pregnancy outcomes of fresh embryo transfer in endometriosis were analysed. The outcomes could be different in a case of frozen embryo transfer. Endometrial receptivity, on the other hand, could be negatively affected in patients with endometriosis. More studies are required to support this point of view.

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ORIGINAL ARTICLE

Ocular co-morbidities in patients with atopic dermatitis - a cross-sectional study from a tertiary referral hospital, Malaysia

Gan Teck Sheng, MRCP[1], Amalina Juares Rizal, MOphthal[2], Nurul Laila Binti Salim, MMed Ophthalmology[2], Lindfay Laura Lau, MOphthal[2], Voo Sook Yee @ Michelle, Adv Master of Derm[1]

[1]Department of Dermatology, Queen Elizabeth Hospital, Ministry of Health Malaysia Sabah, [2]Ophthalmology Department, Queen Elizabeth Hospital, Ministry of Health Malaysia, Sabah

ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic relapsing pruritic inflammatory skin disease that commonly occurs among children as well as adults. AD patients were reported to have high prevalence of ocular manifestations, which may be due to the disease nature or drug complications. This study aimed to determine the prevalence of ocular manifestations in patients with AD.

Materials and Methods: Eighty patients who fulfilled the UK Working Party's Diagnostic Criteria for Atopic Dermatitis were included in the cross-sectional study. A standardized case report form was formulated to collect the demographic data and disease profile of the participants. AD severity was evaluated using the EASI and SCORAD score. All patients underwent a complete ophthalmological evaluation.

Results: The prevalence of ocular manifestations among the patients with AD was 48.8%. Fifty-four (67.5%) patients had facial dermatitis and 37 (46.2%) showed periorbital signs. The mean AD disease duration was 10.99 ± 11.20 years. Majority of the patients had mild to moderate AD. The most frequent ocular manifestation was allergic conjunctivitis (18.75%) followed by cataract (8.75%) and ocular hypertension (8.75%). Among the patients with ocular manifestations, 27 (69.2%) patients regularly applied topical corticosteroids on the face. The use of systemic corticosteroids was seen in 19 (42.2%) patients. Prolonged AD duration was significantly associated with the development of ocular manifestations.

Conclusions: Nearly half of the patients with AD were complicated with ocular disease regardless of the AD severity, facial dermatitis and presence of periorbital signs. Long disease duration is associated with ocular manifestations, especially steroid related complications.

KEYWORDS:
Atopic eczema, ocular co-morbidities, ocular complications, ophthalmic disease, atopic conjunctivitis

INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing pruritic inflammatory skin disease that commonly occurs among children, but it also affects adults.[1] Patients with AD have higher prevalence of ocular co-morbidities compared to the normal population.[2] Various structures of the eyes may be affected, including the lids, ocular surface, conjunctiva, cornea, lens and retina. The frequency of these disorders ranges from 25-50%.[3]

The economic burden of atopic dermatitis to nations varies significantly across countries. The direct healthcare cost of a patient in less developed countries (Malaysia, Indonesia and Philippines) is estimated to range from USD199 to 743 which represents a substantial medical cost.[4] The development of ocular complications directly or indirectly secondary to atopic dermatitis may negatively impact the psychosocial wellbeing of the patients leading to higher incidence of depression and anxiety disorder.[5]

However, ophthalmological evaluation is not a routine standard procedure for patients with atopic dermatitis in Malaysia. Therefore, it can be important to detect ocular complications early and implement annual ocular screening for patients with atopic dermatitis. There is lack of data on ocular complications among patients in Malaysia with atopic dermatitis which necessitates clinical study on this topic.

The primary objective of this study is to determine the prevalence of ocular manifestations in patients with AD. The secondary objective of this study is to determine the association between the severity of AD and systemic corticosteroids use and the presence of ocular complications.

MATERIALS AND METHODS

This was a cross-sectional study done at Queen Elizabeth Hospital, a dermatology referral centre in Sabah, East Malaysia. All patients with AD attending the Dermatology Outpatient Clinic between 18th November 2019 and 31st December 2020 were invited to participate in the study.

The inclusion criteria were patients with atopic dermatitis aged 2 to 60 years. The diagnosis of AD was made based on the United Kingdom Working Party's Diagnostic Criteria for Atopic Dermatitis.[6] All patients were examined and evaluated by two investigators. The exclusion criteria were patients with underlying systemic disease requiring systemic

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Corresponding Author: Dr Gan Teck Sheng
Email: ganteckshengmail.com

Table I: Patient Demographics, Prevalence and Characteristics of Patients with Dysphagia

Variables	n (%)
Gender	
Male	43 (53.8)
Female	37 (46.3)
Age of diagnosis (mean ± SD)	7.67±10.51 years
Age range	2-60 years
Age group	
2-18	47 (58.7)
>1833 (41.3)	
AD disease duration (mean ± SD)	10.99±11.20 years
< 1 year	4 (5)
1 - 5 years	28 (35)
5 – 10 years	19 (23.8)
> 10 years	29 (36.3)
Presence of family history of atopy	63 (78.8)
Past Medical History	
Atopy	40 (50)
- Bronchial asthma	15 (18.8)
- Allergic rhinitis	18 (22.5)
- Asthma & rhinitis	7 (8.8)
Hypertension	2 (2.5)
Others (IDA & fibromyalgia, ectodermal dysplasia, ADHD, hepatitis B)a	4 (5.0)
No past medical history	34 (42.5)
Presence of facial dermatitis	54 (67.5)
Periorbital signs	
- Dennie-Morgan fold	21 (26.3)
- Periorbital darkening	27 (33.8)
- Eyelid dermatitis	30 (37.5)
Severity of atopic dermatitis	
EASI score (mean ± SD)	11.61±10.18
SCORAD score (mean ± SD)	33.69±13.97
EASI	
Almost clear (0.1 – 1.0)	4 (5)
Mild (1.1 – 7.0)	28 (35)
Moderate (7.1 – 21.0)	35 (43.8)
Severe (21.1-50.0)	13 (16.3)
SCORAD	
Mild (<25)	29 (36.3)
Moderate (25-50)	40 (50)
Severe (>50)	11 (13.8)
Cumulative prednisolone dose/ year (mean)[b]	161.07±316.72mg
Range	50.0-9970.0mg
Treatment	
Topical corticosteroids	79 (98.8)
Topical calcineurin inhibitors	18 (22.5)
Systemic steroids	45 (56.3)
Systemic steroid sparing immunosuppressants *(e.g. Azathioprine, methotrexate)*	16 (20.0)

[a] IDA iron deficiency anaemia, ADHD attention deficient hyperactive disorders
[b] Cumulative amount of oral prednisolone used in mg per year

Table II: Types of ocular manifestations

Ocular manifestations	n (%)
Paediatric group (n=47)	22 (46.8)
Adult group (n=33)	17 (51.5)
Lid disorders	
- Blepharitis	2 (2.5)
Conjunctival disorders	
- Allergic conjunctivitis	15 (18.75)
- Keratoconjunctivitis	1 (1.25)
Cataract	
- Anterior subcapsular	3 (3.75)
- Posterior subcapsular	4 (5.0)
Ocular hypertension	7 (8.75)
Dry eye syndrome	1 (1.25)
Epiblepharon	6 (7.5)

Table III: Association between ocular manifestations and steroid use, disease severity & disease duration

Variables	Presence of ocular manifestation Frequency (%) n=39	No ocular manifestation Frequency (%) n=41	p-value
Topical steroid			
Face	27 (69.2)	24 (58.5)	0.319
Others	12 (30.8)	17 (41.5)	
Systemic corticosteroid			
Yes	19 (42.2)	26 (57.8)	0.185
Othersa (other treatment or none)	20 (57.1)	15 (42.9)	
Presence of facial dermatitis			
Yes	28 (71.8)	26 (63.4)	0.424
No	11 (28.2)	15 (36.6)	
Presence of periorbital signs			
Yes	18 (46.2)	19 (46.3)	0.987
No	21 (53.8)	22 (53.7)	
EASI severity index			
Almost clear to mild	14 (35.9)	18 (43.9)	0.465
Moderate to severe	25 (64.1)	23 (56.1)	
EASI severity index			
Mean (SD)	12.1 (10.78)	11.1(9.67)	0.630
SCORAD severity index			
Mild	13 (44.8)	16 (55.2)	0.477
Moderate	22 (55.0)	18 (45.0)	
Severe	4 (36.4)	7 (63.6)	
SCORAD severity index Mean (SD)	34.0 (13.3)	33.4 (14.7)	0.871
Disease duration Median (IQR)	10 (19.0)	5 (8.75)	0.031

[a]Others: Other systemic immunosuppressants such as azathioprine or methotrexate or none

Table IV: Association between steroid-related ocular complications and disease duration

	Steroid-related ocular complications (n=10) Frequency (%)	No ocular complications (n=70) Frequency (%)	p- value
Disease duration Median (IQR)	13.5 (27.0)	6.3 (9.0)	0.006

corticosteroids or immunosuppressants, presence of other skin diseases with ocular manifestations, patients with allergic rhinitis and or allergic conjunctivitis requiring topical immunomodulators and patients who were unable to undergo ocular assessment.

A standardized case report form was formulated to collect the demographic data and disease profile of the participants. The usage of topical corticosteroids on periocular region as well as the cumulative dose of systemic corticosteroids were obtained. AD severity was evaluated using the EASI and SCORAD score.[7] A complete ophthalmological evaluation was performed by an ophthalmologist that included visual acuity, slit lamp examination, ocular tonometry and dilated fundus examination. Eyelid dermatitis, periorbital darkening and Dennie-Morgan fold were categorised as periorbital signs. Posterior subcapsular cataract and ocular hypertension were categorised as steroid-related complication. The ophthalmological evaluation was done once and subsequent review will be provided if any pathology is detected.

The data collected were analysed using Statistical Package for the Social Sciences version 24. Categorical data were analysed using Chi-square test and presented as numbers (percentages). Continuous data were analysed using t test and Mann Whitney test. The analysed data were presented as mean±standard deviation or median and interquartile range. The level of significance was set at $p<0.05$.

RESULTS

A total of 80 patients participated in the study with 43 (53.8%) males and 37 (46.3%) females. The mean age at presentation was 7.67±10.51 years. A total of 63 patients (78.8%) had family history of atopy. The mean disease duration was 10.99±11.20 years. Half of the patients had personal history of atopy which included bronchial asthma, allergic rhinitis, or both. The prevalence of ocular manifestations among the paediatric group (2-18 years) and the adult group were similar (46.8% and 51.5% respectively). Out of the 80 patients, 54 (67.5%) had facial dermatitis and 37 (46.2%) showed periorbital signs including eyelid dermatitis, periorbital darkening and Dennie-Morgan fold. The mean EASI and SCORAD scores were 11.61±10.18 and 33.69±13.97 respectively. The majority of the patients had mild to moderate AD. The mean cumulative dose of oral prednisolone was 161.07±316.72mg/ year. Thirty-nine (48.8%) patients had ocular manifestations and out of which, 15 (18.75%) had allergic conjunctivitis, seven (8.75%) had cataract, seven (8.75%) had ocular hypertension, two (2.5%) had blepharitis and one (1.25%) had keratoconjunctivitis. Table I shows demographic and clinical characteristics of AD

patients with ocular manifestations. Table II shows the types of ocular manifestations among AD patients.

Among the patients with ocular manifestations, 27 (69.2%) patients regularly applied topical corticosteroids on the face including the periorbital region. The use of systemic corticosteroids was seen in 19 (42.2%) patients. There was no significant correlation between presence of ocular manifestations and the use of topical corticosteroids (p=0.32) on the face as well as systemic corticosteroids use (p=0.19). The severity of AD, facial dermatitis and presence of periorbital signs did not affect the prevalence of ocular involvement. Table 3 shows the association between ocular manifestations and steroid use, disease severity and disease duration.

In our study, out of the seven patients with cataract, six (85.7%) had moderate to severe AD, five (71.4%) had history of topical application of class VI corticosteroids on the face or periorbital region; however, five of them also had history of systemic steroid usage with a mean cumulative prednisolone dose of 350-4135mg per year. A longer atopic dermatitis disease duration was significantly associated with ocular manifestations (p=0.002) and the development of steroid-related ocular complications (p=0.03). Table IV shows the association between steroid-related ocular complications and disease duration.

DISCUSSION

Atopic dermatitis (AD) is a chronic inflammatory skin disease that is associated with various ocular manifestations. Patients with AD are at risk of developing ocular comorbidities, which includes allergic conjunctivitis, blepharitis, keratoconjunctivitis, keratoconus, glaucoma, cataract and retinal detachment.[2] These ocular diseases may be asymptomatic and therefore not identified during a routine dermatology review. The high prevalence of ocular manifestations among our AD patients were in line with the findings from previous studies.[8-10] It is important to be aware of these as some of these sight-threatening ocular comorbidities can progress to irreversible visual impairment if left untreated.

We found no association between the presence of ocular manifestations and the severity of dermatitis or presence of periorbital signs. Our findings concurred with the findings from previous studies among children with AD.[8,9] On the contrary, a registry based study found adult patients with AD were significantly at risk of developing conjunctivitis, keratitis and keratoconus and the risk was AD severity dependant; however no relationship was found between AD and glaucoma.[11] Factors possibly contributing to the development of ocular manifestations in adult patients with AD are longer disease duration of AD, habitual rubbing of the eyelids and side effects of topical and systemic therapy.

Blepharitis, or inflammation of the eyelid margin is characterized by pruritus and irritation of the eyelids, dry eyes, burning sensation and photophobia.[12] It is estimated to affect >6% of AD patients compared to the general population which is less than 1%.[2] The pathophysiology of blepharitis is multifactorial, including immune-mediated damage, abnormal lid-margin secretions, bacterial colonisation of the eyelids and Meibomian gland dysfunction.[13] The eyelid tissues in blepharitis showed increased levels of Th2 cytokines such as IL-4, IL-5 and IL-13. Patients with chronic blepharitis often exhibit corneal complications and additional ocular pathologies resulting from prolonged allergic inflammation.14 Patients with AD were more likely to develop blepharitis with an odd ratios of 10.99 compared to the general population.[2] A previous study reported 16 out of 18 patients with eyelid involvement had blepharitis.[8] Another cross sectional study on patients with AD found 41.1% had blepharitis and the affected patients had higher mean periocular skin symptoms score (erythema, infiltration and lichenification).[15] The low prevalence of blepharitis in our cohort might be due to the low prevalence of eyelid dermatitis among our patients.

Allergic conjunctivitis is a non-infectious inflammation of the conjunctiva often caused by an immediate type 1 hypersensitivity reaction to airborne allergens. The estimated prevalence based on previous studies ranged from 15% to 40%.[16] In our study, the prevalence of allergic conjunctivitis was 18.75%. The symptoms of allergic conjunctivitis include hyperaemia of the eye, ocular pruritus, burning discomfort, continuous watery or serous discharge, photophobia and blurring of vision.[17] The risk of conjunctivitis is significantly higher among patients with AD compared to those without AD, especially allergic conjunctivitis, with an eight-fold higher risk.[18] AD and conjunctivitis share the common pathogenesis as the impairment of physical barrier function is present in both disorders. The dysfunctional ocular surface epithelium serves as an entry portal for both pathogens and environmental allergens to enter the eye.[19] Therefore, AD patients are more susceptible to develop allergic conjunctivitis due to ocular barrier dysfunction. Dry eye syndrome has been suggested to be associated with allergic conjunctivitis caused by tear film instability, Meibomian gland dysfunction and excessive evaporation from ocular surface.[20] A study done by Dogru et al., showed the presence of tear film instability was higher in allergic conjunctivitis. The conjunctival squamous metaplasia and loss of goblet cells may lead to reduced conjunctival mucin production which eventually results in tear film instability. The frequent use of antihistamine in patients with AD may be one of the contributing factors for tear film abnormalities due to the anticholinergic properties of antihistamine.[21]

Keratoconjunctivitis is a chronic form of allergic conjunctivitis with the involvement of cornea which is characterised by the presence of cobblestone papillae at the tarsus.[22] Atopic keratoconjunctivitis is characterized by the presence of bilateral eyelid dermatitis which affects patients with AD at any point during their disease, regardless of cutaneous disease severity. The prevalence of keratoconjunctivitis is 1.25% in our study but it is substantially higher in the United States.[23] The difference in prevalence could be due to climate, socioeconomic status and genetic diversity. In addition, patients with keratoconjunctivitis were more likely to have higher periocular skin symptoms score and the habit of slapping around the eyes.[15] Superficial corneal involvement due to

inflamed tarsal conjunctiva and irregular lid margins may progress to frank erosion and ulceration. Persistent inflammation causes corneal scarring and neovascularization which may eventually lead to irreversible vision loss.[24]

We found a statistically significant correlation between prolonged AD disease duration and steroid-related ocular complications. The estimated prevalence of cataract in adults with AD varies between 8% and 11.59%, which is similar with our study.[20,25] The incidence of cataract caused by oral steroid use increases with higher dosage and prolonged duration of treatment, usually at least 1 year or dosage equivalent to oral prednisolone 10mg per day.[26] The association between peri-ocular usage of topical steroid usage and cataract needs further study. Association between application of class III topical steroid and posterior subcapsular cataract has been reported.[27,28] On the other hand, a retrospective study found prolonged use of moderate to potent topical corticosteroid for an average of 6 months a year for almost 5 years was associated with cataract; however those patients with steroid-related cataract had also received oral steroid.[25] The pathogenesis of cataracts in AD is multifactorial, including repetitive trauma secondary to eye rubbing, long-term steroid therapy and oxidative stress. The increased serum lipid peroxide together with decreased superoxide dismutase activity led to high level of free radicals which contribute to the formation of cataracts.[5,19] The cataracts in patients with AD are usually bilateral with anterior or posterior subcapsular opacities. Anterior subcapsular cataract (ASC) is more specific to AD, but steroid-induced posterior subcapsular cataract (PSC) appears to be more frequently described in AD patients.[29] In our study, ASCs and PSCs were seen in three patients and four patients respectively.

Steroid-induced ocular hypertension was first reported in 1950 as intraocular pressure (IOP) was found to be elevated after chronic administration of systemic steroids.[30] Persistent IOP elevation of significant level without treatment may progress to glaucomatous optic neuropathy which is called steroid-induced glaucoma.[31] Aggarwal et al reported a series of patients who developed marked elevations in IOP following topical facial application of steroids.[32] In our study, four out of seven (57.1%) patients with ocular hypertension had history of topical application of low to medium-potency corticosteroids on periorbital region and systemic steroid usage with mean prednisolone dose of range from 50 to 1850mg per year. The elevation of IOP usually develops within the first few weeks of corticosteroids administration. It has been reported that raised IOP secondary to chronic administration of steroids may not return to normal despite discontinuation and refractory to medical therapy.[32] A new clinical entity, atopic glaucoma, has been proposed by Takakuwa et al., in 2015. The diagnostic criteria include the presence of severe atopic dermatitis with face involvement, cup-disc ratio >0.7 and/ or notching, visual field loss, IOP >21mmHg and no association between IOP and glucocorticoid use.[33] Patients with raised IOP are often asymptomatic until advanced stages.[34] Therefore, periodic glaucoma screening would be ideal for patients at risk and those with prolonged history of topical and systemic steroid use. All the six patients in our study were asymptomatic and they were given regular follow-up.

None of the patients had keratoconus or retinal detachment in our study. Keratoconus is a non-inflammatory ocular disease characterized by progressive thinning and cone-shaped bulging of the cornea. Patients often experience reduced visual acuity, irregular astigmatism and light sensitivity due to changes in corneal topography.[3] Rahi et al., reported that a definite history of atopy in 35% of keratoconus compared with 12% in the control group.[35] The most significant factor that causes keratoconus is habitual eye rubbing due to itch of atopy.[36] Retinal detachment is one of the serious ocular complications of AD affecting visual prognosis. It often affects the younger population at a frequency of 8%.[37] Most of the patients with retinal detachment were reported to have facial involvement, especially periorbital regions. The possible theories of pathogenesis of retinal detachment in AD include retinal oedema, retinal breaks secondary to diseased vitreous or retinal vascular changes, and self-inflicted ocular contusion by vigorous rubbing or tapping.[38]

We incidentally found 6 cases of epiblepharon which is not known to be associated with AD. Epiblepharon is a congenital eyelid condition in which a redundant horizontal skin fold results in misdirected lashes towards the cornea. It often involves bilateral lower eyelids and frequently seen in East Asian children with the mean age of 9 years. The majority of the children had no or mild symptoms and are outgrown with the growth of the eyelids and facial bones. However, it is usually associated with potential complications of conjunctival irritation and keratopathy when symptomatic.[39]

Routine ophthalmological evaluation is not a part of the management of patients with AD. Early recognition of these ocular manifestations facilitates appropriate treatment which will prevent potential vision loss. Increased awareness among patients and identification of risk factors such as habitual eye rubbing, and prolonged corticosteroids use can decrease the development of steroid-related ocular complications We recommend incorporating periodic ophthalmological assessment into the management of AD patients with prolonged disease duration regardless of the severity of AD.

This study was limited by its cross-sectional design. A prospective study involving eye assessment upon diagnosis and changes over time with the AD disease progression would provide more valuable information. The sample size was small because the data collection was severely affected due to the constraints during the coronavirus pandemic. There was a lack of information on the lifetime topical and systemic corticosteroids use as the amount of over-the-counter topical corticosteroids and the total dose of systemic corticosteroids given by the referring general practitioners were not available.

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CONFLICT OF INTEREST

There is no conflict of interest.

ETHICAL APPROVAL

Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia.

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ORIGINAL ARTICLE

Calibrating different sounds for sound therapy: A general guide

Nur Afiqah binti Amirullah, BAud[1], Sarah binti Rahmat, PhD[1], Ahmad Aidil Arafat bin Dzulkarnain, PhD[1], Nashrah binti Maamor, PhD[2], Mohd Khairil Azahar bin Jamaludin, BAud[2], Mohd Zulfaezal bin Che Azemin, PhD[3]

[1]Department of Audiology and Speech Language Pathology, Kulliyyah of Allied Health Sciences, International Islamic University Malaysia, Kuantan, Pahang, Malaysia, [2]Centre for Rehabilitation and Special Needs Studies, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia, [3]Department of Optometry and Visual Sciences, Kulliyyah of Allied Health Sciences, International Islamic University Malaysia, Kuantan, Pahang, Malaysia

ABSTRACT

Introduction: Sound therapy is one of the complementary or alternative interventions for various populations. The intensity of the sounds for sound therapy needs to be properly calibrated to ensure their accuracy and effectiveness. This paper aims to provide a general guideline for calibrating sound files using free software, specifically Audacity®.

Materials and Methods: Six sounds (broadband noise, rain, ocean, waterfall, Quranic chapters Al-Fatihah, and Yasin recitations) were calibrated at the intensity levels of 45, 50, 55, 60, 65, 70, 75, and 80dBA. The sounds were delivered through a pair of Sennheiser HD 280 Pro headphones connected to the Sound Blaster X-Fi Surround 5.1 Pro sound card. The long-term average of the sound pressure level over the time of recording (LAseq) was recorded using the 3M SoundPro Class 1 1/3 Octave RTA sound level meter (SLM). The desired intensity levels were obtained by making adjustments to the sound files via the Audacity® software.

Results: All sound files were calibrated at the targeted levels as verified by the value of LAseq.

Conclusions: Calibration of audio files can be done using a free/open-source software, as all six sound files were successfully calibrated at the targeted levels of 45, 50, 55, 60, 65, 70, 75, and 80dBA. The calibration steps provided in this paper can be easily applied by other researchers for similar purposes, with precautions when calibrating at low levels.

KEYWORDS:
Calibration, sound therapy, guidelines, nature sounds, Quranic recitations

INTRODUCTION

Medical interventions may be classified into two general categories: 1) preventive interventions, which aim to prevent the occurrence of a disease, and 2) therapeutic interventions, which aim to treat or alleviate symptoms of diseases that are already progressing in patients.[1] Sound therapy falls under the second category of interventions, as it aims to alleviate the symptoms of certain diseases or disorders.

In audiology, the use of broadband noise (BBN) and nature sounds as sound therapy (ranging from 0 to 100dB SPL) has been shown to provide some degree of relief to tinnitus sufferers.[2,3] Meanwhile, listening to Quranic recitations has been shown to reduce anxiety and pain in patients.[4,5] BBN as contralateral acoustic stimulus (at the level of 60dBA) is also known to be one of the most effective ways to activate the medial olivocochlear system (MOCS).[6-10] The activation of MOCS serves several important functions, such as aiding in selective attention,[11,12] providing protection from noise,[9,13-15] as well as aiding understanding of speech in noise.[6,16] Due to this, some research focused on the potential of using BBN as sound therapy for populations that may require it as a form of intervention. In addition, studies have shown that BBN at 75dBA could help boost the attention of children with attention deficit hyperactivity disorder (ADHD).[17,18]

These earlier studies show that sound therapy interventions aimed at different populations require different types of sounds and different intensity levels in order for it to be effective. Despite this, previous publications that utilized acoustic stimuli at a specific intensity level or at various intensity levels in their experiments do not always report in detail how the calibration process was carried out.[8,19] This may make it difficult for other researchers to refer to or understand the calibration process if they wanted to replicate it in their own studies.

Therefore, the aim of the current paper is to share a general outline of how sound files were calibrated in our study so that it could serve as a guide for other researchers to perform their own sound file calibration for the purpose of sound therapy intervention. In this particular paper, the Audacity® software was used, and six sound files were calibrated: BBN, three BBN-like nature sounds (rain, ocean, waterfall), as well as two Quranic chapters, *Al-Fatihah* and *Yasin*.

MATERIALS AND METHODS

The aim of sound calibration is to ensure that the output of the sound transducer achieves the desired level.[20] To the best of our knowledge, no detailed guidelines on sound file calibration have been published. Thus, the methods of calibrating the sound file in this study was adapted from the procedures used in audiometric calibration for air conduction

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Corresponding Author: Sarah binti Rahmat
Email: sarahrahmat@iium.edu.my

stimulus, as well as from previous experiences of one of the authors in calibrating Schroeder harmonic complexes sound.[20-22]

Sound file acquisition
The three nature sound files as well as the BBN file were downloaded from the Sound Bible website (www.soundbible.com), which provides free sound files as uploaded by various users. All sound files are in the Waveform Audio File Format (WAVE/WAV file). The Quranic recitations were downloaded from YouTube (www.youtube.com) and converted to the WAV format via the Online Video Converter website (www.onlinevideoconverter.com).

The length of the sound files are as follows: 1) BBN: 59 seconds, 2) ocean: 47 seconds, 3) rain: 33 seconds, 4) waterfall: 26 seconds, 5) A-Fatihah: 52 seconds, and 6) Yasin: 12 minutes and one second.

Intensity levels
All sound files were calibrated at intensity levels 45, 50, 55, 60, 65, 70, 75, and 80dBA.

Materials and instruments
The following instrumentations are among those recommended in order to carry out a sound calibration: a sound level meter (SLM), a two-cc or six-cc coupler, an acoustic calibrator, and a weight to place on top of the headphones during the calibration process.[22] For our specific sound file calibration purposes, we also required an external sound card (to bypass the laptop's sound card, so that the output from the headphones would remain constant even if different laptops are used in the future), and an audio editing software.

The following are the specific models used in our calibration process: TSI Quest Technologies Inc. (Shoreview, Minnesota, USA) earphone coupler (model EC-SA), 3M (Saint Paul, Minnesota, USA) SoundPro Class 1 1/3 Octave RTA sound level meter (SLM), Sennheiser (Wedemark, Germany) HD280 Pro headphones, Creative Technology (Jurong East, Singapore) Sound Blaster X-Fi Surround 5.1 Pro sound card, Audacity® (Pittsburgh, Pennsylvania, USA) software version 2.2.0, and TSI Quest Technologies Inc. (Shoreview, Minnesota, USA) audiometric calibration stand (model AS-1550).

Calibration setup
The calibration process was done in a sound treated booth with the ambient noise of 33.0dBA, which did not exceed the recommended ambient noise by the British Society of Audiology.[23] The sound files were played continuously from start to finish via the Audacity® software version 2.2.0 on an Acer Aspire E 14 laptop. The laptop was connected to the Sound Blaster X-Fi Surround 5.1 Pro sound card, and then the Sennheiser HD280 Pro headphones were plugged into the sound card. Fig. 1a) and 1b) show the equipment setup.

The earphone coupler used to calibrate the sound files was connected to the Type One SLM, and was fixed onto the audiometric calibration stand. One headphone was placed over the earphone coupler and a metal weight placed on top of it to secure its position.

Calibration steps
The calibration process began with recording and noting down the intensity levels of the unedited sound files; then, the appropriate amplification values were applied via the Audacity® software to achieve the desired levels (45, 50, 55, 60, 65, 70, 75, and 80dBA). The following is the step-by-step procedure taken to calibrate a BBN audio file to achieve the desired intensity levels. The same steps can be taken to calibrate other types of sound files.

Step One: The output from the right side of the headphone was muted in order to prevent the it from interfering with the calibration process of the left side of the headphone. To do this, the output on the right headphone was muted by going to the advanced settings of the sound card software (the Creative Entertainment Console software).

Step Two: The volume dial on the sound card was turned to the maximum level (100%) throughout the whole calibration process; this was to ensure that the SLM recorded the sound level at maximum output. The desired sound file was opened on the the Audacity® software. Fig. 2 a) shows the display on the Audacity® software once the sound file has been opened. Once opened, the software would display two waveforms: the one on top represents the output of the left channel, while the one on the bottom represents the output of the right channel. Step Three: The SLM measurement started simultaneously with the start of the audio file, which was played using the sound generator software (in our case, the Audacity® software) (Fig. 2b). The SLM measurement was stopped only when the entire audio file had been played from start to finish (Fig. 2c). This way, the duration of the SLM measurement would accurately follow the actual length of the audio file, so that the long-term average of the sound pressure level over time (LAseq) could be obtained.

Step Four: The readings on the SLM were noted down, specifically the long-term average of the sound pressure level over the time of recording (LAseq) value (in dBA), the maximum intensity level (dBA), as well as the intensity levels (dBA) at frequencies 16Hz, 31.5Hz, 63Hz, 125Hz, 250Hz, 500Hz, 1000Hz, 2000Hz, 4000Hz, 8000Hz, and 16,000Hz.

Step Five: After noting down the intensity level displayed on the SLM for the unedited sound file (in our case, the LAseq reading was 87.3dBA for the unedited BBN sound file), the sound file was saved as *'BBN_unedited.wav'* file.

Step Six: Now, the intensity of the sound file can be edited to reach the desired level by applying an amplification or reduction effect (depending on whether the original audio file intensity is lower or higher than the desired intensity) on the audio file using the sound generator software. In the case of Audacity®, this was done by using the *'Amplification'* effect, which was applied in order to reach the first targeted intensity of 80dBA [refer to Fig. 2d) and 2e)]. From our observation, a dB change made in the Audacity® software is linear (i.e., increasing 5dB in the Audacity® software would result in an increase of 5dB output of the sound measured by SLM). Thus, the value of -7.3dB (to compensate the 87.3dBA

Table I: Amplification values applied (in dB) via the Audacity® software for the long-term average (LAseq) reading on the sound level meter (SLM) to reach the targeted intensity levels of 45, 50, 55, 60, 65, 70, 75, and 80 dBA for the left headphone

Sound file	Unedited sound file intensity recorded by SLM (dBA)	Audacity amplification value applied to unedited sound file sound file (dB)	Long-term average, LAseq, recorded by SLM after amplification (dBA)	Maximum sound pressure level, LAsmax, after amplification (dBA)	Long-term average (LAseq) for specific frequencies (Hz)										
					16	31.5	63	125	250	500	1000	2000	4000	8000	16,000
Broadband noise	87.3	-7.3	80.0	80.3	9.9	18.8	34.0	43.8	56.2	68.3	67.3	73.4	77.7	67.6	58.7
		-12.3	75.0	75.3	10.0	15.7	29.3	39.0	51.2	63.3	62.3	68.4	72.7	62.6	53.7
		-17.3	70.0	70.1	10.1	13.8	25.2	34.9	46.2	58.2	57.2	63.2	67.5	57.4	48.5
		-22.3	65.0	65.1	9.3	12.3	21.8	30.5	41.5	53.3	52.2	58.2	62.5	52.3	43.4
		-27.3	60.0	60.3	9.2	13.0	20.9	30.3	37.6	48.5	47.4	53.4	57.7	47.5	38.6
		-32.3	55.0	57.6	8.8	13.5	20.9	33.7	39.0	44.9	42.4	48.3	52.6	42.4	33.5
		-37.3	50.0	54.5	9.1	13.2	20.1	33.0	36.4	41.3	37.3	43.3	47.5	37.4	28.4
		-42.3	45.0	54.5	9.1	13.2	21.2	33.4	35.5	37.5	32.2	37.9	42.1	32.1	23.2
Al-Fatihah	87.5	-7.5	80.0	80.0	84.2	10.2	12.3	19.8	49.3	68.2	75.9	70.4	68.6	72.6	57.1
		-12.5	75.0	75.1	79.2	9.8	13.7	20.3	44.4	63.3	71.0	65.5	63.6	67.6	52.1
		-17.5	70.0	74.9	10.1	12.9	21.2	40.2	59.0	66.9	61.4	59.6	63.5	47.1	34.1
		-22.5	65.0	69.8	8.3	13.2	19.6	35.5	54.1	61.8	56.3	54.4	58.3	42.5	29.3
		-27.5	60.0	64.8	10.1	11.8	19.7	31.1	49.1	56.7	51.3	49.4	53.3	37.4	24.3
		-32.5	55.0	59.8	9.5	11.7	19.6	28.5	44.3	51.8	46.2	44.3	48.2	32.2	19.5
		-37.5	50.0	54.7	9.6	12.2	19.4	27.6	39.6	46.8	41.1	39.3	43.1	27.3	16.2
		-42.5	45.0	55.3	10.2	12.6	19.5	27.8	37.9	43.0	37.1	34.0	37.2	22.7	14.7
Waterfall	87.6	-7.6	80.0	80.5	12.9	13	21.9	34.6	48.1	63.1	63.5	72.4	77.3	73.4	42.3
		-12.6	75.0	75.0	13.0	12.8	21.0	36.1	44.4	58.2	58.5	67.4	72.3	68.4	37.4
		-17.6	70.0	70.5	12.9	13.2	21.3	41	42.5	53.3	53.5	62.4	67.3	63.4	32.4
		-22.6	65.0	65.5	11.7	12.8	20.4	37.6	39.8	48.2	48.5	57.4	62.3	58.4	27.4
		-27.6	60.0	61.0	11.5	12.4	20.6	36.5	36.4	43.5	43.5	52.3	57.2	53.3	22.5
		-32.6	55.0	56.7	11.4	12.4	20	34.2	33	39	38.4	47.2	52.1	48.2	17.3
		-37.6	50.0	52.7	12.2	12.6	20.8	28.6	35.9	37.4	33.4	42.1	47	43.1	14.3
		-42.6	45.0	50.4	12.5	12.4	20.9	30.3	33.6	35.1	28.4	36.8	41.7	37.8	14.3
Ocean waves	86.5	-6.5	80.0	85.6	10.0	16.6	36.4	54.4	70.9	76.6	71.6	70.3	72.2	52.0	33.1
		-11.5	75.0	80.7	10.8	14.3	31.6	49.4	66.0	71.7	66.6	65.3	67.2	47.0	28.1
		-16.5	70.0	75.7	11.0	15.2	27.7	44.5	61.0	66.7	61.6	60.3	62.2	42.0	23.2
		-21.5	65.0	70.7	11.0	13.2	24.1	39.6	55.9	61.7	56.6	55.3	57.2	37.1	18.7
		-26.5	60.0	65.7	12.0	13.9	22.5	35.4	50.9	56.7	51.6	50.3	52.2	32.1	15.1
		-31.5	55.0	60.7	11.7	14.0	21.5	31.7	46.0	51.7	46.6	45.3	47.2	27.4	14.3
		-36.5	50.0	55.7	11.6	13.8	21.5	28.5	41.2	46.8	41.5	40.3	42.2	23.2	14.3
		-41.5	45.0	54.4	12.5	14.4	22.0	37.2	38.6	42.0	36.5	35.4	37.2	20.8	14.3
Rain	86.9	-6.9	80.0	81.5	12.5	14.9	30.1	43.4	50.2	59.7	60.7	71.5	78.5	69.6	59.3
		-11.9	75.0	76.9	11.9	13.3	26.2	38.4	45.2	54.7	55.7	66.4	73.5	64.5	54.2
		-16.9	70.0	71.2	12.3	12.9	23.3	38.1	41.5	49.7	50.6	61.2	68.2	59.2	48.9
		-21.9	65.0	66.6	12.4	13.7	22.1	31.9	38.5	45.8	46.0	56.6	63.6	54.5	44.3
		-26.9	60.0	64.1	12.5	15.7	22.2	38.7	42.4	48.2	41.3	51.6	58.5	49.5	39.2
		-31.9	55.0	56.6	12.1	15.5	23.9	36.5	37.5	38.8	36.0	46.5	53.5	44.4	34.2
		-36.9	50.0	57.9	12.7	13.0	20.7	36.5	39.3	40.1	31.1	41.4	48.3	39.3	29.0
		-41.9	45.0	48.0	14.0	13.0	20.7	26.5	31.1	31.5	26.3	36.1	43.0	34.1	23.8
Yasin	100.3	-20.3	80.0	90.8	9.9	15.5	22.3	44.4	62.5	76.9	69.4	71.4	73.3	53.3	42.9
		-25.3	75.0	80.9	9.5	15.1	21.3	36.9	57.5	71.9	65.0	66.6	68.3	48.9	38.9
		-30.3	70.0	75.9	6.1	11.4	20.0	34.4	52.0	66.6	59.4	61.1	63.2	43.1	32.5
		-35.3	65.0	70.9	6.5	11.5	19.9	29.1	47.3	61.0	53.9	55.4	58.2	37.3	25.8
		-40.3	60.0	65.8	6.9	11.4	19.3	24.1	41.9	56.5	49.4	51.2	53.1	33.1	22.4
		-45.3	55.0	60.8	7.4	11.6	19.6	39.4	41.8	51.7	43.9	45.3	48.1	27.8	17.4
		-50.3	50.0	55.7	7.2	12.2	19.2	24.5	33.4	46.1	38.8	40.2	43.0	23.5	15.0
		-55.3	45.0	50.8	7.4	12.5	20.0	26.3	37.7	44.6	34.9	35.7	37.8	20.4	14.4

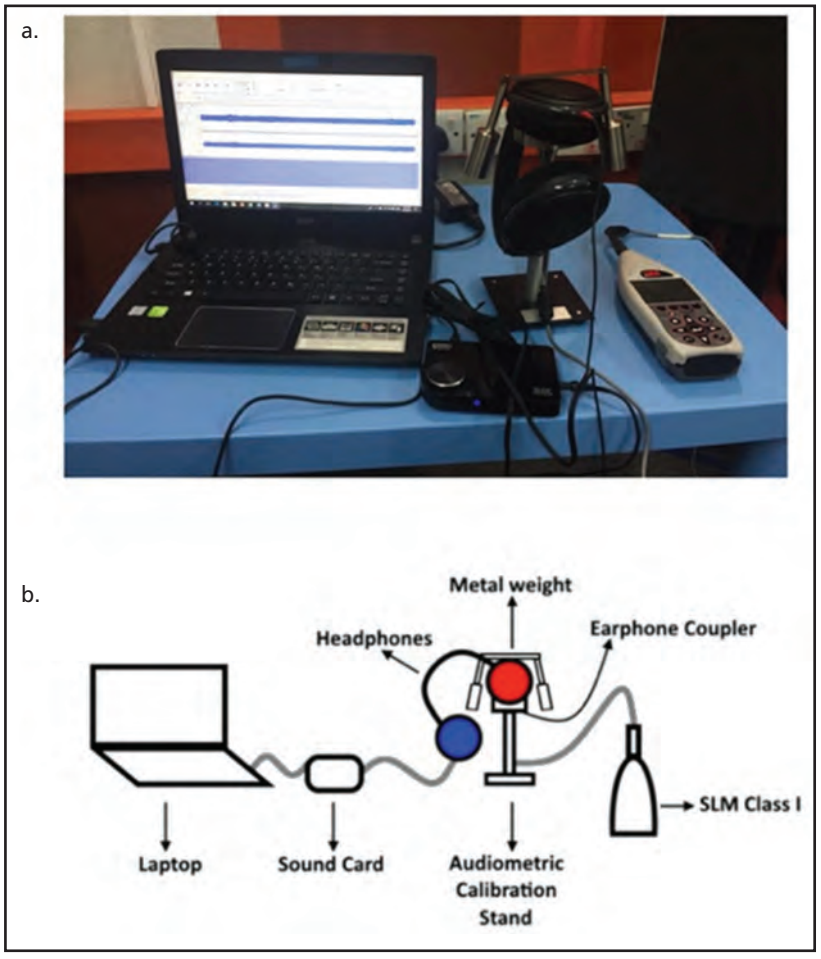

Fig. 1: a) The equipment setup. b) A simplified diagram of the equipment setup.

measured in step five) was entered to adjust the magnitude of the sound file to the targeted level (80dBA). Fig. 2e) and 2f) illustrate this step.

Step Seven: Once the amplification value has been applied to the sound file, Step Three was repeated to record the intensity of the edited sound file on the SLM. This step is conducted to ensure the measured level of the modified sound file (in Step Six) is actually meeting the target level. For this particular step, the SLM reading after the application of the *'Amplification'* effect was 80.0dBA. Apart from the overall LAseq reading, the LAseq values for specific frequencies were also recorded to give the idea of the energy distribution for each frequency components of the sound files.

Step Eight: The edited sound file was then exported and renamed appropriately (in our case, it was renamed as *'BBN_80dBA'*) [refer to Fig. 3a) and 3b)]. We recommend exporting the sound files as a 16-bit WAV format, due to two reasons: this format does not compress the sound file as much as the .mp3 format does, and the 16-bit format is fairly universal and can be found in music compact discs (CDs) as well as digital television sound system. The 16-bit format is also enough for capturing the sound properties of sound files for the purpose of sound therapy.

Steps Six was repeated to the *'BBN_unedited'* sound file in order to obtain the next targeted intensity level (75dBA). -12.3dB was entered into the *'Amplify'* box to achieve this targeted level. The sound file was then exported as a new .wav file and renamed *'BBN_75dBA.'* The same steps were repeated in order to obtain the sound file at the targeted levels of 70, 65, 60, 55, 50, and 45dBA.

Steps Three to Eight were repeated for the other five sound files. For this paper, only the left headphone was shown, should future researchers wish to calibrate both headphones, the steps described above can be repeated on the other headphone. All relevant values are displayed in Table I.

RESULTS

Table I shows the results of the calibration process for the left headphone. The name of the sound files, the intensity of the unedited sound file as recorded by the SLM (in dBA), the amount of amplification applied via the Audacity® software, the LAseq value (in dBA), as well as the LAseq values (in dBA) for specific frequencies are displayed for each sound type.

Based on Table I, it can be seen that for four sound files (BBN, waterfall, rain, and Yasin), the highest intensity occurred at 4,000Hz for all calibrated intensity levels. *Al-Fatihah* has the highest intensity at 1,000Hz at 75dBA and 80dBA, and at 4,000Hz for the rest of the intensity levels. The ocean waves

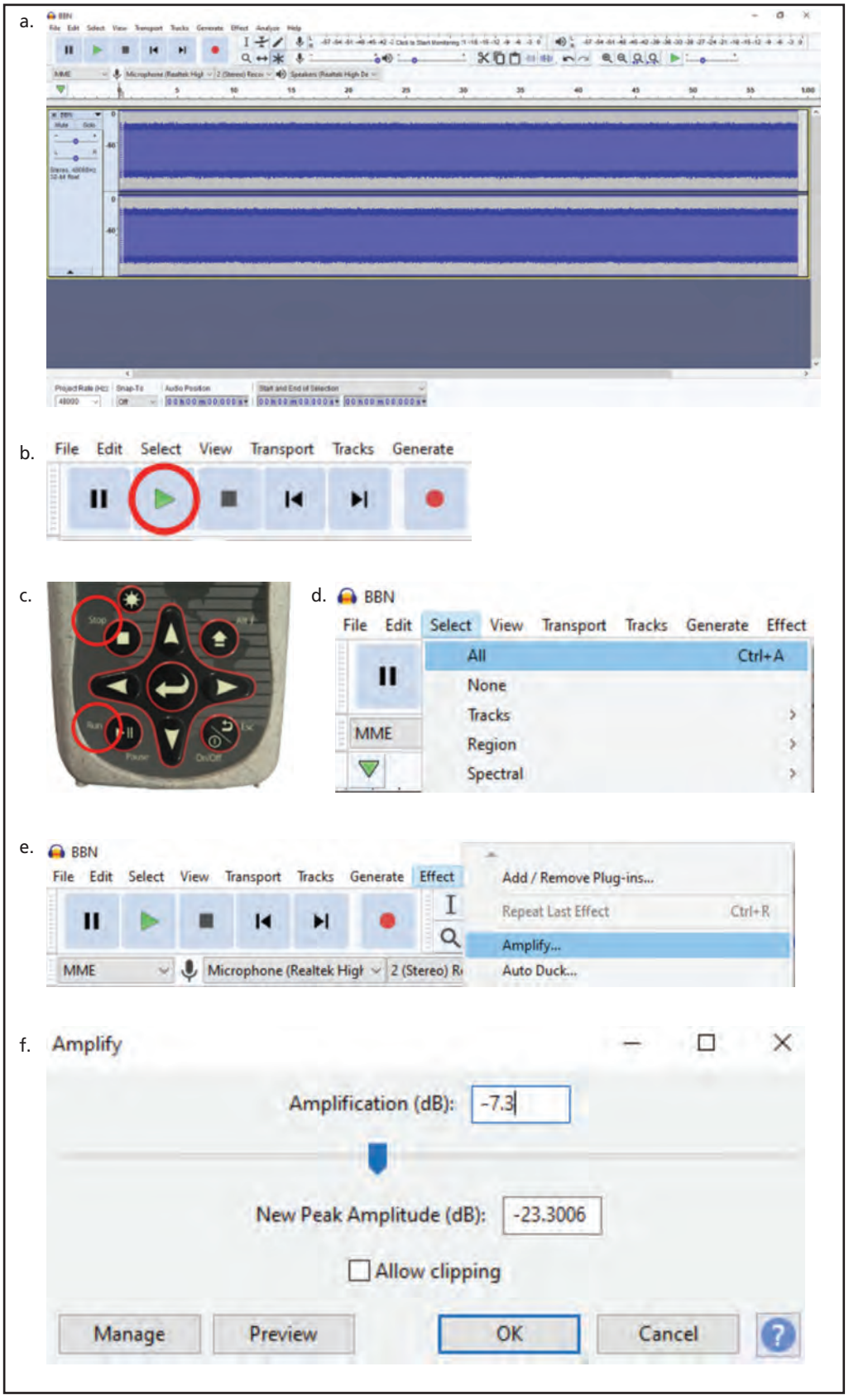

Fig. 2: a) The BBN sound file opened using the Audacity® software. b) The toolbar on the Audacity® software. The 'play' button is circled in red. c) The SLM 'run' and 'stop' buttons circled in red. d) Selecting the entirety of the waveform for the BBN sound file prior to applying the 'Amplifying' effect. e) Selecting the 'Amplify' effect on Audacity®. f) The 'Amplify' box; the value -7.3 dB was entered into the appropriate box.

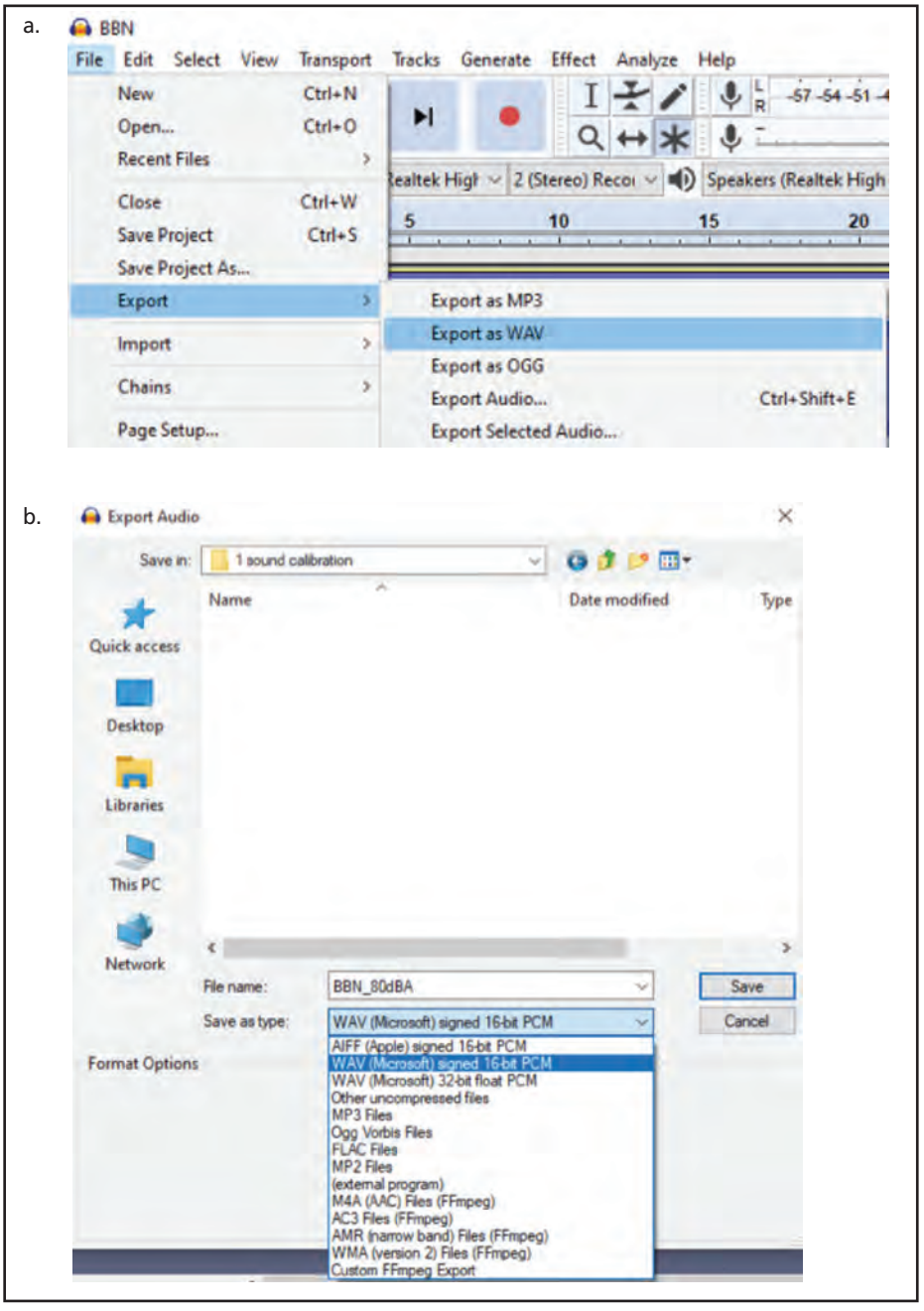

Fig. 3: a) The new sound file is exported as a .wav file. b) The new sound file is saved as 16-bit .wav file.

file, on the other hand, has the highest intensity occurring at 500Hz for all calibrated intensity levels.

Fig. 4 depicts the first 25 seconds of the waveforms of all six sound files at 80 dBA. Only the first 25 seconds of the files are shown as all the sound files are looped afterwards, except for Yasin, which is too long (12 minutes) for its waveform to be shown in its entirety. It can be see that BBN and waterfall have similar waveforms throughout the audio files; rain has a slight increase in energy at around three seconds into the audio file; ocean has the most fluctuation of energy throughout the audio file; both *Al-Fatihah* and *Yasin* have multiple fluctuations, as both are speech sounds.
When used in experiments, the different characteristics of these sound files may come in handy as they may help researchers explain the findings of the experiments.

DISCUSSION

In this discussion section, several caveats regarding the calibration process, as well as the implications of this current paper for the field of audiology are covered. Some limitations of the paper are also discussed.

Weighting scale: The sound files were calibrated using the A weighting, as it has a similar frequency response to that of the human ear, and is typically used in measuring the intensity of a sound.[24] The current paper measured the long-

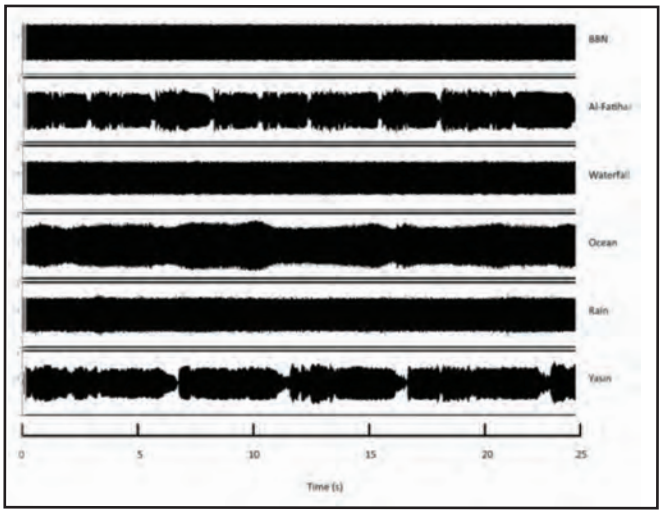

Fig. 4: The first 25 seconds of the waveforms of the six sound files.

Fig. 5: Switch off the 'threshold' option on the SLM in order to calibrate soft sounds.

term average of the sound pressure level (LAseq) instead of the peak value, as it is useful in specifying the average level of speaking voices (in this case, *Al-Fatihah* and *Yasin* recitations that contain wide ranges of fluctuations throughout the files) that span minutues, hours, or even days.[25]

Calibrating soft sounds

The aim of this study is to calibrate sounds from 45dBA and above. The ambient noise recorded in the sound-treated room was 33.0dBA which is fine for the targeted intensity levels; but could pose a problem when calibrating the sound files at lower levels. One step that could be taken when measuring sounds at lower levels is to turn off the 'threshold' setting in the SLM to allow any level of sound to be measured.[26] Fig. 5 shows the setting of the threshold in the SLM. Another precautionary step is to use the appropriate ear coupler adapter ring that could fit snugly around the headphone; otherwise, the sound might leak out and the SLM reading might not be accurate. By taking into account these factors, the first and second authors consequently did a separate calibration session at a different setting, and managed to calibrate one sound file to a level as low as 20dBA.

Using the unedited sound file

As a precautionary step, the authors had consistently applied the *'Amplification'* effect only on the original unedited sound file, and never on another already-edited sound file. This was done in order to avoid any possible distortions to the sound files as the calibration process continued on.

Implications

In this current paper, the six calibrated sounds have been incorporated in the development of 'Natural Acoustic' software (software used for sound therapy) which has been used in two studies for sound therapy purposes (ongoing study); i) investigated the effects of suppressor noises on the MOCS in normal hearing school-age children, and ii) investigated the effect of sound therapy on the working memory among normal hearing school-age children with suspected ADHD. The information obtained from the current calibration steps, such as the calibrated intensity level and the frequency specific energy distribution, may give an insight on the level and the frequency that are the most effective to activate the MOCS, as well as to optimize the working memory among the subjects. Future studies involving sound therapy, or even sound presentation to various populations, may use the calibrated sound files from the current paper, provided similar set up as in the current paper is also used (i.e., type of headphone and sound card).

Study limitations

In this study the calibration method has several limitations. Firstly, the calibrated intensity levels are only applicable for the Sennheiser HD 280 pro headphones. Therefore, future studies that aim to replicate our calibration methods will have to expect slight variations in their data if a different headphone model is used. Similarly, this study specifically used the Audacity ® software. There should be no restrictions if other researchers choose to use different free audio editing software other than Audacity®, but they should expect some differences in the calibration steps. Secondly, the current calibration method requires the use of a laptop or a computer and could not be performed with standalone music players such as MP3 devices. Lastly, the calibration was done in dB A, and the conversion to dB HL was not done in the current paper. This could be an area worth expanding into for future research in addition to the studies related to the reproducibility of the results using different devices and software mentioned earlier.

CONCLUSION

This paper has detailed out the procedure for calibrating sound files using free/open-source software for the purpose of sound therapy. The adjustments made using the software has achieved the targeted levels and were successfully used in other experiments. The calibration steps provided in this

paper can be easily applied by other researchers for similar purposes, with precautions to be taken when calibrating at low levels.

ACKNOWLEDGEMENT

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ORIGINAL ARTICLE

Factors associated with severe envenomation of snakebite cases at emergency department, Hospital Sultan Abdul Halim, Kedah, Malaysia

Mhd Nazrul Fitri Mhd Nizar, MB Bch BAO[1,3], Andey Rahman, MMed (EM)[1,2], Kamarul Aryffin Baharuddin, MMed(EM)[1,2], Mohammad Zikri Ahmad, MMed(EM)[1,2], Mashitah Mohamed Ismail, MMed (EM)[3]

[1]Department of Emergency Medicine, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia [2]Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [3]Department of Emergency and Trauma, Hospital Sultan Abdul Halim (HSAH), Sungai Petani, Kedah, Malaysia

ABSTRACT

Introduction: Snakebite envenomation is a medical emergency and cases continue to be encountered in Malaysian hospitals. This study aims to determine the prevalence of snakebite presentations and the associated factors with severe envenomation of snakebite in Sungai Petani, Kedah, Malaysia.

Materials and Methods: This was a retrospective, cross-sectional study involving snakebite patients presented at the Emergency Department (ED), Hospital Sultan Abdul Halim (HSAH), Kedah from 1 July 2015 to 30 June 2019. The cases were extracted from the computerized system and the case records of patients were retrieved from the Medical Record Unit. Patients that met the study criteria were included and their sociodemographic features, clinical presentations including use of anti-venom were collected. Logistic regression analysis was performed to determine the factors associated with severe envenomation.

Results: A total of 220 snakebite cases with the mean age of patients was 39.66 (SD±21.79) years old. Majority of them were Malay and males. 41.4% of snakebite cases occurred in late evenings and the mean time-lapsed to arrive at HSAH was 108.6 minutes. 81.4% of snakebite cases occurred while engaging in outdoor activities and 43.6% of the snakebite cases involved work-related incidents. 58.2% of the patients were bitten in the lower limb. 78.6% of patients were bitten by the identified snake species, predominantly from Viperidae family. The prevalence of severe envenomation was 50.9%. Malay ethnicity (adj. OR =2.549, 95% CI =1.277,5.089), bite to the upper limb (adj. OR =2.125, 95% CI =1.192, 3.790), and bite by snakes from Viperidae family (adj. OR =3.017, 95% CI =1.613, 5.642) were found to have significant associations with severe envenomation of snakebite.

Conclusion: The prevalence of severe envenomation was more than 50% of snakebite cases. Malay ethnicity, upper limb snake bites, and snakebite from a Viperidae family had a higher chance of severe envenomation

KEYWORDS:
Snakebite, snake envenomation, viperidae, antivenom, emergency medicine

INTRODUCTION

Snakebite envenomation is a medical emergency and cases continue to be encountered in Malaysian hospitals. However, clinical management of snakebite cases may still be suboptimal due to negligence, failure to identify the species and anticipate the severity of envenomation in snakebite patients.[1,2] Furthermore, older age of victims, delayed presentation to the hospital and treatment by non-medical personnel also add to the risk of morbidity and mortality.[3-5] In addition, due to a lack of documentation, the true extent of snakebite mortality and morbidity in Malaysia is uncertain.[6]

The clinical severity of a snakebite is determined by its location on the body, depth, amount of venom injected, the species of the snakes and its size, the age and size of the victim , and susceptibility to the venom.[7] Although most snakes in Malaysia are non-venomous and regarded relatively harmless to humans, certain snakes can cause mild to severe envenomation and eventually mortality. According to the database, around 17 of Malaysia's 105 strictly land snakes are venomous.[8] The vast majority of the venomous terrestrial snakes in Malaysia are classified as Elapidae or Viperidae.[9] Nevertheless, most venomous snakebites reported are defensive in nature and snakes may not deliver sufficient amounts of venom.[10]

Currently, snakebite in Malaysia is not classified as a notifiable disease. Hence, it is one of many reasons causing the lack of reliable information as many cases were not adequately documented or reported. The demographic characteristics and clinical presentations also differ globally, even between states in Malaysia. This study aims to determine the prevalence of snakebite presentations and the associated factors with severe envenomation of snakebite in Sungai Petani, Kedah.

MATERIALS AND METHODS

Patients, setting, inclusion and exclusion criteria

This was a retrospective, cross-sectional study involving snakebite patients who presented at the Emergency Department (ED), Hospital Sultan Abdul Halim (HSAH), Sungai Petani, Kedah, Malaysia from July 1, 2015, to June 30, 2019. HSAH covers the emergency services for approximately 1/3 third of population in Kedah. Inclusion criteria were all

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Corresponding Author: Dr. Andey Rahman
Email: andey@usm.my

snakebite patients from all age groups, all identified snakebite (venomous and non-venomous) with or without envenomation, and all unidentified snakebite with evidence of local and/or systemic envenomation. Exclusion criteria were incomplete medical records and referral cases from other hospitals that arrived through ED HSAH, as there was a potential discrepancy in snakebite envenomation assessment and documentation. Geographical location of the cases came from Kuala Muda district or historically known as Central Kedah.

Sample size and sampling
The sample size was calculated using PS Power and Sample Size Calculations Version 3.0. The total number of samples required was 182 cases. Patient's registration numbers with the diagnosis of snakebite were extracted from the computerized system and the case records of patients were retrieved from the Medical Record Unit, HSAH. Case records that met the inclusion criteria were selected. All data were recorded in a data collection form. Logistic regression analyses were performed to determine the factors associated with severe envenomation.

Operational definition
Based on the Clinical Practice Guideline (CPG) for the Management of Snakebite, Ministry of Health Malaysia (MOH), severe envenomation of a snakebite is defined as clinical evidence of systemic manifestations that are potentially fatal and/or clinical evidence of progressive swelling of bitten limb to indicate local envenomation. Progressive swelling of the bitten limb should be measured using the rate of proximal progression rather than the circumference of the limb. These conditions warrant the administration of anti-venom.

On the other hand, non-severe envenomation is defined by the absence of significant swelling or redness, including dry bite, as well as the absence of clinical evidence of local gangrene or systemic symptoms.[6]

The decision for anti-venom administration was made by the emergency physician on duty. Some of the complicated cases were discussed with the Remote Envenomation Consultancy Services (RECS) team for snake species identification and anti-venom administration. The RECS team is a group of emergency physicians from the Malaysian Society on Toxinology who has strong enthusiasts in snakebite management in Malaysia. It is also recommended in the CPG to consult the RECS team, particularly on the identification of snake species and appropriate management.[6]

Statistical analysis
Data obtained were entered into and analyzed using IBM Social Package Social Sciences (SPSS) version 26.0 statistical software. For the descriptive analysis, numerical data were presented as mean (SD) and categorical data were presented as frequency (percentage). To determine which factors were associated with severe envenomation, single and multiple logistic regression were applied. A p-value < 0.25 which was significant in univariable analysis were selected for multivariable analysis. The adjusted odds ratio (Adj. OR) and 95% confidence interval (CI) were calculated. In multivariable analysis, statistical significance was defined as a 2 tailed p-value of < 0.05.

Ethical considerations
This study received ethical boards approvals from Human Research Ethics Committee of USM (USM/JEPeM/19050330) and Medical Research and Ethics Committee of MOH (NMRR-19-2179-48616 (IIR). Permission from the Director of HSAH was also obtained to review the medical records.

RESULTS

A total of 246 snakebite cases were presented at the ED, HSAH, from July 2015 till June 2019. However, 26 cases were excluded from the study due to incomplete data and referral cases as defined in the exclusion criteria. Two hundred twenty snakebite cases were included in this study. The socio-demographic and clinical presentation of snakebite cases were presented in Table I.

The mean age of all the cases was 39.66 (SD±21.79) years old, and the mean age based on the envenomation are presented in Table I. The most affected age group was between 16 and 45 years old (45.9%). The youngest victim was one year old and the oldest was 90 years old. In all, 146 cases (66.4%) were males. Malay patients accounted for 76.8% (176 patients) of all snakebite cases.

The mean time-lapsed to arrive at the hospital was 1.81 hours or 108.6 minutes (SD±3.78). The mean of time-lapsed to hospital based on the envenomation are presented in Table I. The earliest time-lapsed from the data was 0.2 hour and the latest was 46 hours. Many cases were presented to the hospital within 0-6 hours (214 cases or 97.3%). Most of the cases occurred between 1800 to 2359 hours, which was late evening and night. A total of 179 (81.4%) snakebite cases occurred while engaging in outdoor activities. Most of the patients had tried non-medical intervention (185 cases; 84.1%) prior to arriving at the hospital.

In terms of anatomical bite location, most of the patients were bitten at the lower limb (128 cases; 58.2%) as compared to the upper limb (92 cases; 41.8%). A total of 173 cases (78.6%) were bitten by the identified snake species. 151 (68.6%), 17 (7.7%), 3 (1.4%), 2 (0.9%) and 47 (21.4%) patients were bitten by the snakes from the Viperidae family, Elapidae family, reticulated pythons, non-venomous water snakes and unidentified snakebites, respectively. Fang marks were noted in 212 snakebite cases (96.4%).

From these 220 cases, the prevalence of severe envenomation of snakebite cases was 112 (50.9%). A total of 78 and 15 of them had progressive local envenomation and systemic manifestations, respectively. There were 19 (8.6%) cases with mixed of local and systemic envenomation. There was one case of severe envenomation resulting in mortality due to a snakebite from Elapidae family. The prevalence of envenomation among the variables also presented in Table I. Table II showed a single logistic regression analysis where factors such as age group 46-64 and > 65, female gender, Malay ethnicity, time of injury between 1800-2359 hours and 0000-0559 hours, outdoor location, work-related incident,

Table I: Socio-demographic and clinical presentation of snakebite cases and prevalence of severity of envenomation among the variables

Variables	Mean SD	Frequency	Envenomation	
			Non-severe n (%)	Severe* n (%)
Total (N)			108 (49.1)	112 (50.9)
Socio-demographic				
Age, mean (SD)	39.66 ± 21.79		36.94 ± 21.12	42.29 ± 22.20
Age group (years)				
0-15		30 (13.6)	18 (60.0)	12 (40.0)
16-45		101 (45.9)	54 (53.5)	47 (46.5)
46-65		55 (25.0)	23 (41.8)	32 (58.2)
> 65		34 (15.5)	13 (12.0)	21 (61.8)
Gender				
Male		146 (66.4)	77 (52.7)	69 (47.3)
Female		74 (33.6)	31 (41.9)	43 (58.1)
Ethnicity				
Malay		169 (76.8)	74 (43.8)	95 (56.2)
Others				
Chinese		12 (5.5)	8 (66.7)	4 (33.3)
Indian		12 (5.5)	10 (83.3)	2 (16.7
Foreigners		27 (12.3)	16 (59.3)	11 (40.7)
Clinical presentation				
Time-lapsed to hospital, mean hours (SD)			1.61 ± 2.45	1.99 ± 4.71
Time-interval to hospital				
0-6 hours		214 (97.3)	106 (49.5)	108 (50.5)
> 6 hours		6 (2.7)	2 (33.3)	4 (66.7)
Time of injury (H)				
0600-1159		51 (23.2)	17 (33.3)	34 (66.7)
1200-1759		51 (23.2)	22 (43.1)	29 (56.9)
1800-2359		91 (41.4)	55 (60.4)	36 (39.6)
0000-0559		27 (12.3)	14 (51.9)	13 (48.1)
Location during bite				
Indoor		41 (18.6)	26 (63.4)	15 (36.6)
Outdoor		179 (81.4)	82 (45.8)	97 (54.2)
Work-related incident				
No		124 (56.4)	68 (54.8)	56 (45.2)
Yes		96 (43.6)	40 (41.7)	56 (58.3)
Pre-hospital intervention				
Medical		35 (15.9)	18 (51.4)	17 (48.6)
Non-medical		185 (84.1)	90 (48.6)	95 (51.4)
Anatomical location of bite				
Lower limb		128 (58.2)	75 (58.6)	53 (41.4)
Upper limb		92 (41.8)	33 (35.9)	59 (64.1)

*Requiring anti-venom.

bites to the upper limb, identified the type of snake, and bites by the snake from Viperidae family were statistically associated with severe envenomation outcome. However, multivariable logistic regression analysis found that Malay ethnicity, upper limb bites, and snakebites from the Viperidae family were significantly associated with severe envenomation (Table III).

Malays were 2.55 times more likely than other ethnic groups to experience severe envenomation (Adjusted OR =2.549, 95% CI =1.277,5.089). Patients who were bitten on the upper limb had a 2.13-fold higher risk of experiencing a severe outcome compared to those cases involving the lower limb (Adjusted OR =2.125; 95% CI =1.192, 3.790). This study also found that snakebites from the Viperidae family had a 3.02-fold higher risk of severe envenomation when compared to other snake groups (Adjusted OR =3.017; 95% CI =1.613, 5.642).

DISCUSSION

The high number of snakebite cases in our study indicates that the cases are not uncommon and continue to be seen today, particularly in the semi-rural district of Sungai Petani. This district is surrounded by agricultural sites such as rubber and palm oil estates, paddy fields and forests. A Kuala Muda River runs through the district, with mangrove forest growing along its banks. This forest has become a natural habitat for snakes from the Viperidae family, namely Malayan pit viper *(Calloselasma rhodostoma)* and Mangrove pit viper *(Cryptelytrops purpureomaculatus)*. In addition, both fishing and farming activities have become occupational hazards and presumably increase the risks of getting snakebite.[8]

Most of the patients were between the age of 16 and 45 years old. Our finding is consistent with the profiles of other tropical countries in South Asia (Bangladesh, Bhutan, India, Nepal, Pakistan, and Sri Lanka).[12–15] In contrast, a few of local studies in Perlis and Kelantan reported in a younger age range, between the age of 10-19 years old.[8,11] Our findings

Table II: Factors associated with severe envenomation by univariable logistic regression analysis

Variables	B	Crude OR (95% CI)	p-value*
Age group			
0-15		1	
16-45	0.267	1.306 (0.570,2.990)	0.528
46-65	0.736	2.087 (0.844,5.163)	0.111
> 65	0.885	2.423 (0.886,6.626)	0.085
Gender			
Male		1	
Female	0.437	1.548 (0.880,2.722)	0.129
Ethnicity			
Other ethnicities		1	
Malay	0.943	2.568 (1.331,4.952)	0.005
Time-interval to hospital			
0-6 hours		1	
> 6 hours	0.674	1.963 (0.352,10.945)	0.442
Time of injury (H)			
0600-1159		1	
1200-1759	-0.417	0.659 (0.295,1.472)	0.309
1800-2359	-1.117	0.327 (0.160,0.671)	0.002
0000-0559	-0.767	0.464 (0.179,1.205)	0.115
Location during bite			
Indoor		1	
Outdoor	0.718	2.050 (1.018,4.130)	0.044
Work-related incident			
No		1	
Yes	0.531	1.700 (0.992,2.912)	0.053
Pre-hospital intervention			
Medical		1	
Non-medical	0.111	1.118 (0.542,2.303)	0.763
Anatomical location of bite			
Lower limb		1	
Upper limb	0.928	2.530 (1.456,4.396)	<0.001
Snake identification			
Unidentified		1	
Identified	1.002	2.723 (1.375,5.390)	0.004
Snake group			
Non Viperidae		1	
Viperidae	1.148	3.152 (1.727,5.753)	<0.001

B= Regression Coefficient; CI = Confidence Interval; OR = Odds Ratio
*p-value < 0.25 which is significant on univariable analysis is selected for multivariable analysis.

Table III: Factors associated with severe envenomation by multivariable logistic regression analysis

Variables	B	Adjusted OR (95% CI)	p-value*
Ethnicity			
Other ethnicities		1	
Malay	0.936	2.549 (1.277,5.089)	0.008
Anatomical location of bite			
Lower limb		1	
Upper limb	0.754	2.125 (1.192,3.790)	0.011
Snake group			
Non Viperidae		1	
Viperidae	1.104	3.017 (1.613,5.642)	<0.001

*Multiple logistic regression with Forward LR method were applied; The model fits reasonably well; Constant = -1.765; Hosmer and Lemeshow test, p-value = 0.081; There are interaction between anatomical location of bite and species group; However, no multicollinearity problem was found; Classification table 64.1% correctly classified; Area under Receiver Operating Characteristic (ROC) curve was 70.3% (95% CI :63.5,77.2).

could be explained by the involvement of active groups of adults, especially those who live and work in rural areas, rural estates and agricultural areas. This condition could be considered as an occupational health-related injury that affects the farmers, plantation workers, herders and fishermen.

From our study, males were more exposed to snakebite with a ratio of 2:1. A similar ratio was reported from the earlier studies done in the northern states in Malaysia[8,10,16] and South Asia country.[15] However, this ratio varies across the states in Malaysia. Chew et al. reported a 1.5: 1 ratio in Kelantan and Jamaiah I et al reported a 3: 1 ratio in Kuala Lumpur.[11,17] In comparison, a Brazilian study had a higher male to female ratio of 4:1.[3]

The prevalence of severe envenomation cases was 50.9%, higher than the previous studies done in the state of Kelantan (37.7%)[11] and Brazil (8.1%).[3] The commonest snake species that lead to envenomation was from the Viperidae family. This finding is comparable with the old studies in Penang (1960s) and Central Kedah (1980s) that showed the majority of venomous bites were due to pit vipers.[10,16] Viperidae family are mostly lowland snakes that live in areas near plantation farms or estates and are widely distributed along the mangrove forest. Therefore, areas with those characteristics should expect similar dominant species and envenomation.

To date, factors associated with risks of getting severe envenomation, particularly in Malaysia, have not been fully studied. This study found three factors that were significantly associated with the severity of the snakebite cases. Firstly, Malay ethnicity was significantly associated with severe snakebite envenomation (adjusted OR =2.549, 95% CI =1.277,5.089). The up-to-date literature for ethnic differences in snakebite cases is scarcely reported. Previous epidemiology studies in Malaysia reported that the highest snakebite cases happened among Malays.[8,10,16] However, no evidence of significant association with the severity of envenomation was stated. Possible explanation in this study is the Malay ethnic group is a predominance in Sungai Petani district and living in outskirt areas.

Secondly, envenomation from the Viperidae family is a risk factor for severe envenomation (adjusted OR =3.017; 95% CI =1.613, 5.642). This finding is contrary to the studies in Kelantan, Perlis and Kuala Lumpur, where severe envenomation cases were caused by cobra bites (Elapidae family).[8,11,17] This finding should alert the high-risk group of people in Sungai Petani as Malayan pit viper is the predominant species in Penang and central Kedah.[10,16] In fact, it is always thought that pit vipers' envenomation are less lethal compared to cobra.

Thirdly, patients bitten on the upper limb were more likely to develop severe envenomation (adjusted OR =2.125; 95% CI =1.192, 3.790). This unexpected finding is in contrast with the Malaysian and global studies.[3,8,10,11] One of the studies found that most snakebites occurred due to stepping on the snake by accident.[10] Based on Table I, there were considerable number of cases occurred during work-related activities. Since fishing and agriculture are the main economic activities in the area, this might expose them to the natural habitat of the snakes. Therefore, being bitten on the upper limbs could be related to their works that require using one's hands, such as clearing bushes, gardening, farming, and fishing.

In this study, most snakebites occurred in the evening, from 1800-2359 hours. A similar pattern was observed in Kelantan by Chew et al., and most of them presented within 6 hours (97.3%).[11] Our study also found that 84.1% of patients had non-medical pre-intervention prior to their arrival at the hospital, but it was not a factor for the delay or severe envenomation. The finding can be explained in two ways: either the snakebite was non-venomous, or the patients arrived at the hospital in a short period despite non-medical interventions such as self-tourniquet, cloth tying, or herb application. The mean time-lapsed arrival to the hospital was 108.6 minutes, which is better than other Malaysian study.[11]

Identification of snake species had significant value in managing these cases. Some of the patients were able to recognize the snakes through the snake pictures catalog. Consultation with the RECS team also had contributed to a significant success in identifying the snakes. As a result, about 78.6% of snakes were identified, and the management plans were successfully implemented during the admission.

There were some limitations to this study. It was conducted in a single center in central Kedah, Malaysia, which might have limited heterogenicity of the data. The confidence interval can be wide and may be associated with a small number of certain variables, particularly ethnicity. Secondly, this is a retrospective study where researchers relied on accurate recordkeeping about the clinical features, management, and outcome findings.

CONCLUSION

The prevalence of severe envenomation among snakebite cases at HSAH is more than 50% of snakebite cases. Malay ethnicity, upper limb snake bites, and snakebite from the Viperidae family had a higher chance of severe envenomation. It is likely that work-related activities might expose the patients to snakebite envenomation. There was only one mortality case due to Elapidae envenomation.

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ORIGINAL ARTICLE

Malaysian parental attitudes toward medicine use in children

Nurulain Nadiah Abdul Hadi, BPharm, Chandini Menon Premakumar, PhD, Noraida Mohamed Shah, PhD

Centre of Quality Management of Medicines, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, 50300 Kuala Lumpur, Malaysia

ABSTRACT

Introduction: Parental attitudes can have a significant impact on the use of medicines in children. This study aimed to investigate parental attitudes towards medicines used in children in Malaysia and the sociodemographic factors associated with it.

Materials and Methods: A cross-sectional study using convenience sampling was conducted among 230 parents with children aged 12 years and below in Malaysia. Data were collected between November 2020 and January 2021 through online platforms.

Results: The majority of respondents were mothers (67.8%) and aged between 40-49 years (43.0%). The results showed that antipyretics were the most commonly used medicines followed by cough and cold medicines, antibiotics, and analgesics. The results further revealed that parents have neutral attitudes toward the use of medicines in children (69.90 ± 12.12 from a total score of 105), and mothers and younger parents having a significantly more positive attitude than fathers and older parents, respectively ($p < 0.05$).

Conclusion: This study provided insights into the types of medicines commonly used in children and parental attitudes towards medicines used in children in Malaysia.

KEYWORDS:
Attitudes; children; medicines; parents

INTRODUCTION

Children are especially vulnerable to medication errors due to their unique state of physiological development.[1] Also, given that the misuse or abuse of medications in children can lead to numerous health problems, parental monitoring is imperative in administrating children's medications.

Previous studies revealed that most parents had positive attitudes toward the necessity of medicines but mostly worried about the adverse effect and interactions of medicines in children.[2,3] This can be observed among parents with Attention Deficit Hyperactivity Disorder (ADHD) children whereby they discontinued the medications of their children due to the side effect experienced and perceived lack of medication effectiveness.[4] Similarly, a study involving parents of epileptic children admitted to the importance of medication and expressed concerns about its detrimental effects.[5] As a result, parents with concerns on the risk of medicines demonstrated preference towards Complementary and Alternative Medicines (CAMs).[6] The practice of parental self-medication has also been widely discussed. Parents tend to self-medicate their child if they are familiar with the illness or symptoms or when they consider the disease as mild.[7]

Apart from that, parents can influence the adherence of medication and the medicine-taking behaviour of children because children often grow up to emulate behaviour of the parents. Experience with medicines or observing medication-taking behaviour among family members may also affect beliefs and expectations of children on the use of medicines.[8] This can be observed in a study among self-medicated adolescents in Kuwait which showed that parents were their common source of information on medications.[9]

To date, general studies on parental attitudes toward medicines use in children in Malaysia is scarce compared to its study on specific medical conditions. Moreover, little is known about factors that contribute to parental attitudes toward medicine used in children. Therefore, this study aimed to investigate parental attitudes toward medicines used in children in Malaysia and its association with sociodemographic factors.

MATERIALS AND METHODS

This was a cross-sectional study using a convenience sampling method. The inclusion criteria include Malaysian parents of children aged 12 years and below who can understand Malay or the English language. Those who did not fulfil the inclusion criteria were excluded. A questionnaire was created using Google Forms and shared by the researchers across various social media platforms such as Facebook, WhatsApp, and Twitter, which was then shared to other contacts, i.e. snowball sampling. The data were collected from November 2020 until January 2021 in Malaysia. The calculated sample size using the Raosoft® calculator for this study was 385 respondents.

Prior to answering the online questionnaire, information on the study and invitation to participate were shared at the social media platforms. The participants would need to read the information about the study before answering the questionnaire. Participation in this study was voluntary and they had the right to withdraw from this study at any time. By answering the questionnaire, they were considered to have consented to participate in the study. The questionnaire was

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Corresponding Author: Noraida Mohamed Shah
Email: noraida_mshah@ukm.edu.my

answered once by the respondent regardless of the number of children that they have. The data of the respondents were checked thoroughly to ensure that no duplicate responds were recorded. All information gathered in this study were kept anonymous and strictly confidential.

The present study was approved by the Research Committee of Faculty of Pharmacy and the Research Ethics Committee of Universiti Kebangsaan Malaysia (UKM PPI/111/8/JEP-2020-647).

Instrument

A questionnaire to explore attitudes of parents towards medicating children was adapted from a validated questionnaire tested in Australia [10], which had also been used on Finnish and Jordanian parents [2,3]. The English version of the questionnaire was translated into Malay using the forward-backward method and both versions were administered among the participants. The content of the questionnaire was examined by five experts consisted of pharmacists and academicians and was amended accordingly. The questionnaire comprised of three sections described below.

a) Section A

This section consisted of questions on the demographical data of parents such as age, ethnicity, religion, education level, employment status, household monthly income and number of children.

b) Section B

The health status of children was assessed in this section. The questions required a 'Yes' or 'No' answer on medically diagnosed disease, and the current use of prescription and over-the-counter (OTC) medicines in their children. Participants were also asked to select types of medicines commonly used in treating their children.

c) Section C

This section consisted of attitudinal statements of 21 items to analyse parental attitude towards medicating children. Each item was rated using the five-point Likert scale (strongly disagree, disagree, neutral, agree, and strongly agree). The scoring of negative statements was reversed and the total score of attitudes was computed. The total scores ranged from 21 to 105 and were classified into negative (21-48), neutral (49-76), and positive (77-105) attitudes [2].

A pilot study was conducted among 30 parents to test the suitability and reliability of the questionnaire. Cronbach's alpha was used to test questionnaire scale reliability and a coefficient value of 0.837 was obtained, indicating good internal consistency. Based on the findings of the pilot study, evaluations and amendments were made to the questionnaire including simplification of medical terms to improve participants' comprehension.

Statistical analysis

Data collected were analysed using the IBM® SPSS (version 25.0). Descriptive statistics were tabulated for demographic data, the health status of children, commonly used medicine, and responses of parents towards attitudinal statements using percentages for categorical variables. Parental attitudes towards medicine were determined using the total score of attitudes with a higher score indicated a more positive attitude. The normality test showed that the data were normally distributed. Independent samples t-test was used to compare the score of attitude of parents toward children's use of medicine between the genders, while one-way analysis of variance (ANOVA) was utilised to test the score difference between the age group, ethnicity, religion, level of education, household monthly income, and number of children. Tukey test was performed following one-way ANOVA with the statistical significance level at $p < 0.05$. Pearson correlation was used to identify correlation between the age of youngest child and total attitude score of the parents.

RESULTS

A total of 272 parents returned the questionnaire; however, only 230 parents were included (84.56%). The remaining were excluded as they did not fulfill the inclusion criteria. The mean±SD of the youngest child was 5.62±3.79. Majority of the respondents were mothers (67.8%) aged between 40-49 years old (43.0%), Malay (91.3%), had college or university qualifications (89.6%), and working (86.5%). Details of the sociodemographic data are presented in Table I.

Table I also demonstrated that only 13.5% of the parents currently used prescription medicines and 34.8% used OTC medicines and vitamins for their children. Antipyretic was noted as the most commonly used medicines by parents (79.1%), followed by cough and cold products (66.1%), antibiotics (38.7%), and analgesics (16.5%). Most of the parents reported having neutral attitude (68.7%) i.e. neither agree or disagree towards medicines used in children. The overall score of parental attitude is categorised as neutral (69.90 ± 12.12). Furthermore, it was revealed that most parents agreed that medicines (85.7%) and prescriptions by a doctor (88.3%) are necessary for treating illnesses.

Prescription medicines were regarded as effective and safe for 76.5% and 77.4% of the parents, respectively, whereas 60.8% and 55.2%, respectively believed so about over the counter (OTC) medicines. Only 27.4% generally agreed to the statement that they would try to avoid giving medicines to children and 36.5% of the parents considered medicines as unnatural to the human body. Moreover, more than half of the parents expressed concerns about the side effects of medicine (53.5%), and 47.4% worried about the interactions of medicines toward their children. The complete parental responses toward medicines used in children are presented in Table II.

Table III showed the comparison of parental attitude scores between different groups. Mothers displayed a more positive attitude towards medicating children with significantly higher mean scores of attitudes (71.41±12.03) compared to fathers (66.72±11.77). The results also showed that attitude scores were significantly different across age group of the parents. The attitudes score of parents aged 20-29 and 30-39 were significantly higher in comparison to other age groups

Table I: Demographic of respondents and child's clinical data (n=230)

Demographic characteristic		Frequency (n%)
Relationship to the child	Mother	156 (67.8)
	Father	74 (32.2)
Age group	20-29	22 (9.6)
	30-39	85 (37.0)
	40-49	99 (43.0)
	≥50	24 (10.4)
Ethnicity	Malay	210 (91.3)
	Chinese	11 (4.8)
	Indian	4 (1.7)
	Others	5 (2.2)
Religion	Islam	214 (93.0)
	Buddha	10 (4.3)
	Christian	3 (1.3)
	Hindu	3 (1.3)
	Others	0 (0)
Highest level of education	Primary school	1 (0.4)
	Secondary school	23 (10.0)
	College or university	206 (89.6)
Current employment status	Student	2 (0.9)
	Housewife	25 (10.9)
	Working (Full time/Part time)	199 (86.5)
	Unemployed	3 (1.3)
	Retired	1 (0.4)
Household monthly income	<RM4000	48 (20.9)
	RM4000 – RM9000	124 (53.9)
	>RM9000	58 (25.2)
Number of children	1	40 (17.4)
	2	46 (20.0)
	3	63 (27.4)
	4	34 (14.8)
	≥5	47 (20.4)
Age of youngest child (mean ± SD)		5.62±3.79
Child has illness diagnosed by doctor	Yes	32 (13.9)
	No	198 (86.1)
Current use of prescription medicine by the child	Yes	31 (13.5)
	No	199 (86.5)
Current use of OTC medicine and vitamin by the child	Yes	80 (34.8)
	No	150 (65.2)
Types of medicines commonly used by child	Antipyretic	182 (79.1)
	Cough and cold	152 (66.1)
	Antibiotics	89 (38.7)
	Analgesic	38 (16.5)
	Others	22 (9.6)
Parental attitudes towards medicines used in children	Overall mean ± SD	69.90 ± 12.12
	Positive	63 (27.4)
	Neutral	158 (68.7)
	Negative	9 (3.9)

Table II: Parental attitudes towards the use of medicine in children (n=230)

Statement	Frequency (% of the responses)				
	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Medicines are necessary in treating illnesses.	0 (0)	5 (2.2)	28 (12.2)	108 (47.0)	89 (38.7)
Medicines that a doctor has prescribed for the child are necessary.	0 (0)	2 (0.9)	25 (10.9)	94 (40.9)	109 (47.4)
Prescription medicines are effective.	0 (0)	3 (1.3)	51 (22.2)	126 (54.8)	50 (21.7)
I try to avoid giving medicines to my child.	44 (19.1)	61 (26.5)	62 (27.0)	34 (14.8)	29 (12.6)
Prescription medicines are safe.	2 (0.9)	7 (3.0)	43 (18.7)	110 (47.8)	68 (29.6)
Over-the-side counter (OTC) medicines are effective.	2 (0.9)	8 (3.5)	80 (34.8)	113 (49.1)	27 (11.7)
Over-the-counter (OTC) medicines are safe.	2 (0.9)	7 (3.0)	94 (40.9)	99 (43.0)	28 (12.2)
I take care of my child's minor ailments (eg: diarrhoea, sore throat, cough, fever) by using OTC medicines.	6 (7.0)	29 (12.6)	55 (23.9)	101 (43.9)	29 (12.6)
Fever, a natural means of defense of the child's body, should not be treated artificially with medicines.	31 (13.5)	82 (35.7)	66 (28.7)	35 (15.2)	16 (7.0)
Doctors prescribe antibiotics to children too often.	33 (14.3)	70 (30.4)	74 (32.2)	41 (17.8)	12 (5.2)
Medicines are unnatural to the human body.	12 (5.2)	40 (17.4)	94 (40.9)	52 (22.6)	32 (13.9)
Medicines can disturb the child's body's capability to heal illnesses on its own.	19 (8.3)	65 (28.3)	83 (36.1)	38 (16.5)	25 (10.9)
I try to take care of my child's ailments by some other means rather than using medicines.	21 (9.1)	54 (23.5)	78 (33.9)	54 (23.5)	23 (10.0)
I take my child to see a doctor only when other ways of treatment at home did not help.	26 (11.3)	46 (20.0)	49 (21.3)	75 (32.6)	34 (14.8)
Medicines are dangerous for my child, even when used according to the instructions.	54 (23.5)	96 (41.7)	49 (21.3)	23 (10.0)	8 (3.5)
I usually give less dose of medicines to the child than is recommended in the instructions.	59 (25.7)	91 (39.6)	46 (20.0)	24 (10.4)	10 (4.3)
The child needs to learn how to bear the symptom (eg. pain) to avoid taking medicines (eg. painkiller).	53 (23.0)	64 (27.8)	56 (24.3)	42 (18.3)	15 (6.5)
Side effects of medicines towards children worries me.	6 (2.6)	30 (13.0)	71 (30.9)	63 (27.4)	60 (26.1)
Interactions of medicines worry me.	10 (4.3)	32 (13.9)	79 (34.3)	63 (27.4)	46 (20.0)
Long-term use of medicines (eg. painkiller) reduces the symptom (eg. pain) threshold for your child.	14 (6.1)	28 (12.2)	81 (35.2)	67 (29.1)	40 (17.4)
The more you need to use a medicine (eg. painkiller) on your child, the less effective they are for the symptom (eg. pain).	15 (6.5)	30 (13.0)	92 (40.0)	55 (23.9)	38 (16.5)

($p<0.05$; Table IV). No significant differences were observed between total attitude scores parents with other sociodemographic variables. There was a significant negative correlation between age of the youngest child and total attitude score ($r=-0.188$, $p< 0.05$).

DISCUSSION

In this present study, age group and respondents' relationship to the child were the only sociodemographic factors that were significantly associated with the attitudes of parents towards the use of medicines in children. Results showed that mothers had significantly more positive attitudes in medicating their children compared to fathers, which might ascribe to the mother's common role in taking care of the family's health.[2] Other studies also concurred that mothers are the main caretaker of their children and they have better capabilities to manage children's ailment.[3,11,12]

The present study also found that parents aged 40 years old and above had more negative attitudes in medicating children compared to younger parents. This result is in line with a study by Hameen-Anttila et al. which reported that older parents tend to avoid medicines and had more fears about the risks of medicines.[2] These were corroborated by a study on parental attitudes towards antibiotic use, which showed that older parents were more likely to worry over the side effects of antibiotics.[13] In contrast, a previous study among the general population in Sweden reported that attitude towards medication improved with age.[14] Similarly, Suleman et al. demonstrated that respondents aged 56-65 years old had more positive views toward medicines than the lower age groups.[15] These conflicting findings could be attributed to different medication-taking experiences by the older parents that may influence their attitudes toward medicines.

This study established that antipyretic was the most frequently used medicine by Malaysian parents to treat their children. Similar results were observed in studies conducted among Indian and Korean parents.[16,17] Other reports also showed that parents often self-medicate their children at home with antipyretics.[18-21] The result might be attributed to fever being the common illness experienced by children as well as perturbation of parents about the discomfort of their child, persistently high body temperature, and fear of untreated fever complications.[22,23] Moreover, antipyretics such as paracetamol are readily available at community pharmacies and parents usually have antipyretics stocked at home.[7] These findings could be due to the fact that paracetamol is considered safe to be used for children if administered at the proper dosage.

Table III: Comparisons of parental attitudes scores between different groups

Variable		Mean ± SD Attitude score	P-value
Relationship with the child [a]	Mother	71.41 ± 12.03	0.006*
	Father	66.72 ± 11.77	
Age group [b]	20-29	75.91 ± 13.15	0.001*
	30-39	72.44 ± 12.96	
	40-49	67.54 ± 10.66	
	≥50	65.17 ± 10.07	
Ethnicity [b]	Malay	69.99 ± 12.23	0.167
	Chinese	65.91 ± 9.59	
	Indian	64.50 ±11.90	
	Others	79.40 ± 8.62	
Religion [b]	Islam	70.13 ± 12.21	0.669
	Buddha	65.40 ± 9.95	
	Christian	70.67 ± 15.50	
	Hindu	67.67 ± 12.34	
Highest level of education [b]	Primary school	61.00 ± 0.00	0.718
	Secondary school	69.09 ± 8.34	
	College or university	70.03 ± 12.50	
Current employment status [b]	Student	63.50 ± 20.51	0.176
	Housewife	74.80 ± 11.04	
	Working (Full time /Part time)	69.46 ± 12.17	
	Unemployed	61.67 ± 4.73	
	Retired	72.00 ± 0.00	
Household monthly income [b]	<RM4000	69.75 ± 11.59	0.986
	RM4000 – RM9000	70.02 ± 13.06	
	>RM9000	69.76 ± 10.54	
Number of children [b]	1	71.68 ± 13.64	0.086
	2	73.46 ± 12.82	
	3	68.97 ± 11.04	
	4	68.62 ± 10.56	
	≥5	67.09 ± 11.93	

*Indicates significant difference at p<0.05
[a] Independent T-test
[b] One-way ANOVA

Table IV: Post-hoc analysis (Tukey Test)

Variable			Mean difference	P-value
Age group	20 -29	30-39	3.47	0.61
		40-49	8.37	0.02*
		≥50	10.74	0.01*
	30-39	20-29	-3.47	0.61
		40-49	4.90	0.03*
		≥50	7.27	0.04*
	40-49	20-29	-8.37	0.02*
		30-39	4.9	0.03*
		≥50	2.37	0.81
	≥50	20-29	-10.742	0.01*
		30-39	-7.269	0.04*
		40-49	-2.369	0.81

*The mean difference is significant at P<0.05

Cough and cold drugs were the next most commonly used medicine by parents in this study (66.1%). A previous study in Kuala Lumpur revealed that almost 90% of parents had administered cough and cold medicines to their child to relieve the symptoms of upper respiratory tract infections (URTIs) and some parents admitted to administering it for sleepiness effect.[24] Nevertheless, it is not encouraged to use cough and cold medicines in children less than two years old because of the unsuitable active ingredients that lack efficacy data and may cause safety concerns in young children.[25,26]

Parents in this study displayed neutral attitudes toward medicines use in children with a mean score of 69.90 ± 12.12 (max score =105). However, majority of the parents in this study agreed that medicines are necessary for children, which may indicate that most of them have an optimistic attitude towards medicines. This is in accord with an earlier local study by Dawood et al., whereby majority of the parents agreed that medicine is important for their children.[12] The results of this study further showed that more respondents agreed that prescription medicines are effective and safe compared with OTC medicines. Other studies had also shown differing views on prescription and OTC medicines by parents.[2,3]

Aside from that, small proportions of parents found to preferably avoid giving medicines to their children and more than half of the respondents felt worried about the side effects and interactions of medicines and may choose to use lower dose of medicines for their children. This happened as some parents are not knowledgeable about the side effects of medicines and consequently might avoid medicines or find other alternatives.[3,12] Prior studies reported parallel results with 69% and 80% of Finnish and Jordanian parents expressed concerns regarding medicine interactions and side effects and suggested the need for education on these aspects.[2,3] Therefore, physicians and pharmacists should help educate parents on medicines' side effects and interactions as some parents admitted willingness to initiate medication after being more informed about the medicines.[27]

There were several limitations to this study. The convenience sampling method employed may have resulted in selection bias. Additionally, the relatively small sample size, which did not cover all the states and unequal representation of each ethnicity in Malaysia, might limit the generalisation of the population. Furthermore, the accuracy of the findings in this survey was dependent on the honesty and understanding of the respondents. Future research could benefit from a stratified random sampling method to reduce sampling bias and to ensure proper representation of the Malaysian population. Despite these limitations, this study was the first to report on Malaysian parental attitudes towards medicines used in children.

CONCLUSION

This study provides valuable baseline information into the types of medicines commonly used in children and the parental attitudes towards medicines use in children in Malaysia. Antipyretics were reported as the most commonly used medicines and the majority of the parents had a neutral attitude towards medicine used in their children. Also, mothers and younger parents displayed a more positive attitude towards medicines than their counterparts. Efforts to improve the attitude of parents towards medication use are imperative such as providing education to them particularly regarding the importance of medicines as well as its efficacy and safety. This can be done by disseminating relevant information through mainstream and social media or conducting awareness campaigns focusing on children's health and medicines. Further researches are needed to explore other factors that may influence parental attitudes toward medicine used in children in Malaysia.

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A nationwide survey on awareness and knowledge about Bronchial Provocation Test amongst doctors in Malaysia

Khai Lip Ng, MRCP[1], Nai-Chien Huan, MRCP[1], Fatimah Azmah Mohammad, MRCP, Nur Husna Mohd Aminudin, MMED[1], Fatimah A'tirah Mohammad, PhD[2], Jamalul Azizi Abdul Rahaman, MMED[1]

[1]Department of pulmonology, Serdang Hospital, Selangor, Malaysia, [2]Faculty of resource science and technology, Universiti Malaysia Sarawak (UNIMAS), Kota Samarahan, Sarawak, Malaysia, [3]Department of medicine, Universiti Putra Malaysia (UPM), Selangor, Malaysia

ABSTRACT

Background: Bronchial provocation test (BPT) is widely used internationally not only to evaluate bronchial responsiveness in conditions especially asthma, but is also utilized as a marker of control, severity and prognosis for asthma. However, the uptake of BPT in certain countries including Malaysia remains low. We aimed to explore this lack of knowledge by assessing the current level of awareness and knowledge on BPT amongst doctors in Malaysia.

Materials and Methods: A nationwide web-based questionnaire targeting doctors was sent through social media (Facebook, WhatsApp and Telegram) and Malaysian Medical Association (MMA) mailing lists between 1 October 2020 – 5 February 2021.

Results: In all 415 survey responses were analysed from doctors of various grades namely medical officers to consultants. A total of 404 (97.35%) encountered patients with asthma in their daily practice. According to specialty: 169 (40.72%) were from primary care, 121 (29.16%) internal medicine, 50 (12.05%) pulmonary medicine and 75 (18.07%) others. Only 163 (39.28%) were aware of BPT as a tool to diagnose asthma. 232 (55.90%) and 124 (29.88%) regarded BPT as an important test and felt confident to refer patients for BPT respectively. Of those participants who were not confident to refer: 35.17% were unsure of BPT indications, 33.21% were unsure of centres providing BPT, 8.17% cited logistic reasons, 6.04% were concerned of possible BPT side effects. 387 (93.25%) wanted more training in BPT. The median BPT knowledge score was 20% (1 out of 5). Awareness and knowledge were affected by specialty but not by: region of practice, gender, age and grade from logistic regression analysis.

Conclusion: Various national level programs and targeted local interventions are much needed to increase the awareness, knowledge and uptake of BPT in Malaysia.

KEYWORDS:
bronchial provocation test, knowledge, awareness, questionnaire, survey, bronchial asthma

INTRODUCTION

Asthma is a common but potentially serious medical condition characterised by chronic airway inflammation. Typical symptoms include wheezing, shortness of breath, cough and/or chest tightness that varies in both intensity and over time.[1] The diagnosis of asthma requires a history of suggestive symptoms together with clear demonstration of variable expiratory airflow limitation.[1-3] Diagnosing asthma in daily clinical settings can be challenging as various conditions such as gastroesophageal reflux, chronic obstructive pulmonary disease and anxiety disorders can present with asthma-like symptoms.[1] Attempts to obtain a confident diagnosis of asthma from a single time-constrained doctor-patient encounter can be complicated as asthma is often episodic, variable and follows a relapsing remitting course.[4] This has led to a common practice of empirical asthma treatment in Malaysia and certain countries abroad. Studies have clearly shown that many patients with asthma are poorly investigated in the community setting.[5-7]

Bronchial provocation test (BPT) is widely used internationally to evaluate for the presence of airway hyper-responsiveness (AHR) in conditions especially (but not limited to) asthma, but also as a marker of disease control,[8] severity[9,10] and prognosis[11] for asthma. BPT is commonly used to confirm the diagnosis of asthma among patients presenting with asthma-like symptoms with normal or near normal volume of air at the end of the first second of force expiration (FEV1).[12] However, the uptake of BPT in some countries including Malaysia remains low. In Malaysia, BPT was first available back in July 2008 but to date, only very few specialized centres (Serdang Hospital, Selangor; Queen Elizabeth Hospital, Sabah; Sarawak General Hospital, Sarawak) are offering the test.[12] The primary aim of this study was therefore to evaluate the level of awareness and knowledge of BPT amongst doctors in Malaysia.

MATERIALS AND METHODS

Study design

We conducted a nationwide, cross sectional, self-administered web-based questionnaire among medical doctors in Malaysia. The questionnaire was generated by using Google Forms and consisted of a total of 23 questions that were subdivided into 2 parts: part A with 18 questions and part B

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Corresponding Author: Ng Khai Lip
Email: khailip08@yahoo.com

with 5 questions (see Appendix). All questions were written in English. Part A questions included gender, grade of doctor (medical officer, general practitioner, family medicine specialist, physician, consultant), specialty (primary care, internal medicine, pulmonary medicine, others), age range, region of practice as well as current and previous working experience in pulmonary medicine. Malaysian identity card number were requested to identify any potential duplicate responses. Respondents were asked about the frequency they encountered patients with asthma in daily practice, awareness of BPT to aid in diagnosis of asthma, perceived importance of BPT, confidence in referring patients for BPT, frequency of referral for BPT in daily practices, reason(s) for never / rarely referring patients for BPT, perceived sufficient training in BPT, perceived need for further training in BPT and perception on whether BPT should be made more available in Malaysia. The final question of part A asked broadly for any additional thoughts or comments. Part B included 5 short questions to assess the level of knowledge regarding BPT. Respondents were required to select the most appropriate answer for each question. The first question explored regarding the safe FEV1 threshold for BPT. The second question asked about agents that can be used for BPT. The third question assessed respondents' knowledge on indications of BPT while the final 2 questions required respondents to interpret BPT results.

To the best of our knowledge, there are no existing validated questionnaires on the topic of BPT. We therefore deployed the following steps for the design and development of our study questionnaire: (1) literature review on BPT by researchers, (2) conduct interviews with focus groups (doctors from Malaysia of various grades and specialty to identify how they conceptualized and describe the topic of interest), (3) development of online questionnaire in concordance with latest evidence guidelines on BPT, (4) review and validation by content experts (panel of expert respiratory and internal medicine physicians), and finally (5) conduct pilot testing.

The web-based questionnaire was sent to medical doctors nationwide through social media (Facebook, WhatsApp, and Telegram) as well as Malaysian Medical Association (MMA) mailing lists between 1st October 2020 to 5th February 2021. Inclusion criteria were fully registered doctors of any grade from both government and private sectors within Malaysia. Incomplete responses, duplicate responses, doctors working outside of Malaysia and non-doctors (medical students, allied health members) were excluded. The questionnaire was not specifically targeted towards any particular specialty. We did not restrict access or sharing of questionnaire in order to facilitate dissemination. Respondents were able to invite other participants by sharing the online questionnaire link.
This study was conducted in accordance with the latest amended Declaration of Helsinki. The study protocol was approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia (approval number: NMRR-20-2420-56805 Investigator initiated research (IIR)).

Statistical analyses
Numerical data are reported as mean and standard deviation (SD) if they follow normal distribution. Non-normally distributed data are expressed as median and interquartile range (IQR). Categorical data are stated as frequencies and percentages. Binary logistic regression analysis was used to assess if region of practice, specialty and / or grade of doctor were predictive of awareness of BPT, perceived importance of BPT, confidence to refer for BPT and knowledge on BPT. Statistical analyses were done using IBM SPSS Statistics for Windows Version 16 (IBM Corp., Armonk, NY, USA).

RESULTS

During the study period, a total of 423 responses were recorded. We excluded 4 duplicate responses, 2 incomplete responses and further removed 2 respondents who did not meet the inclusion criteria (1 medical student and 1 doctor not practicing within Malaysia). Figure 1 illustrates included and excluded respondents in a flowchart.

Respondent demographics
Of the 415 responses that were analysed, 231 (55.66%) were from females. Most respondents identified themselves as medical officers: 195 (46.99%) out of 415. Other grades in order of descending frequency were physicians (15.90%), family medicine specialists (14.22%), general practitioners (13.73%) and consultants (9.16%). In terms of specialty, the largest response rate was from primary care doctors (169 or 40.72%), followed by 121 (29.16%) from internal medicine, 50 (12.05%) from pulmonary medicine and 75 (18.07%) others. According to age, most respondents (54.94%) belong to age 30 – 39-year-old sub group. Considering region in Malaysia, 346 (83.37%) respondents were from Peninsular Malaysia while 69 (16.63%) were from East Malaysia (Sabah, Sarawak and Labuan). The summary of respondent demographics who were included for analysis is shown in table I.

Quantitative results
Most respondents (97.35%) encountered patients with asthma in their daily practice. Only 163 (39.28%) reported good awareness (understand the test; can demonstrate/explain the test) of BPT to diagnose asthma. 232 (55.90%) and 124 (29.88%) regarded BPT as an important test and felt confident to refer patients for BPT respectively. Of those who were not confident to refer, 35.17% were unsure of BPT indications, 33.21% were unsure of centers providing BPT, 8.17% cited logistic reasons, 6.04% were concerned of possible BPT side effects. Only 30 (7.23%) felt that they received sufficient training in BPT while nearly all participants, 387 (93.25%), wanted more training in BPT. Additionally, the majority, 327 (78.80%) agreed that BPT should be made more available in the country. Table II gives the summary of results.

The median score for the 5 questions on BPT knowledge assessment was 20% (IQR 0 – 40%): one out of 5 questions answered correctly. In all 106 (25.54%) correctly named the safe FEV1 threshold for BPT. Only 79 (19.04%) participants knew all the agents that can be used for BPT. Indications of BPT was correctly answered by 81 (19.52%). The final 2 questions (question 4 and question 5) on reporting BPT results were correctly answered by 108 (26.02%) and 136

Table I: Demographics of participants who returned responses to our survey

		N	%
Gender	Male	184	44.34
	Female	231	55.66
Grade	Medical officer	195	46.99
	General practitioner	57	13.73
	Family medicine specialist	59	14.22
	Physician	66	15.90
	Consultant	38	9.16
Specialty	Pulmonary medicine	50	12.05
	Internal medicine	121	29.16
	Primary care	169	40.72
	Others	75	18.07
Age	20-29	59	14.22
	30-39	228	54.94
	40-49	58	13.98
	50-59	39	9.40
	>60	31	7.47
Region	Perlis	4	0.96
	Kedah	8	1.93
	Penang	29	6.99
	Perak	57	13.73
	Selangor	101	24.34
	Putrajaya	5	1.20
	Kuala Lumpur	47	11.33
	Negeri Sembilan	22	5.30
	Melaka	20	4.82
	Johor	30	7.23
	Pahang	7	1.69
	Kelantan	12	2.89
	Terengganu	4	0.96
	Sarawak	21	5.06
	Labuan	9	2.17
	Sabah	39	9.40

(32.77%) respondents respectively. Importantly, 252 (60.72%) and 245 (59.04%) answered "not sure" for questions 4 and 5 respectively. Refer to table III for results of knowledge assessment on BPT. Logistic regression analysis revealed that participants' awareness of BPT, perceived importance of BPT, confidence to refer for BPT and knowledge on BPT were affected by specialty but not by: region of practice, gender, age and grade (Table IV). Respondents from pulmonary medicine demonstrated better awareness and knowledge scores on BPT compared to other specialties (Figures 2 and 3).

Qualitative results

A recurrent theme in the responses was that the respondents did not feel they had received enough exposure or experience to identify patients eligible and suitable to be referred for BPT:

"Many of my older patients are already on empirical treatment for suspected bronchial asthma when they present to my clinic. I am not sure about the indications, sensitivity and specificity of BPT for my patients."

"Not much is advertised about the test."

"I have not heard of the test despite managing patients with asthma in my daily practice!"

Besides, many respondents appreciated the importance of BPT and frequently suggested more educational sessions to promote the test:

"Would definitely like to learn about the test if educational sessions / training modules were offered."

"Not many are aware of the test! Please provide online courses for primary care doctors for better exposure and knowledge regarding BPT."

Furthermore, some respondents went on further by suggesting that merely blaming inadequate training and poor advertising of BPT were overly simplistic. It was repeatedly suggested that better and easier access to BPT may have a positive impact on the uptake of BPT in Malaysia:

"If BPT services are only available in major cities (Kuala Lumpur) then its uptake will remain low despite with increasing awareness. NOT many patients will go all the way to Kuala Lumpur for this test!"

"Making BPT more easily available for doctors and patients is the FIRST step to increase its acceptability and uptake."

DISCUSSION

An estimated 300 million individuals globally are living with asthma, making it one of the most common chronic diseases worldwide.[1] However, despite being a common condition, diagnosing asthma can be tricky and challenging. This has led to a common practice of empirical treatment of asthma with inhaled medications in Malaysia and many other countries abroad.[5-7] An early study reported that up to 34% of patients treated as asthma based on symptoms alone actually did not have asthma.[13] Empirical pharmacological

Table II: Quantitative Results of Survey Responses and Knowledge Assessment of BPT

Quantitative results of survey responses		
	N	**%**
Encounter patients with asthma in daily practice		
Yes	404	97.35
No	11	2.65
Aware of BPT to diagnose asthma		
No	126	30.36
Only heard of name	126	30.36
Understands test	135	32.53
Can demonstrate/explain test	28	6.75
Perceived importance of BPT		
No	2	0.48
Neutral	181	43.61
Important	232	55.90
Confidence in referring patients for BPT		
No	163	39.28
Neutral	128	30.84
Confident	124	29.88
Frequency of referral for BPT in daily practice		
Never	312	75.18
Rarely	56	13.49
Sometimes	38	9.16
Frequent	9	2.17
Reason for never/rarely referral for BPT		
Total reasons given by responders	563	
Unsure of indications	198	35.17
Concerns of side effects	34	6.04
Unsure of centres providing service	187	33.21
Long waiting list	8	1.42
Logistic issues	46	8.17
Never encountered patients requiring BPT	90	15.99
Perceived sufficient training		
Yes	30	7.23
No	385	92.77
Perceived need for further training		
Yes	387	93.25
No	28	6.75
Perception on whether BPT should be made more available		
No	3	0.72
Neutral	85	20.48
Yes	327	78.80
Results of knowledge assessment on BPT		
	N	**% (correct answer)**
Question 1: Safe FEV1 threshold for BPT	106	25.54
Question 2: Agents that can be used for BPT	79	19.04
Question 3: Correct indications of BPT	81	19.52
Question 4: Interpreting BPT test results	108	26.02
Question 5: Interpreting BPT test results	136	32.77
	Median	**IQR**
Knowledge score	20%(1/5)	0-40

treatment of all patients with suspected asthma will inadvertently lead to delay in attaining competing differential diagnoses such as gastroesophageal reflux disease, allergic rhinitis and chronic obstructive pulmonary disease in some. In addition, inhaled medications for asthma are not without adverse effects. For example, inhaled corticosteroids can affect the hypothalamic-pituitary-adrenal axis, bone growth and density and is linked to increased risk of oral candidiasis and pneumonia.[14,15,16] Empirical treatment of asthma without proper investigation should therefore be discouraged.

The initial recommended test for asthma is spirometry coupled with bronchodilator response (BDR) testing where improvement of more than 12% and 200mL in FEV1 post BDR testing is diagnostic.[1,2] A recent study reported that in subjects with self-reported physician diagnosis of asthma, absence of BDR had a negative predictive value of only 57% to exclude asthma.[17] Hence, among patients with negative BDR testing results, a further confirmatory BPT is widely used internationally for measurement of AHR.[17] Studies have shown that a negative BPT result is highly reliable for ruling out asthma.[18,19,20] Moreover, apart from diagnosing asthma, BPT can be utilised as a marker of disease control,[8], severity[9,10]

Table III: Logistic regression analysis for awareness, perceived importance, confidence to refer and knowledge on BPT

		Wald	Freedom	p-value
Awareness of BPT (understand test and can demonstrate test)	Region	20.268	15	0.162
	Grade	**17.092**	**4**	**0.002**
	Gender	2.037	1	0.153
	Specialty	**30.586**	**3**	**0.000**
	Age	8.11	4	0.088
Perceived importance of BPT (very and somewhat important)	Region	24.229	15	0.061
	Grade	1.244	4	0.871
	Gender	1.231	1	0.267
	Specialty	**17.88**	**3**	**0.000**
	Age	3.85	4	0.427
Confidence to refer for BPT (very and somewhat confident)	Region	13.316	15	0.578
	Grade	0.794	4	0.939
	Gender	0.583	1	0.445
	Specialty	**33.774**	**3**	**0.000**
	Age	5.612	4	0.230
Knowledge on BPT (score of at least 4 out of 5 or 80%)	Region	6.406	15	0.972
	Grade	6.379	4	0.173
	Gender	0.83	1	0.362
	Specialty	**57.046**	**3**	**0.000**
	Age	0.295	4	0.990

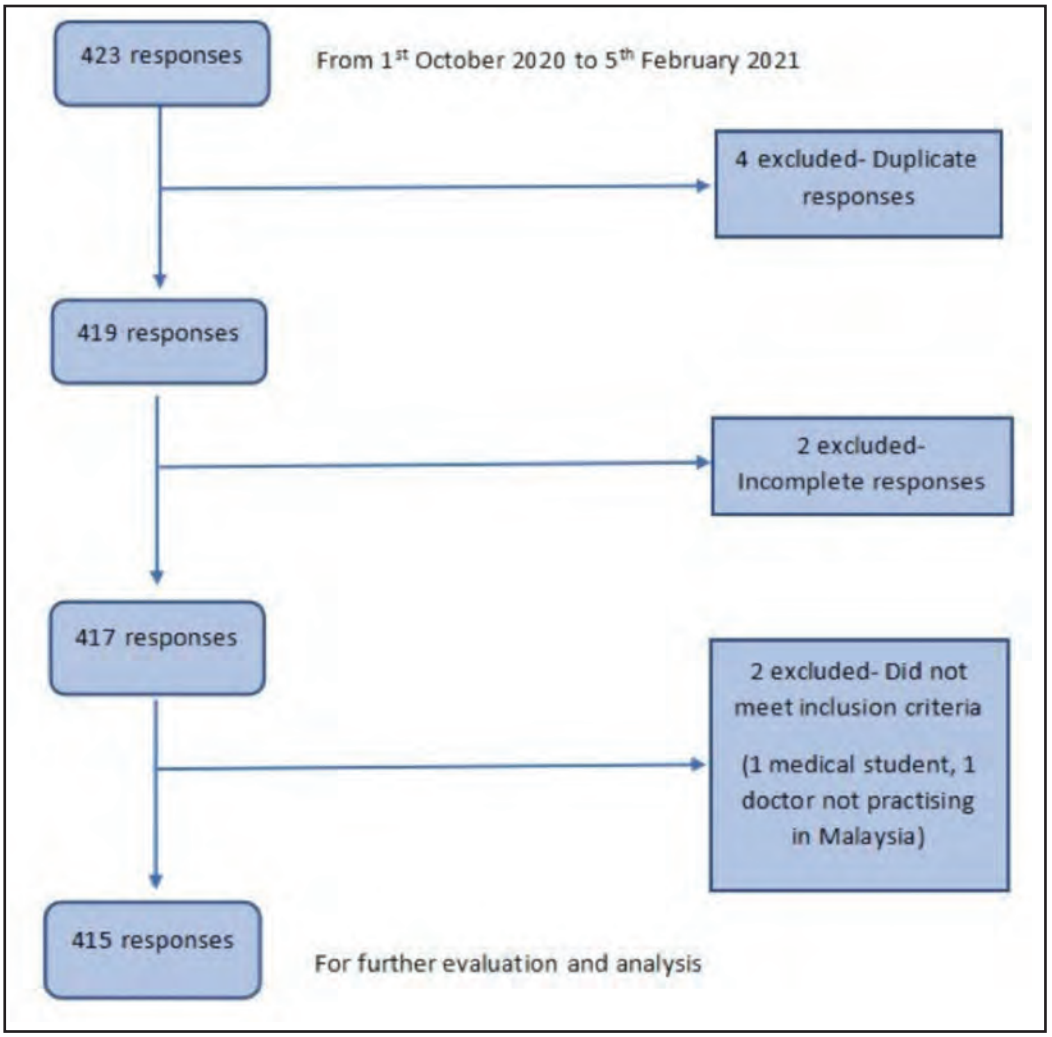

Fig. 1: Flowchart of Respondents of BPT Questionnaire.

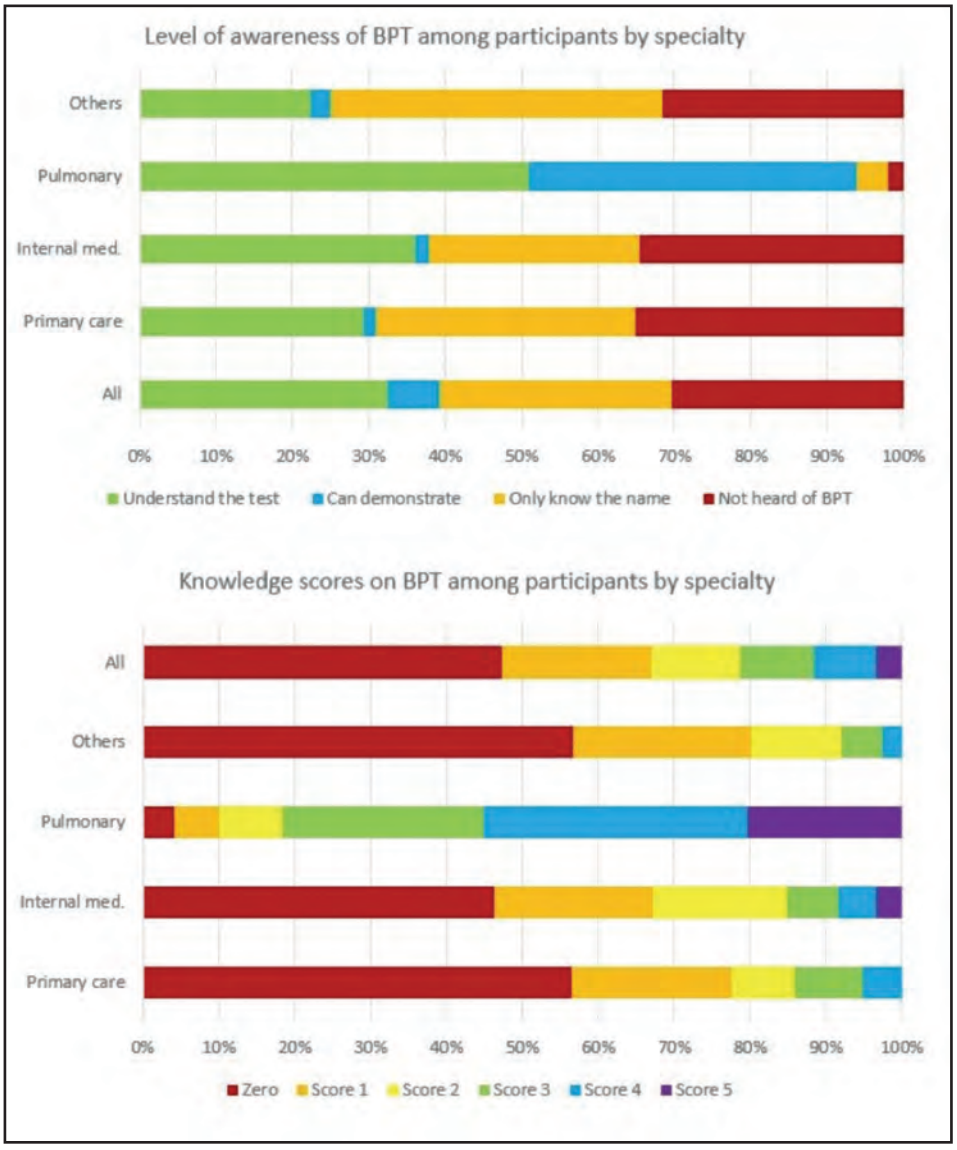

Fig. 2: Level of Awareness and Knowledge Score on BPT Among Participants by Specialty.

and prognosis[11] for asthma. The role of BPT in detecting exercise induced bronchoconstriction which occurs in up to 90% percent of patients with asthma is clearly stated in the latest Malaysian clinical practice guidelines on management of asthma in adults which was published back in 2017.[21] All three centres in Malaysia utilise methacholine,[12] a derivative of acetylcholine that stimulates muscarinic M3 receptors on bronchial smooth muscles for BPT.[18] In Malaysia, BPT services have been available since July 2008.[12] Nevertheless, to date, the uptake of BPT in Malaysia remains poor. We attempt to explore this phenomenon by unveiling the level of awareness, confidence, knowledge and perspectives of doctors practicing within Malaysia regarding the role of BPT in diagnosing asthma.

Our respondents comprised of doctors of all grades from all states of Malaysia. Most identified themselves as primary care doctors (40.72%), followed by internal medicine doctors (29.16%). According to regions in Malaysia, 83.37% participants were from Peninsular Malaysia with the remaining 16.63% from East Malaysia (Sabah, Labuan, Sarawak). Such location dispersal is consistent with the national distribution of doctors where approximately 80% and 20% of Malaysian doctors reside in Peninsular Malaysia and East Malaysia respectively.[22] Besides, a vast majority of doctors who participated in this survey (97.35%) encountered patients with asthma in their daily clinical practice. Accordingly, questionnaire respondents were regarded as suitable participants in this study.

Within our study sample, a significant proportion of doctors did not demonstrate good awareness and knowledge of BPT to diagnose asthma. We accept a knowledge score of at least 60% (at least 3 out of 5 questions answered correctly) as an indicator of sound knowledge regarding BPT. Nevertheless, the median knowledge score was only 20% (1 out of 5 questions answered correctly), suggesting significant deficiencies in understanding the basic principles of BPT

itself, let alone interpretation of BPT results. This corroborates with the qualitative results where many respondents confessed that they barely knew about BPT despite managing patients with asthma in daily practice. We further performed logistic regression analysis to assess if respondents' awareness and knowledge were influenced by variables including specialty, region of practice, gender, age and grade. As expected, doctors working in pulmonary medicine department had better awareness and knowledge on BPT. Senior and high ranked doctors (consultants), interestingly, did not score better in both knowledge and awareness compared to their younger counterparts, suggesting that poor BPT knowledge and awareness may be a widespread problem. We hypothesize that in Malaysia, BPT remains an 'exclusive' test that is only well known among the pulmonary medicine fraternity. This information could potentially be utilised to determine and guide strategies to promote the usage of BPT.

When considering various national level programs and targeted local interventions to increase awareness and knowledge on BPT among doctors in Malaysia, we suggest structuring educational and training programs at various levels. Firstly, doctors working in pulmonary medicine departments play vital roles in promoting awareness and education regarding BPT. Training in undergraduate, internship and primary care should all emphasize on the importance to avoid empirical pharmacological treatment of asthma and to introduce BPT as a potential confirmatory test for asthma. Targeted local interventions such as webinars, workshops and podcasts are among ways to allow dissemination of knowledge and awareness regarding BPT. Pamphlets and brochures should be made available for both doctors and patients in outpatient clinics and in wards to encourage and facilitate referrals for BPT when indicated. Concurrently, postgraduate training should focus on medical, primary care and respiratory consultants or specialists to ensure that they are able to maintain good knowledge and skills on BPT and thus able to contribute in promoting awareness and training of junior colleagues. We hope that detailed analysis of effects of local interventions to promote BPT could inform planning and shaping of national level programs, policies and resource allocation of BPT in Malaysia in the near future.

We accept that there is a limitation in the size of the study sample and, therefore, increasing generalisability and applicability of findings may have been found with a larger sample size. As of August 2020, there are 71041 medical doctors working in both the public and private sectors in Malaysia.[19] Our study thus represents 0.6% of potentially available respondents. Besides, selection and participation bias might occur in online based questionnaire studies. Doctors more engaged in care of patients with respiratory conditions such as asthma may have been more likely to participate in the questionnaire. Nevertheless, no incentives were given to survey participants that would have caused conflicts of interest. Survey participation was fully voluntary and was not deliberately targeted towards doctors with previous knowledge or working experience in respiratory medicine. Besides, we relied heavily on the Malaysian Medical Association (MMA) mailing lists for distribution of questionnaires. MMA has a wide network that linked all Malaysian doctors regardless of specialty and grade. Other than that, we did not collect data on location of both undergraduate and/or postgraduate training, which may have affected the study results as well.

CONCLUSION

Our questionnaire survey highlighted significant gaps in level of awareness and knowledge of BPT among doctors in Malaysia. Various national level programs and targeted local interventions are much needed to increase the update of BPT in Malaysia. We hope that data from this study could be used to inform for the purposes of planning and resource allocation of BPT in Malaysia.

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Achalasia cardia: A five-year review in Hospital Tuanku Ja'afar, Seremban

Daniel Hong Jeng Chin, MBBS[1], Kean Ghee Lim, FRCS (Edin)[1], Hong Shawn Peh, MBBS[1], Ismail Abdul Sattar Burud, MSURG[1], Mahadevan Deva Tata, MSURG[2], Jasiah Zakaria, MSURG[2]

[1]Department of Surgery, Clinical School, International Medical University, Jalan Rasah, Seremban, Negeri Sembilan, Malaysia,
[2]Department of Surgery, Hospital Tuanku Ja'afar Seremban, Ministry of Health, Malaysia

ABSTRACT

Introduction: Achalasia cardia is an oesophageal motility disorder that affects various age groups. This study focused on the epidemiological features of achalasia, its risk factors, treatment modalities offered and the clinical outcomes in a tertiary hospital.

Materials and Methods: A retrospective search was carried out on all patients with a diagnosis of achalasia cardia in Hospital Tuanku Ja'afar (HTJ), Seremban, Malaysia between 2014 and 2018. Demographic data, patient symptomatology, and definitive management options were determined from the records. Telephone interviews were conducted to evaluate patient satisfaction with the outcome of treatment.

Results: There were 30 patients with a newly diagnosed achalasia cardia in that 5-year period, with an equal incidence among men and women. The mean age of presentation was 44.63 ± 18.21 years. Malays formed the largest group. The mean weight and body mass index were 46.8 ± 10.4 kg and 18.0 ± 4.4 kg/m2 respectively. There was a wide range of duration of symptoms at presentation with a mean of 30.11 ± 35.29 months. Almost all patients presented with dysphagia (96.7%) while 70% also noted loss of weight. All patients underwent oesophagogastroduodenoscopy (OGDS) and 26 patients (86.7%) had barium swallow as part of diagnostic workup. A total of 18 patients underwent a laparoscopic Heller myotomy with or without Dor Fundoplication and/or cruroplasty while two patients (6.7%) underwent pneumatic dilatation as first treatment. Iatrogenic mucosal perforations were detected in 8 patients who underwent myotomy and fundoplication and were repaired intraoperatively. Of the patients who underwent myotomy and fundoplication, the mean weight increase was 15.6kg, increasing from 43.0 ± 8.4 kg to 58.6 ± 13.7 kg. All the patients who underwent treatment were satisfied with their treatment outcomes.

Conclusion: Most patients with achalasia cardia deemed suitable for surgery and counselled accordingly accept surgery resulting in high levels of satisfaction and weight gain in almost all these patients. A small minority who opt for pneumatic dilatation may also achieve satisfactory outcomes comparable to surgery in the short term. Although rare, clinicians should be able to recognise this disease early as early intervention often leads to satisfactory long-term outcomes.

KEYWORDS:
Achalasia Cardia, Dysphagia, Hellers myotomy, Dor Fundoplication

INTRODUCTION

Achalasia cardia is a form of motor dysphagia which results from progressive degeneration of ganglion cells in the myenteric plexus, leading to failure of relaxation of the lower oesophageal sphincter, accompanied by a loss of peristalsis in the distal oesophagus.[1] First described over 300 years ago, there has been much debate over the aetiology of achalasia with several potential triggers being implicated as the cause for the inflammatory destruction of inhibitory neurons in the oesophageal myenteric plexus. These include autoimmune responses, infectious agents and genetic factors.[2] Although there have been strong associations between these triggers and primary achalasia, none have been proven conclusively. It is likely to involve a multifactorial aetiology following an initiating event.[1,2]

Achalasia is considered a relatively uncommon disorder with incidence rates between 0.5-1.2/100000 per year.[1] Incidence rates have been reported to be as low as 0.03/100000 per year in Zimbabwe to as high as 1.63/100000 per year in Canada and the incidence rates of achalasia appear to be rising over time.[1,2,3] Whether this geographical variation and rise in incidence reflects a true rise in incidence or greater awareness and improved diagnosis remains uncertain.[1] There have been no distinct patterns of achalasia incidence based of sociodemographic factors with the disease affecting both genders, all races and all ages.[4] A few studies have demonstrated a bimodal distribution of incidence by age with peaks at around age 30 and 60 years while others have shown a generally increased risk with increased age.[5-7] Several studies show that females have a higher incidence of achalasia while others have shown equal incidence among genders.[5,6,7,8]

In Malaysia, Ganesananthan et al described a 6-year case series of achalasia cardia in Hospital Kuala Lumpur from year 2000-2005 which had a sample size of 61 patients.[9] His series noted a trend towards a younger age group with a mean age of 48 years, a female predilection (M:F = 1:1.4) and a slight Malay majority (56%).[9] Fifty patients from this series underwent pneumatic dilatation without complications and had excellent symptomatic relief with an average post-

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Corresponding Author: Daniel Hong Jeng Chin
Email: danielchin.hj@gmail.com

procedural weight gain of 4kg over 3-24 months.[9] No patients from this series underwent a Heller myotomy.[9] More recently, Siow SL et al described a series of 55 cases enrolled in a study of clinical outcomes of laparoscopic Heller myotomy and anterior Dor fundoplication between 2010-2019.[10] His series showcased a similar mean age of 49 years but noted a male predilection instead (53%).[10] Patients in this series reported a 100% satisfaction rate with no mortalities.[10] The patients were from 4 institutions with consultant level expertise in Sarawak, Johore, Penang and Kedah.[10]

We undertook a retrospective study of patients seen at Hospital Tuanku Ja'afar (HTJ), Seremban to describe the epidemiological features of achalasia in this area, its risk factors, treatment modalities offered to them and the clinical outcomes in a tertiary upper gastrointestinal surgery hospital. We also aimed to raise awareness among clinical practitioners on the recognition of this enigmatic disease as early diagnosis with prompt treatment often yields good long-term clinical outcomes for most patients across the entire spectrum of the disease.

MATERIALS AND METHODS

A retrospective search of all patients with a discharge diagnosis of achalasia cardia (ICD 10 code of K22.0) in HTJ between 2014 and 2018 was conducted. Medical records of patients were procured from the hospital records and were retrospectively reviewed and analysed. A parallel search of records of all patients who underwent oesophageal manometry in HTJ from 2014 onwards was also undertaken to augment and complement the search. Through this parallel search, we found an additional 8 patients with achalasia cardia and 2 further patients with diagnoses of primary motility disorder. These patients were initially missed by the preliminary search based on the discharge diagnosis of achalasia cardia as they were neither admitted nor underwent definitive treatment in HTJ throughout the duration of our study.

Demographic data, patient symptomatology, data required to confirm diagnoses and definitive management options were determined from these records. Patients' regions of residence were categorized into either urban or rural based on postcodes.

Patients with errors in coding who were diagnosed with pseudoachalasia due to other causes of dysphagia such as gastroesophageal reflux disease, corrosive ingestion, carcinoma of the oesophagus or scleroderma were excluded. Those with established diagnoses before the study period or were no longer treatment naïve were also excluded from this study.

Ethical clearance was obtained from the International Medical University Joint Committee as well as the National Medical Research and Ethics Committee.

Follow-up data was obtained via both surgical outpatient department records and telephone interviews where appropriate. The outcome status of patients, including their satisfaction was determined in June and July 2020 via contact tracing by phone. Patient satisfaction was determined using a questionnaire asking patients to self-report their change in quality of life. Their satisfaction status was then classified into "Satisfied", "Dissatisfied", or "Neither".

Data was collected and presented using a combination of Google Drive, Microsoft Word and Excel. The data was then analysed using IBM SPSS version 23.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 30 patients were diagnosed with achalasia of the cardia. The mean age of presentation was 44.63 years ± 18.21 years, with a range from 16 years to 80 years (Table I). There was equal incidence of achalasia among men and women (1:1). Malays formed the largest group (n = 24, 80%). Almost all patients originated from the Southern half of Peninsular Malaysia, namely Negeri Sembilan, Melaka and Johor. Only one patient came from Selangor, a close neighbour to Seremban. Conspicuously, 63% (19/30) of the patients resided in urban areas. The Chinese were all from urban areas while the sole Indian patient had a rural address.

The mean weight and body mass index (BMI) of the cohort was 46.8 ± 10.4 kg and 18.0 ± 4.4 kg/m^2 respectively. Half the patients in this series presented with no medical comorbidities. Only two patients (6.7%) had diabetes, two (6.7%) had hypertension while only one patient was found to have cerebrovascular disease, liver disease or peptic ulcer disease. 23% (7) were smokers and five (16.7%) had pulmonary diseases.

The mean duration of symptoms at presentation in this series was 30.11 months ± 35.29 months (Table II). Almost all patients presented with dysphagia (n = 29, 96.7%) while loss of weight (n = 21, 70.0%) and vomiting (n = 18, 60.0%) were the next most common symptoms. (Table II) All other symptoms such as heartburn (13.3%), abdominal pain (16.7%), regurgitation (13.3%), choking sensation (16.7%) and chest pain (6.7%) were uncommon.

All patients in this series were treatment naïve upon presentation at this centre. All patients underwent oesophagogastroduodenoscopy (OGDS) during diagnostic workup. In addition 26 patients (86.7%) were investigated with barium swallow and 16 (53.3%) oesophageal manometry.

A total of 18 patients (n = 18, 60%) underwent a laparoscopic Heller myotomy with or without Dor Fundoplication and/or cruroplasty (Table III). Two patients (6.7%) underwent pneumatic dilatation as first treatment. One patient with a sigmoid oesophagus as seen on barium swallow underwent a thoracoscopic assisted oesophagectomy which was converted to a transhiatal 3-stage oesophagectomy plus gastric pull-up. One refused a referral for treatment and opted for conservative observation. The remaining 8 patients (26.7%) were also not treated, of which half were lost to follow up while the other half were referred to other centres.

Table I: Demographic characteristics of Achalasia patients in Hospital Tuanku Ja'afar, Seremban

Sociodemographic Characteristics		N (%)	
Gender	Male	15	(50.0)
	Female	15	(50.0)
Race	Malay	24	(80.0)
	Chinese	5	(16.7)
	Indian	1	(3.3)
State	Negeri Sembilan (urban)	7	(23.3)
	Negeri Sembilan (rural)	3	(10.0)
	Melaka (urban)	5	(16.7)
	Melaka (rural)	4	(13.3)
	Johor (urban)	7	(23.3)
	Johor (rural)	3	(10.0)
	Selangor (urban)	1	(3.3)
BMI (kg/m^2)	>15	4	(13.3)
	15 – 19.9	14	(46.7)
	20 – 24.9	4	(13.3)
	25 – 29.9	1	(3.3)
	>30	1	(3.3)
	No record	6	(20.0)
Weight Category (kg)	31.0 – 40.9	11	(36.7)
	41.0 – 50.9	8	(26.7)
	51.0 – 60.9	2	(6.7)
	61.0 – 70.9	2	(6.7)
	71.0 – 80.9	1	(3.3)
	No record	6	(20.0)
Age Group (age at diagnosis)	11 – 20	4	(13.3)
	21 – 30	3	(10.0)
	31 – 40	6	(20.0)
	41 – 50	4	(13.3)
	51 – 60	9	(30.0)
	61 – 70	1	(3.3)
	71 – 80	3	(10.0)

Table II: Clinical characteristics of patients with achalasia of the cardia

Clinical Characteristics	N(%)	
Dysphagia	29	(96.7)
Heartburn	4	(13.3)
Abdominal Pain	5	(16.7)
Loss of Weight	21	(70.0)
Loss of Appetite	3	(10.0)
Vomiting	18	(60.0)
Regurgitation	4	(13.3)
Choking Sensation	5	(16.7)
Lethargy	2	(6.7)
Chest Pain	2	(6.7)
Dyspnoea	1	(3.3)
Odynophagia	1	(3.3)
Cough	1	(3.3)
Duration of Symptoms		
0 – 6 months	11	(36.7)
7 – 12 months	6	(20.0)
13 – 18 months	0	(0.0)
19 – 24 months	2	(6.7)
More than 24 months	11	(36.7)
ASA score		
I	15	(50.0)
II	15	(50.0)
III	0	(0.0)
IV	0	(0.0)

Table III: Interventions and outcomes of achalasia patients in Hospital Tuanku Jaafar

Interventions and Outcomes		Count	Column N %
OGDS		30	100.0%
Barium		26	86.7%
Manometry		16	53.3%
Chest X-ray		3	10.0%
CT		10	33.3%
Treatment	Laparoscopic Heller Myotomy with Dor Fundoplication	14	46.7%
	Laparoscopic Heller Myotomy with Dor Fundoplication and Cruroplasty	1	3.3%
	Laparoscopic Heller Myotomy with Cruroplasty only	3	10.0%
	Pneumatic Dilatation	2	6.7%
	Oesophagectomy	1	3.3%
	Not treated (Under follow up)	1	3.3%
	Referred out	4	13.3%
	Not treated (Lost to follow up)	4	13.3%
Complications	Iatrogenic mucosal perforation	8	26.7%
	Poor motility	1	3.3%
	Stricture	2	6.7%
	No complications	21	70.0%
Satisfaction (N=21)	Satisfied	21	100.0%
	Dissatisfied	0	0%
	Neither	0	0%

Patients with surgery had a follow up period ranging from 9-62 months (median 45.5 months, mean 40.4 months). Of the patients who underwent myotomy and fundoplication, their mean weight increase was 15.6kg, increasing from 43.0 ± 8.4 kg to 58.6 ± 13.7 kg (n-17, no record for 1 patient). One patient reportedly lost weight from 50kg (BMI 20.8) to 48kg. The greatest weight gain was observed in a patient of 39kg (BMI15.2) who increased to 80kg (BMI 31.3). The patient with oesophagectomy also had a weight gain of 4kg after one year. The outcome status of patients as determined in June and July 2020 revealed no deaths.

One patient who had eleven pneumatic dilatations over 15 months gained 7kg in weight. Another who had 3 dilatations and subsequently discontinued treatment reported a stagnant weight (40kg).

Iatrogenic mucosal perforations were detected in 8 patients who underwent myotomy and fundoplication (44.4%) intraoperatively and repaired immediately. Two patients (11.1%) sustained oesophageal strictures post myotomy for which they underwent successful dilatations. One patient with associated mega-oesophagus and hiatal hernia developed poor motility post myotomy for which subsequent dilatation was also done. Four patients were not treated because they were either unfit or refused any intervention. The outcome of these four patients is not known as they were lost to follow up.

At follow up tracing, patients who underwent intervention were asked to rate their subjective assessment as "satisfied", "dissatisfied", or "neither". All of the 21 patients who underwent surgical treatment were satisfied with the treatment received and overall clinical outcomes.

DISCUSSION

This is a review of all treatment naïve patients diagnosed at HTJ, a hospital with tertiary upper gastrointestinal surgical services up until 2018. The majority of the cohort included in this series had surgical treatment. However, as with any service some patients may decline any form of treatment, be lost to follow up or receive treatment finally in a different hospital. There were 10 (33.3%) such patients in this series. Four of these were patients from Johor. This affirms the mobility of Malaysians have in seeking treatment in the network of public hospitals. A check with the authors of Siow et.al [10] confirm that there are no duplicate patients in this series and theirs.

In the presenting cohort, we noted, similar to other Malaysian series [9,10] that there is no gender predilection for achalasia in Malaysia. Similarly, most do not have many co-morbidities and have good ASA scores. Malays form a large majority in our sample as they form the largest majority of the population and are the population that depends most heavily on our public hospitals. Our data does not suggest the disease is more common in either the urban or rural setting.

Only 53.3% of patients in HTJ underwent manometry prior to initiation of treatment. OGDS and barium swallow were deemed adequate for evaluation in many cases. This rate was similar compared to Siow et al's [10] 45.5% despite manometry being the gold standard for diagnosis of achalasia due to its high sensitivity.[11] Manometry was used to rule out other motility disorders. Although the use of manometry enables the classification of achalasia into subtypes with subsequent therapeutic considerations[12], it is not considered routinely essential for satisfactory surgical outcomes.[10]

The preferred surgical procedure offered and deemed suitable for most patients remains a myotomy with an antireflux procedure.[10,13,14] Follow-up shows that most patients gained weight and achieved good long-term outcomes. Peroral endoscopic myotomy, with promising early results, has gained popularity in the last decade as the definitive procedure for achalasia.[10,15] However, the issue with troublesome postprocedural reflux, the lack of long-term data and its relatively long learning curve means that the former

remains the preferred procedure at the present time.[16,17,18]

Pneumatic dilatation was offered and accepted by two patients. One patient was judged unsuitable for Heller's myotomy and the other declined surgery. Another four patients were referred out in 2018 due to the lack of an upper gastrointestinal surgeon servicing the hospital. The surgeons servicing the hospital during the duration of study affirmed that most patients were in fact referred for surgical intervention after conservative measures had failed. Options of pneumatic dilatation versus surgical myotomy were discussed with patients with patient preferences also taken into account.

The rate of perforation is high compared to other studies. Nevertheless, they were all detected and managed intraoperatively and did not result in early post-operative morbidity. A similar recent study in Malaysia reported a perforation rate of 7.3%[10,19] and an acceptable rate of intraoperative perforation is considered to be below 10%.[20] The use of different energy devices in the form of hook cautery, harmonic scalpel in performing cardiomyotomy could be a reason.[21] Another reason for high perforation rate could be attributed to the fact that HTJ is a training centre and the operations were performed by surgeons with varying levels of experience, an independent risk factor as demonstrated by Tsuboi K et al.[22]

Although achalasia remains a disease with relatively low incidence in most communities, the prospect of a good outcome makes it important that clinicians recognise the disease early in order for patients to seek the required surgical expertise.

This study had a few limitations. Due to the retrospective nature of this review, the medical records of patients were dependent on manual documentation, thus variable and had some inconsistency. Subjective data, such as patient satisfaction was open to interviewer and patient recall bias because of the time gap and was dependent on the patients' memory. Our sample size was dependent on the numbers available and was not as large as we had hoped.

The main strength of this study was the robust search because of three parallel search avenues. The records of patient were adequate for complete data extraction and all patients were contactable via telecommunication. Patients' data was collected from the study subject and/ or their legal representative. One investigator was assigned to collect the data through telemedicine to ensure consistent bidirectional communication.

CONCLUSIONS

Most patients with achalasia cardia deemed suitable for surgery and counselled accordingly readily accept surgery. Laparoscopic Heller Cardiomyotomy and fundoplication results in high levels of patient satisfaction and weight gain in almost all these patients with minimal incidence of postoperative complications. A small minority who opt for pneumatic dilatation may also achieve satisfactory short-term outcomes comparable to surgery. Additional studies with long-term outcomes are required to further determine treatment durability as well as patient satisfaction in the long term.

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Factors associated with unsuccessful quitters in stop smoking services in Perlis, Malaysia

Muhammad Ikhwan Ismail, MPH[1], Noor Aman Hamid, PhD[2], Nor Izwana Hamzah, MPH[3]

[1]Department of Community Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [2]Department of Community Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [3]Head Department of Development of Family Health Unit, Perlis State Health Department, Kangar, Perlis

ABSTRACT

Introduction: Tobacco smoking is one of major risk factor of non-communicable disease worldwide. As a prevention strategy, stop smoking services has been advocated at primary care. However, evidence suggests that worldwide there is high rate of unsuccessful quitters. In Malaysia, such evidence has come from small studies or single site study, and evidence on factors associated with failure to quit is scarce. This study aimed to identify the factors associated with unsuccessful quitters among smokers in Stop Smoking Services provided by government health clinics at North Peninsular of Malaysia.

Materials and Methods: This was a retrospective study record review using data from the Stop Smoking Services registry and patient file card between January 2017 and Jun 2019. Independent variables included in this analysis are sociodemographic data, comorbidity, number appointments attended, duration of smoking, age of starting smoking, previous attempt to quit, fagerstrom score and type of treatment. The outcome of interest, is unsuccessful quitters defined as those who continued to smoke at 6 months after attending the service. A total of 427 sample randomly cases selected from 490 eligible sample was analysed. Logistic regression was used to model factors associated with unsuccessful quitters.

Results: The study suggested that clients who attended 0-3 clinic sessions (AdjOR 6.57; 95% CI: 4.14, 10.43) and being single, unmarried (AdjOR: 2.78; 95%CI: 1.07, 7.18) was associated with increased risk of being unsuccessful quitters among smokers in Northern state of Malaysia

Conclusion: The number of clinic sessions attended and marital status were factors associated with unsuccessful quitters among smokers in the State of Perlis, of Malaysia.

KEYWORDS:
Stop Smoking Services, Factor Associated, Unsuccessful Quitters

INTRODUCTION

Tobacco Smoking is one of the risk factors for many chronic diseases such as diabetes mellitus, hypertension, cancer and cardiovascular disease. It is estimated that there are around 1.1 billion people who smoke tobacco cigarettes worldwide. Nicotine, the pharmacological active drug inside the tobacco is highly addictive that may cause quitting a challenge.[1] Results from the National Health Morbidity Survey (NHMS) 2015, showed approximately 22.8% of Malaysian aged 15 years and above were smokers which relatively increased in trend from 21.5% in 2006.[2] Furthermore, smoking causes 15% hospitalization and 35% inpatient death in Malaysia. In fact, smoking also caused 20000 deaths per year in Malaysia.[3] To minimise the impact of tobacco use, the World Health Organisation (WHO) had promoted the Framework Convention on Tobacco Control (FCTC) worldwide which is the only public health treaty under the auspices of WHO since 2003.[4] The framework including the MPOWER package as a technical measure and resources that will assist in reducing the demand for tobacco products at country-level. Despite recommendation from WHO FCTC, the rate of unsuccessful quitters still varies across state and even countries ranging from 44.3-82.7%.[5-9]

There are many factors known from previous studies that may contribute to unsuccessful quitters, for example amount of cigarette smoked per day, previous attempts to quit, motivation, level of stress, number of clinic sessions, living alone or sharing living place with other smoker and many others.[7,9-14] Several studies in Malaysia showed that the prevalence of unsuccessful quitters in stop smoking services ranged between 40% and 82.7%.[7,15,16] Even though the Stop Smoking Services had started since 2004, there was no evaluation done in the state of Perlis as yet. The northern peninsular states have the highest prevalence of tobacco smokers among adolescents as compare to other states in Malaysia, thus strengthening the purpose of this study.[17] It has also been demonstrated that those who started smoking before the age of 16 years old had a two-fold increase risk of being as unsuccessful quitter.[18] This is a worrying trend as it may impact on the rise of chronic diseases burden in the future, therefore it is necessary to know how the service needs to be improved by targeting key smokers at risk in the population.

This study aimed to identify the factors associated with unsuccessful quitters among smokers in Stop Smoking Services provided by the Malaysian government health clinics in North Peninsular State of Malaysia. Data are selected from the Stop Smoking Services registry available. This may optimise the service as there is limited state wide

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Corresponding Author: Noor Aman Hamid
Email: na.hamid@usm.my / drikhwan@student.usm.my

evidence regarding factor associated with unsuccessful quitters among smoker who registered in stop smoking services in primary health care.

MATERIALS AND METHODS

Perlis is a state located at North Peninsular end of Malaysia with a population estimated of 254,000 people mainly Malays, followed by Chinese, Indians and others including Siamese.19 This was a retrospective record review study where the data were collected from the Stop Smoking Services (SSS) registry from 10 government health clinics. SSS are provided by medical officer, trained paramedics and pharmacists who always contribute to trustworthiness of the registry data. Smokers more than 18 years old that registered with SSS between January 2017 and June 2019 were included for this study. This duration has been selected in view of the format of SSS registry has been updated to latest version among all government health clinics in Malaysia since January 2017. From total 691 sample available, 490 met the inclusion and exclusion criteria. A pre-calculated sample size of 427 was selected by random sampling using a random number of samples generated from Microsoft excel. From the random sample generated number, the data filtered according to rank of the random generated number and first 427 sample listed were selected. Data were extracted from the Stop Smoking Clinics registry and patient file card from the clinics involved. The variable collected included sociodemographic data, age started smoking, comorbidity, Fagerstrom score, previous attempt to quit, type of treatment given, and outcome either successfully quit form smoking or not. Comorbidity was defined as either client having hypertension, diabetes mellitus, asthma or pulmonary tuberculosis at time of the stop smoking treatment given. The primary outcome (unsuccessful quitters) defines as those who continued to smoke at 6 months after attending the service. The Fagerstrom score was categorise as 0-3(Low),4-5(Moderate) and 6-10(High).[20] Counselling only and Combine Counselling and Pharmacotherapy treatment (combine) are provided in this service. Counselling, also known as Behaviour Therapy can be delivered individually or as a group.[21]

Statistical analysis

Data was entered and analysed using SPSS version 24. Multiple logistic regressions were performed with the aim to find the predictive factor of unsuccessful quitters among smokers. The dependent variable was outcome of the stop smoking services at 6 months either successful quitters or unsuccessful quitters with the successful quitters as the reference category. Clients lost to follow up were excluded from this study. There were missing data for variable occupation, education level, marital status, Fagerstrom score and age started smoking. Missing data from Fagerstrom score and age started smoking were replaced by mean value before proceed to simple logistic regression. After replacing the missing data, the variables were reassessed and there was no extreme deviation of the mean from original data for both variables. The variable 'Occupation' was not included in simple logistic regression since the missing data was not at random and contained more 25% of the data. The preliminary main effect template was obtained base on factor with p-value <0.25 at univariate level. Factor included in Multiple logistic regression were age, gender, ethnicity, marital status, education level, hypertension disease, number of clinic session, previous attempt to quit, duration of smoking and type of treatment.

This study was approved by Jawatankuasa Etika Penyelidikan (Manusia) JEPeM of Universiti Sains Malaysia (JEPeM Code: KKM/NIHSEC/P19-2534(6)) and Malaysia Research and Ethics Committee (MREC) (NMRR-19-3235-51279).

RESULTS

From 427 cases selected by simple random sampling, the successful quitters were 158 (37%) and the unsuccessful quitters were 269 (63%). Overall mean (SD) for age client registered in stop smoking services was 51.8 (16.2) years with 74.9% of client aged 40 and above. Mean (SD) for age start smoking was 19.5 (6.45) with age '19 years old or less' comprised 42.9% of clients and mean (SD) for Fagerstrom score was 2.6 (2.5) with score of 0-3 (Low) comprised 72.6% of clients. Mean (SD) for numbers of clinic sessions follow up was 3.2 (2.2) with number of clinic session 0-3 times comprise 64.2% of clients. Table I shows the population characteristics of this study.

From the simple logistic regression, 10 factors were significant at p<0.25 these included age, gender, ethnicity, marital status, education level, hypertension disease, number of clinic session, previous attempt to quit, duration of smoking and type of treatment. These were selected for multiple logistic regressions. Only 3 factors remained significant to be included in the final model which are Number of Clinic session, marital status and age.

In the final model (Table III) showed that the number of clinic sessions attended and marital status were significant factors associated with unsuccessful quitters of smoking. The number of clinic sessions attended, those who attended 0-3 sessions was six times more likely to be as an unsuccessful quitter as compared to those who attended 4 or more sessions. For marital status, being single or unmarried had double the risk of being an unsuccessful quitter when the frequency of clinic session attended and age was adjusted.

DISCUSSION

Tobacco smoking remains the main factor that may contribute to the Non-communicable disease globally. As the SSS implemented worldwide, the rate of unsuccessful quitters remained as a public health concern. Many studies had been done globally to understand the risk factor that associate with the unsuccessful quitters. Results from many studies are varied. The marked difference in unsuccessful quitter's rate between each study may depend of different sociodemographic factors, religious sensitivity and availability of trained staff that might influence the unsuccessful rates.[16] Current study had been proposed to study the associated factors with unsuccessful quitters among smoker who registered in stop smoking services in Perlis.

Table I: Sociodemographic, Clinical Characteristic and Outcome of Client in Stop Smoking Services Attending Health Clinic in Perlis January 2017-Jun 2019 (N=427)

Variable	Number (%)
Age group	
18-24	25 (5.9%)
25-39	82 (19.2%)
40-54	111 (26.0%)
≥ 55	209 (48.9%)
Gender	
Female	14 (3.3%)
Male	413 (96.7%)
Ethnicity	
Malay	380 (89.0%)
Chinese	32 (7.5%)
Others	15 (3.5%)
Marital status	
Single, unmarried	58 (13.6%)
Married	354 (82.9%)
Missing	15 (3.5%)
Education level	
No education/ Primary	67 (15.7%)
Secondary	223 (52.2%)
Diploma or Higher	40 (9.4%)
Missing	97 (22.7%)
Occupation	
Professional or manager	32 (7.5%)
Clerical, service, arm forces or technician	53 (12.4%)
Manual	137 (32.1%)
Retiree, housewife, student or unemployed	80 (18.7%)
Missing	125 (29.3%)
Hypertension	
No	253 (59.3%)
Yes	174 (40.7%)
Diabetes mellitus	
No	328 (76.8%)
Yes	99 (23.2%)
Ischemic heart disease	
No	413 (96.7%)
Yes	14 (3.3%)
Pulmonary tuberculosis	
No	423 (99.1%)
Yes	4 (0.9%)
Asthma	
No	416 (97.4%)
Yes	11 (2.6%)
Number of clinic session attended	
0-3	274 (64.2%)
4 or more	153 (35.8%)
Previous attempt to quit	
No	82 (19.2%)
Yes	273 (63.9%)
Missing	72 (16.9%)
Age started smoking	
<20	183 (42.9%)
≥20	133 (31.1%)
Missing	111 (26.0%)
Duration of smoking	
≤ 15 years	79 (18.5%)
>15 years	348 (81.5%)
Level of Fagerstrom score	
Low	310 (72.6%)
Moderate	53 (12.4%)
High	64 (15.0%)
Type of treatment	
Counselling	339 (79.4%)
Combine therapy	88 (20.6%)

Table II: Simple Logistic Regression of Factors Associated with Unsuccessful Quitters among Smokers who attended Stop Smoking Services in Perlis between January 2017-Jun 2019, N=427

Factors	Crude OR , B (95% CI)	*p*- value
Age		
18-24	1	
25-39	0.26(0.07,0.96)	0.042
40-54	0.32(0.09,1.15)	0.081
55 or more	0.17(0.05,0.58)	0.005
Gender		
Female	1	
Male	3.19(1.05,9.69)	0.041
Ethnicity		
Malay	1	
Chinese	0.69(0.33,1.44)	0.323
Others	0.20(0.06,0.63)	0.006
Marital status		
Married	1	
Single, unmarried/widow	3.73(1.78,7.84)	<0.001
Education level		
No education/Primary		
Secondary	1.61(0.93,2.78)	0.091
Diploma or higher	1.31(0.60,2.89)	0.499
Hypertension		
No	1	
Yes	0.59(0.40,0.88)	0.010
Diabetes Mellitus		
No	1	
Yes	0.78(0.50,1.24)	0.300
Ischaemic Heart Disease		
No	1	
Yes	0.58(0.20,1.68)	0.311
Asthma		
No	1	
Yes	1.03(0.30,3.57)	0.965
Number of clinic sessions		
4 or more	1	
0-3	6.68(4.31,10.37)	<0.001
Previous quit attempt		
No	1	
Yes	0.60(0.33,0.95)	0.031
Age Start Smoking		
<20	1	
≥20	0.96(0.63,1.47)	0.865
Duration of Smoking		
≤ 15 years	1	
>15 years	0.37(0.20,0.66)	0.001
Fagerstrom Score		
0-3 (Low)	1	
4-5 (Mod)	1.13(0.61,2.09)	0.694
6-10 (High)	0.85(0.49,1.47)	0.562
Type Of Treatment		
Counselling		
Combine Therapy	0.64(0.40,1.03)	0.066

Number of clinic sessions attended is a strong predictor of being unsuccessful quitter.[22] The recommended schedule of appointments were to come for follow-up sessions at their respective clinics once a week for the first month, every two weekly for the second and third month, once a month for the fourth to sixth month and three monthly appointment for one year period thus making it a maximum of 15 visits for the total appointment.[20] However the schedule was practised flexibly.[16] For example, clients who are also attending other chronic disease clinic appointment, the Stop Smoking Clinic appointment will be scheduled on the same day in order to ease the attendance and avoid default.

In this study those who attended their appointments 3 times or less showed higher risk of being an unsuccessful quitters as compared to those with who attended four times or above. This finding was consistent with others studies where the risk of unsuccessful quitters increased if the clinic sessions were less than four times. The dose-response relationship for SSS has proven that the minimum of four to five appointments for at least 15 minutes each session was needed to ensure the optimum service can be delivered to client.[7,23] Another study also found that the main factor that contribute to successful quitters are treatment adherence.[12] Appointment may not be necessary for the client to attend to the clinic in person,

Table III: Multiple Logistic Regression of Factors Associates with Unsuccessful Quitters among Smokers Attending Health Clinic in Perlis January 2017-Jun 2019, N=412

Variable	Adjust OR , B (CI)	P- value
Number of Clinic Session		
≥ 4	1	
0-3	6.57(4.14,10.43)	<0.001
Marital status		
Married	1	
Single, unmarried	2.78(1.07,7.18)	0.035
Age		
18-24	1	
25-39	0.46(0.08,2.48)	0.364
40-54	0.77(0.13,4.48)	0.774
≥55	0.38(0.07,2.14)	0.272

Model Nigelkerke's R2= 0.28

instead these can be done via phone call as alternative as long as individual motivational support was delivered to educate the client.[12] Fagerstrom score of 0-2 (very low) and 6-10 (high) are prone to default scheduled treatment.[24] This may contribute to increase risk of unsuccessful quitters. In the current study, the Fagerstrom level was not a predictive factor in the final model possibly due to the different classification used. This study use the Fagerstrom group 0-3 (low), 4-5 (moderate) and 6-10 (high) as compared to other study available where they categorised the groups according to 0-2 (very low), 3-4 (low), 5 (medium), and 6-10 (high).[24] Different Fagerstrom score classification group may give a different result.

Being single or unmarried status was a risk for unsuccessful quitters as compared to being married. Persons who are married will normally undergo separation from their families and such separation may increase their interdependence of each other between the married couple and may influence each other in daily life activity.[25] For example, if the smoker had a spouse or partner who is also a smoker, the risk of unsuccessful quitters may increase; however this might not applicable in Malaysia since only 1.4% of women smoked.[26,27] On other hand, married smokers may also receive more support from their spouses who are not smokers thus increasing their motivation to quit while being single or unmarried may lack such support.[9] Other similar approach for an optimum achievement to quit smoking can be seen by targeting family members or community peers may increase the successful quitters even when motivation to quit is low.[28] According to the theory of reason action and planned behaviour, behaviour may be influenced by consequences of the behaviour (behavioural belief), belief about normative expectation from other (normative belief) and belief about factor that may impact performance of the behaviour (control belief). When a client who doesn't receive support from the spouse (normative belief) it may influence the outcome which mean the risk of unsuccessful quitter increases.[29]

This study has several limitations. This study was a retrospective record review study that used secondary data. It depended on the quality of data recorded in SSS registry and patient file card. There was no verification method can be done for secondary data. Different health staff may have different definition and understanding on what should be recorded. Besides, certain variables may be poorly recorded or neglected such as occupational status and education level in this study since clients might refuse this personal information to be known. Other important variables were not recorded namely status of house living partner, motivational status and income. The unavailable variables may contribute and improve the final model. Despite these limitations, this study was able to explore the factors associated with unsuccessful quitters among smokers in a state-wide sample using the available data from stop smoking clinic registry. The finding from this study is consistent with other studies.

CONCLUSIONS

Although SSS clinics has been implemented worldwide after FCTC ratification in 2003, the unsuccessful quitters' rate among smokers still high. This study concludes that frequency of attending the SSS and being single/unmarried status does contribute to the risk of unsuccessful quitters. Hence, primary health care should re-strategize to improve the clients' adherence to clinic attendance and involvements of family members in stop smoking services should also be considered. The result from this study can be adopted in the healthcare system to improve the outcome of stop smoking services.

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CONFLICT OF INTEREST

Izwana Binti Hamzah is the SSS data manager who contributed to idea of the study and assisted with data collection but did not involve in data analysis or interpretation of this study.

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Treatment prioritization and risk stratification of head and neck cancer during COVID-19 pandemic: A systematic review

Marlinda Adham, PhD, Khoirul Anam, MD, Lupita Adina Reksodiputro, MD

Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine Universitas Indonesia, Indonesia

ABSTRACT

Introduction: Treatment of head and neck cancer patients amidst the COVID-19 pandemic is challenging, whereas prolonged treatment initiation in head and neck squamous cell carcinoma may increase mortality and likelihood of recurrence. Special attention is needed to ensure safe and appropriate care of these patients. This article aims to review and discuss existing research on treatment prioritization and risk stratification of head and neck cancer patients during the pandemic.

Materials and Methods: The authors conducted literature search in three databases (PubMed, Cochrane, and Clinical Key) on July 15th, 2020. The keywords were ("Head and Neck Mucosal Malignancy" OR "Head and Neck Cancer") AND ("Management" OR "Head and Neck Surgery") AND ("COVID-19" OR "Pandemic"). The inclusion criteria were cancer in adult patients, published from 2020 in English, and with available access to full text. The exclusion criteria were comments, letters, and case reports. The articles were critically appraised using the Centre of Evidence-based Medicine (CEBM), University of Oxford and Duke University. The literature search strategy is illustrated using Preferred Reporting Items for Systematic review and meta-analysis (PRISMA) flow diagram.

Results: A total of 150 articles were identified; 21 articles were gathered from Clinical Key, 33 from Cochrane, and 96 from Pubmed. After screening abstracts and reviewing the full text, the authors determined five articles met the inclusion criteria. There are several key points of head and neck cancer management in the COVID-19 pandemic. Head and neck cancer management is considered a high-risk procedure; the clinician should use proper personal protective equipment. Before operative treatment, all patients should undergo a PCR test 14 days before surgery. In diagnosing head and neck cancer, laryngoscopy should be considered carefully; and cytology should be preferred instead. Medically Necessary, Time-sensitive (MeNTS) score is recommended for risk stratification and surgery prioritization; it has three domains: procedure, disease, and patient. However, it is not specified to head and neck cancer; therefore, it should be combined with other references. Stanford University Head and Neck Surgery Division Department of Otolaryngology made surgery prioritization into three groups, urgent (should be operated immediately), can be postponed for 30 days, and can be postponed for 30-90 days. Some urgent cases and should be operated on immediately include cancers involving the airways, decreased renal function, and metastases. For chemoradiation decision to delay or continue should refer to the goal of treatment, current oncologic status, and tolerance to radiation. In terms of patient's follow up, telephone consultation should be maximized.

Conclusion: MeNTS scoring combined with Guideline from Department of Otolaryngology at Stanford University prioritizing criteria can be helpful in decision making of stratifying Risk and prioritizing surgery in head and neck cancer management.

KEYWORDS:
COVID-19, head and neck cancer, head and neck surgery, surgical priority

INTRODUCTION

World Health Organization (WHO) declared the COVID-19 outbreak to be a global pandemic on March 11, 2020. As of June 2021, the number of COVID-19 cases exceeded 180 million cases. The speed and scale of the spread of COVID-19 have resulted in massive pressures on health services worldwide. COVID-19 can be transmitted from one person to another through droplets.[1] It has been reported that nasopharynx and oropharynx secretions have a high viral load, putting clinicians, especially otolaryngologists, at high risk for nosocomial transmission. Staff shortages due to illness and viral transmission concerns to healthcare workers and other patients have led to a limitation of healthcare capacity and resources. Otolaryngologists have had to adapt new strategies for care delivery.[2]

While many otolaryngology operations are elective and can be delayed, head and neck malignancy treatment cannot be delayed for long periods. Prolonged time to treatment initiation in head and neck squamous cell carcinoma lead to an increase in mortality and likelihood of recurrence. On the other hand, this group of patients is at increased risk for severe COVID-19 disease.[2] According to data from China, cancer patients faced an increased risk of death from COVID-19.[3] They are also more susceptible to COVID-19 infection and more likely to transmit the disease to otolaryngologists, due to repeated visits to health facilities, recurring diagnostic and treatment procedures, and immunosuppression caused

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Corresponding Author: Marlinda Adham
Email: marlinda.adham@yahoo.com

by the malignancy and its therapy. It is recommended that the risk and benefits of treatment be assessed individually to identify patients eligible for treatment delay without serious consequences.[3] Therefore, Prachand wrote a medically necessary, time-sensitive (MeNTS) system that can be used as a reference for surgery prioritization during the pandemic. Higher score is associated with poorer outcome, meaning the procedure is not justified. However, this scoring system is not a specific guide for head and neck cancer.[4] Several studies have presented other stratification and prioritization strategies for head and neck cancer by its urgency, including surgery and chemoradiation.

This study aims to review existing research on treatment prioritization and risk stratification of head and neck cancer patients. In this pandemic era, it is important to be alert and assess the risk for the welfare of patients and health care providers. Priority of patients who must be treated immediately and when treatment can still be postponed with non-surgical therapy should be established.

MATERIALS AND METHODS

This study is a literature review. The authors conducted an article search using three databases, namely Pubmed, Cochrane, and Clinical Key on July 15th, 2020. The authors did advanced search used Boolean operator, and the keywords were ("Head and Neck Malignancy" OR "Head and Neck Cancer") AND ("Management" OR "Head and Neck Surgery") AND ("COVID-19" OR "Pandemic"). The keyword search above used the mesh term. The inclusion criteria used were studies in the English language, study on adult cancer patients, studies published from 2020 to 2021, and available full text.

The initial search found 150 articles. After doing a screening for studies found in more than one database, deduplication obtained 86 articles. The authors then screened all the studies title and abstract, 13 articles were appropriate with the study title. The exclusion criteria were then applied. The exclusion criterias were comments, letters, case reports study types. Five articles were included in the final literature review. The literature search strategy is illustrated using Preferred Reporting Items for Systematic review and meta-analysis (PRISMA) flow diagram (Figure 1.). After reading the full text, the articles were critically appraised using critical appraisal tool from Centre of Evidence-based Medicine (CEBM), University of Oxford and Duke University. In the critical study, an assessment is made based on validity, importance, and applicability. Critical review is carried out by all authors, an ENT surgeon and residents.

RESULTS

Based on the literature searches from three databases, 21 articles were obtained from Clinical Key, 33 from Cochrane, and 96 from Pubmed. A total of 150 articles were identified through database search, after screening abstracts and reviewing full text, the authors determined five articles appropriate with the study title. The procedure is illustrated in the flowchart (Figure 1). The five articles are "American Society of Clinical Oncology (ASCO) Special report: a guide to cancer care delivery during the COVID-19 pandemic" by ASCO[6], "Global radiation oncology's targeted response for pandemic preparedness" by Simcock et al[7], "Status and strategies for the management of head and neck cancer during COVID-19 pandemic: Indian scenario" by Gupta et al[11], "Practice recommendation for Risk-Adapted Head and Neck Cancer Radiation Therapy During the COVID-19 Pandemic: An American Society for Radiation Oncology and the European Society for Radiotherapy and Oncology (ASTRO-ESTRO) Consensus Statement" by Thomson et al[9], and "Framework for prioritizing head and neck surgery during the COVID-19 pandemic" by Topf et al[10]. All studies discussed in this article have been carried out and reviewed with critical appraisal of qualitative studies from CEBM University of Oxford. These journals discuss recommendations for the management of head and neck cancer in the pandemic era, some focus on surgery strategy, the rest provide complete strategies from infection prevention, teleconsultation, risk stratification to various therapeutic options, the study's results are summarized in Table I.

DISCUSSION

In the COVID-19 pandemic, protective measures must be followed by surgeons, especially in procedures that generate aerosol secretion. Any transmucosal head and neck procedure such as nasolaryngoscopy, endotracheal intubation, transnasal endoscopic surgery should be considered high risk. Personal protective equipment (PPE) should include an N95 respirator, face shield, surgical gown, and gloves.[5,6] The surge in COVID-19 cases in Indonesia has caused an increased demand for the health care system. Hospitals report shortages on equipment, personal protective equipment (PPE), healthcare workers, and ventilators. Prioritization and risk stratification for head and neck malignancy management is needed during the pandemic to conserve PPE, free up inpatient beds, and limit exposure of patients and staff. From the five articles obtained, the authors discussed key points to consider in dealing with head and neck cancer cases during the COVID-19 pandemic that will be further discussed in the subsections, including preoperative screening needed for patients undergoing surgery during the pandemic, increased risk of postoperative mortality in COVID-19 patients, risk stratification and prioritization for surgery and chemoradiation.

Preoperative Screening

In Wuhan, China, Patients scheduled to undergo head and neck surgery were required to have two negative COVID-19 polymerase chain reaction (PCR) swab examinations before surgery, and were asked to self-isolate for 14 days before surgery.[5] The decision is based on the incubation period of the SARS-CoV-2. The median incubation period is 5.1 days, and most patients became symptomatic within 14 days after exposure. Several other hospitals ensure patients have at least one negative COVID-19 PCR swab before surgery. In some centers, patients are screened with PCR and COVID-19 antibody tests 24 hours before surgery, and then the patients are being isolated. If the PCR shows positive results, they are isolated, and COVID-19 protocols are followed. If the PCR is negative while the antibody is positive, it will not require further testing. If both the PCR and antibody show negative results, they are tested weekly during their stay in the hospital.[5]

Table I: Previous Recommendations and Guidelines on Risk Stratification and Prioritization of of Head and Neck Cancer During COVID-19 Pandemic

S/N	Author (year)	Study design	Source	Recommendation	Annotation
1.	American Society of Clinical Oncology (2020)	Guideline	Committee members	Surgeries • Local resumption of elective surgery guidance: ○ COVID-19 awareness: screening, community numbers (prevalence, incidence) ○ Preparedness: bed capacities, intensive care units, and ventilators ○ Patient issues: testing policies, counselling, collaborative process, consider list of postponed cases, priority with MeNTS scoring, local strategy to increase operating room time availability, etc.	
2.	Simcock et al (2020)	Simcock et al (2020)	121 individuals from 17 countries	Consensus-based guideline • Minimising the risk of transmission: promote telephone consultation and remote monitoring, minimum family members attendance • Prioritising treatment by evidence, risk of COVID infection multiplied by risk of serious morbidity/mortality • Radical treatment • Adjuvant treatment: long term survival patient can avoid radiotherapy • Palliative treatment: smallest number of hospital visit	Head and neck cancer recommendation • Radiotherapy in patients with head and neck cancer is not recommended to be delayed. • Radical radiotherapy may be reduce from IMRT standard dose (evidence level II)
3.	Gupta et al (2020)	Literature review	16 major head and neck health care	Brief guidelines and recommendations given by FHNO during COVID • Diagnosis: avoid laryngoscopies, biopsies of benign lesions, FNACs should be preferred • Treatment: Surgery (consider if likelihood curing cancer), Radiotherapy (patients should be triaged and prioritized), Chemotherapy (judiciously on the expected benefit) • Follow up: minimize all follow-up appointments	Risky medical procedures should be avoided unless absolutely mandatory
4.	Thomson et al (2020)	Literature review	29 members from panel of international experts from ASTRO, ESTRO	• Treatment prioritization: Do not postpone initiation of HNSCC radiation, a very high priority. • Intercurrent SARS CoV-2 infection: Delay initiation until test is negative, do not interrupt after 2 weeks of radiation for mild symptoms, do not interrupt radiation for severe symptoms • Case-specific radiation therapy and chemotherapy practice: Continue to use concomitant chemotherapy, use a hypofraction radiation schedule • Operating room closures and the management of surgical cases: Radical chemoradiation therapy for oral tongue SCC (T3N2bM0) and sinonasal maxilla SCC (T4aN1M0), wait up to 4 weeks for oral tongue SCC (T3N2bM0), consider waiting for surgical within 4 weeks for locoregionally advanced oral cavity cancer • Adjustment to outpatient clinic appointments and supportive care: Reduce in-person consultation and replace with teleconsultation routine weekly	

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Table I: Previous Recommendations and Guidelines on Risk Stratification and Prioritization of of Head and Neck Cancer During COVID-19 Pandemic

S/N	Author (year)	Study design	Source	Recommendation	Annotation
5.	Topf et al (2020)	Literature review	Head and Neck Surgery in the Department of Otolaryngology at Stanford University	Stanford University Head and Neck Surgery Division Department of Otolaryngology Criteria for prioritizing patients requiring head and neck surgery • Urgent - proceed with surgery: HPV-negative HNSCC eps. with airways concerns, HPV-positive HNSCC with significant burden, HNSCC with complications of cancer treatment, Thyroid (anaplastic carcinoma, medullary carcinoma, >4 cm follicular lesion, etc), Skull base malignancy, etc. • Less urgent - consider postpone > 30 days: Low-risk PTC without metastasis, low-grade salivary carcinoma • Less urgent - consider postpone 30 to 90 days: Thyroid (goiter without airway/respiratory compromise, etc), Benign salivary lesions, skin cancer (melanoma ≤ 1 mm thickness, basal cell carcinoma where cosmetic impact, low-risk SCC)	All considerations are important looking at case by case basis, then follow the prioritization process during COVID-19 pandemic chart. If the patient is required to undergo surgery, preoperative screening is carried out following the pathway on wileyonlinelibrary.com.

Abbreviations: MeNTS; medically necessary, time-sensitive, IMRT; Intensity-Modulated Radiation Therapy, FHNO; Foundation for Head and Neck Oncology, FNACs; Fine needle aspiration cytology , HNSCC; Head and neck squamous cell carcinoma, SCC; Squamous cell carcinoma, HPV; Human papillomavirus, esp; especially, etc; et cetera, PTC; Papillary thyroid carcinoma

Table II: Medically Necessary Time Sensitive (MeNTS) Sugery Prioritization Scoring Developed by Prachand, et al4

Procedure	1	2	3	4	5
OR time	< 30 min	31-60 min	61-120 min	121-180 min	≥180 min
Anticipated length of stay	outpatient	23 hours	24-48 hours	≤3 days	>4 days
Post-operative ICU need	Very unlikely	<5%	5-10%	11-25%	≥25%
Bleeding risk	≤100cc	101-125 cc	251-500 cc	501-750 cc	≥750 cc
Number of surgical team	1	2	3	4	>4
Intubation probability	≤1%	1-5%	6-10%	11-25%	≥25%
Surgical site	None of the following	Abdominal MIS surgery	Abdominopelvic surgery, infraumbilical	Abdominopelvic open surgery, supraumbilical	OHNS, Upper GI, Thoracic
Disease	**1**	**2**	**3**	**4**	**5**
Non Operative effectiveness	None available	Available, <40% as effective as surgery	Available, 40-60% as effective as surgery	Available, 60-95% as effective as surgery	Available, equally effective
Non-operative treatment option resource use/exposure risk	Significantly worse	Somewhat worse	Equivalent	Somewhat better	Significantly better
Impact of 2 weeks delay in disease outcome	Significantly worse	Worse	Moderately worse	Significantly worse	Minimally worse
Impact of 2 weeks delay in surgical difficulty	Significantly worse	Worse	Moderately worse	Significantly worse	Minimally worse
Impact of 6 weeks delay in disease outcome	Significantly worse	Worse	Moderately worse	Significantly worse	Minimally worse
Impact of 6 weeks delay in surgical difficulty	Significantly worse	Worse	Moderately worse	Significantly worse	Minimally worse
Patient	**1**	**2**	**3**	**4**	**5**
Age	< 20 yo	21-40 yo	41-50 yo	51-65 yo	>65 yo
Lung disease (asthma, COPD, CF)	None			Minimal (rare inhaler)	>Minimal
OSA	Not present			Mild/moderate (non CPAP)	On CPAP
CV disease (HT, CHF, CAD)	None	Minimal (no meds)	Mild (1 med)	Moderate (2 meds)	Severe (≥3 meds)
Diabetes	None		Mild (no meds)	Moderate (PO meds only)	>Moderate (insulin)
Immunocompromised	No			Moderate	Severe
ILI symptoms	None (asymptomatic)				Yes
Exposure to known COVID-19 positive patients within 14 days	No	Probably not	Possibly	Probably	Yes

Morbidity and Mortality in COVID-19 Patient Undergone Surgery

Postoperative pulmonary complications occur in half of patients with COVID-19, and it is associated with increased risk of mortality. The overall 30-day mortality in patients undergoing surgery with perioperative COVID-19 infection was 23.8%, all-cause mortality rate 18.9% in elective patients, 25.6% in emergency patients, 16.3% in minor surgery, and 26.9% in major surgery.[8] This increased risk should be considered when planning surgery during COVID-19 pandemic. Postponing non critical surgery should be considered and the use of non-operative treatment should be maximized.[8]

Risk Stratification and Surgical Prioritization

Some factors are considered when deciding to proceed with medically necessary time-sensitive procedures (MeNTS); unfortunately, this scoring system is not specific to head and neck cancer cases, but the ASCO guideline still recommends its use for now.[4,6] There are twenty-one factors as significant contributors to MeNTS prioritization, grouped into 3 domains; procedure (7 factors), disease (6 factors), and patient (8 factors), total score ranging from 21 to 105 (Figure 2). Higher MeNTS score is associated with poorer outcomes, increased COVID-19 transmission, and increased hospital resources use.[6,9]

Each point of the MeNTS score can be scored from 1 to 5 (Table II). The procedure domain for MeNTS score includes operation duration, estimated length of stay, postoperative intensive care unit (ICU) needs, anticipated blood loss, number of the surgical team needed, probability of intubation, and surgical scale. Disease domain includes the effectiveness of other treatment options besides surgery, exposure risk of other treatment options, impact in disease outcome with a two-week delay, impact in surgical risk with a two-week delay, impact in disease outcome with six-week delay, and. Impact in surgical risk with six-week delay. Meanwhile, the patient domain includes: age, presence of lung disease, obstructive sleep apnoea, cardiovascular disease, diabetes, immunocompromised, influenza-like symptoms, and exposure to COVID within 14 days.[9]

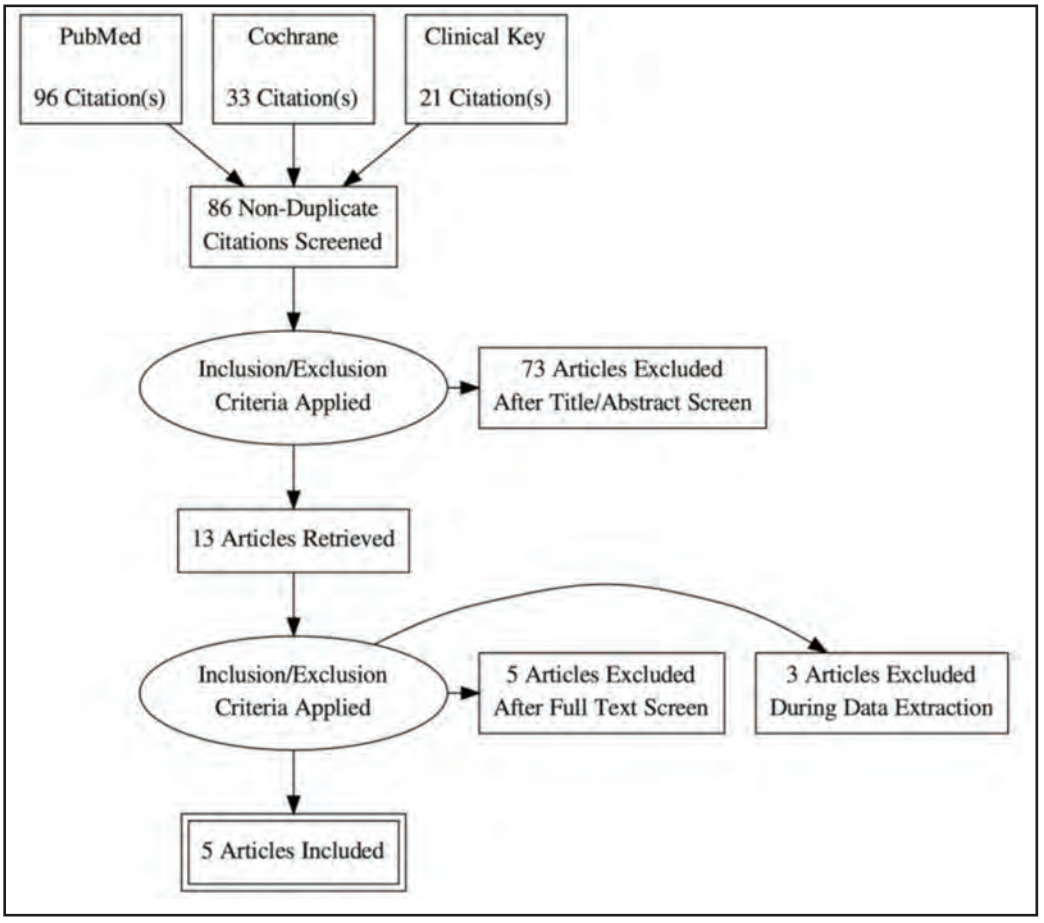

Fig. 1: Summary of procedure in this study.

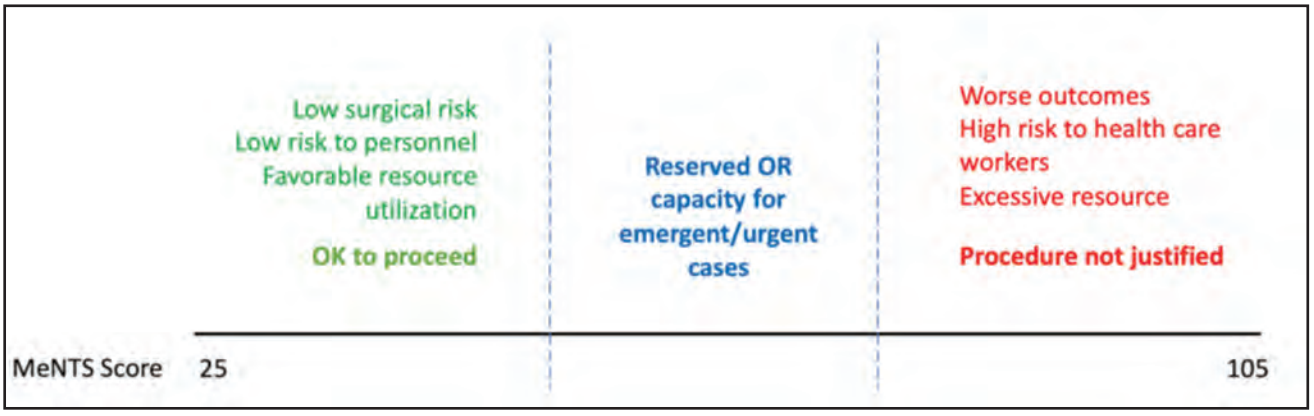

Fig. 2: MeNTS Score Range[11,12]

Surgical site on the head and neck gave a score of five on the procedure domain, giving a higher MeNTS score in procedural domain. However, delay of head and neck surgery causes worsening of outcome, giving a lower total score of MeNTS. Lower total MeNTS score indicates the surgery should be performed. There is no specific MeNTS score cut off to decide wheter the surgery should be performed or delayed, it should be adjusted based on resources availability and local condition.

Guideline from Department of Otolaryngology at Stanford University also prioritize surgery based on cancer's primary location. As mentioned before, any cancer involving the airways are considered urgent and need to be operated on immediately. Thyroid cancer, including anaplastic carcinoma, medullary carcinoma, and large follicular lesion, are also considered urgent cases. On the other hand, benign thyroid nodules, goitre, and thyroiditis can be postponed for > 30 days. Salivary cancers that are considered urgent include salivary duct carcinoma, high-grade mucoepidermoid

carcinoma, adenoid cystic carcinoma, and acinic cell carcinoma. Surgical management of benign salivary lesions can be postponed > 30 days. Advanced skin cancers are also considered urgent, meanwhile, melanoma < 1 mm thickness, basal cell carcinoma with low risk of morbidity, and low-risk squamous cell carcinoma can be postponed > 30 days.[10]

Meanwhile, Gupta et al. divide treatment criteria based on the choice of treatment to be given. They are divided as cancer prognosis, cancer type, and surgery type, and comorbidity. Surgical procedures are aimed at patients with the likelihood of curing cancer, but delay surgery in patients with low-grade tumours, avoid extensive surgery, avoid surgery for patients with low haemoglobin.[11] The discussion of therapeutic priorities by Simcock et al. is very interesting, which is explained through a simple model by multiplying the risk of COVID-19 infection by the mortality and morbidity of the patient.[7] Considering various references to determine management priorities, it is still important to consider each case itself.

Chemoradiation Prioritization

According to the American Society for Radiation Oncology (ASTRO), radiotherapy should be given as early as possible if it is used as a curative procedure.[10] Every month delay causes a 16% increased risk of mortality. For COVID-19 positive patients, the decision to delay or continue treatment should be individualized, based on the goal of treatment, current oncologic status, and tolerance. For palliative treatment, it is recommended to exhaust other options before undergoing radiotherapy. From ASCO advised postponing patient visits without delaying chemotherapy, especially patients with respiratory symptoms and fever. In order to reduce the frequency of hospital visits, it can be considered to change the treatment of the patients from intravenous to oral-systemic regimens and shorter radiotherapy fraction. Chemotherapy needs to be done wisely, considering its benefits, whilst also at the same time considering the risk of being exposed to the COVID-19.[11]

This topic is still relevant since the pandemic is still ongoing. Further study is still needed since the previous studies are based on expert opinions and then applied in daily practice as a guideline. There is also no further study regarding the success rate of these prioritization strategies when applied to clinical practice. Therefore, studies about effectivity of these strategies are recommended to figure out which one is the most appropriate recommendation for risk stratification and surgical prioritization of head and neck cancer patients during the pandemic.

CONCLUSIONS

Risk stratification and prioritization in treating head and neck malignancies should be individualized based on the diagnosis, patient, and procedure. The strategies to adopt this are by applying MeNTs scoring combined with the Stanford University Department of otolaryngology Head and Neck Surgery prioritizing criteria can be helpful in decision making; for chemoradiation, ASTRO recommendation can be used. Risk stratification in patients becomes important and will determine the next step of therapy. In limited resources, prioritization can help guide therapy flow in patients with head and neck cancer especially during this COVID-19 pandemic.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Types and risk factors of ambulance accidents: A scoping review

Keng Sheng Chew, PhD[1], Mook Yuang Low, MMed[2]

[1]Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, Kota Samarahan, Sarawak, Malaysia, [2]Emergency and Trauma Department, Sarawak General Hospital, Jalan Hospital, Kuching, Sarawak

ABSTRACT

Background: A scoping review was conducted to map out the common research focusses on ambulance accidents, their key findings and some of the major knowledge gaps in this area.

Materials and Methods: Relevant, peer-reviewed, English-language articles on land ambulance accidents were independently searched by the authors using the MEDLINE and CINAHL databases. Anecdotal reports, testimonies and stories in trade or popular magazines and other grey literature were excluded. Articles that do not directly address ambulance accidents were also excluded. Additional articles were identified from the reference lists of the selected articles and from Google search engine.

Results: From an initial yield of 879 articles, 19 articles were included. Most of these articles were published from 2001 – 2005 (5 articles, 26.3%) and 2006 – 2010 (5 articles, 26.3%). Eighteen articles (78.3%) are original articles (18 articles, 78.3%) and another one article is a review article. Most of these articles focused on (1) the types of collisions and (2) the risk factors of ambulance accidents. Nine risk factors were identified to have contributed to ambulance accidents: (1) driving in urban areas (2) driving on dry road (3) the use of lights & sirens (4) the failure to use restraints (5) driving for emergency use (6) back seating (7) at road intersection (8) driver's previous records of accidents and (9) inter-facility transfer. The two most common risk factors studied were (1) the use of lights & sirens and (2) driving at intersection.

Conclusions: Most of the above risk factors can be mapped into three categories of risk factors: task-related factors, vehicle-related factors and environment-related factors. The category of risk factors least studied is the category of driver-related factors.

KEYWORDS:
scoping review, ambulance, emergency vehicle, collision, accident

INTRODUCTION

To achieve quick responses to and from an incident site, ambulances often have to travel at high-speed using lights and sirens (L&S). Unfortunately, high-speed travel and L&S use increases the risk of ambulance accidents.[1-5] Inevitably, this problem must be viewed with utmost seriousness as ambulance is a dedicated vehicle that is supposed to arrest the progression of the illnesses or injuries of patients and to deliver them safely into the healing hands of healthcare providers in hospitals.

Although ambulance accidents can be of grave consequences, there is a paucity of a literature review to systematically analyze prior studies on ambulance accidents. We embarked on a scoping review on peer-reviewed publications related to ambulance accidents. The main purpose of this review is to broadly map out the key research findings on ambulance accidents.[6,7] To conduct this review, the methodological framework by Arksey and O'Malley was adopted.[6] Specifically, the objectives of this review were to identify (1) the common research focusses that have been conducted in the area of ambulance accidents; (2) key findings or trends reported in these studies; (3) major knowledge gaps that could be addressed in future research on ambulance accidents.

MATERIALS AND METHODS

Procedure

The procedure used in this scoping review was based on the 5-step framework by Arksey and O'Malley.[6] These five steps are: (1) defining our research objectives or research questions; (2) identifying the relevant studies; (3) selecting studies to be included based on our inclusion and exclusion criteria; (4) charting and interpreting the data and (5) collating, summarizing, synthesizing and reporting the results.

Eligibility criteria

Only peer-reviewed articles focusing on land ambulance accidents that were published in academic journals were included in this review. Articles such as anecdotal reports, testimonies and stories published in trade or popular magazines as well as in other grey literature were excluded. Articles describing aspects of ambulance safety but do not directly address ambulance accidents; or where the main focus of the articles are not on ambulance accidents, were also excluded. Articles that merely describe air ambulance accidents (but not on land ambulances) were excluded as well. Only English-language articles were included. We did not set a limit on the publication period of our literature search. Search strategy was conducted using the methodology described by Aromataris & Riitano.[8] The keywords and Boolean operators used included the following phrases: ambulance AND crash*, ambulance AND accident*,

This article was accepted: 08 November 2021
Corresponding Author: Keng Sheng Chew
Email: kschew@unimas.my

ambulance AND collision*, emergency vehicle AND crash*, emergency vehicle AND accident* and emergency vehicle AND collision*. The search was conducted using the National Library of Medicine (NLM) MEDLINE database via PubMed search engine and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) database via EBSCOhost search engine. All study designs – quantitative, qualitative and mixed triangulated studies – were included. The reporting was done in compliance with the Preferred Reporting Items for Systematic reviews and Meta-analysis extension for Scoping Reviews (PRISMA-ScR) guideline.[9]

Following the initial generation of records found in MEDLINE and CINAHL databases, titles and abstracts were screened for potentially eligible articles. Both authors (KSC and MYL) independently screened the eligibility of these potential articles. If there was any disagreement between the authors, the authors discussed this together in an attempt to reach a consensus; failure of which, an independent third reviewer would be called in to resolve the disagreement. Additional relevant articles were identified by the authors from the reference lists of the selected articles. All eligible articles identified and agreed upon by both authors were then charted using the PRISMA flow diagram for scoping review process.

Quantitative and qualitative synthesis of the studies were then conducted. For quantitative synthesis, data on countries of origin (where the articles came from), types of articles (i.e., original research, case series, editorial, mortality report, review article, etc.), the journals where the articles were published, the year of publication as well as the objectives and key findings of the articles were extracted. For qualitative synthesis, the full texts of the identified articles were coded using thematic content analysis by labelling the keywords and phrases. After the initial open coding, a second axial coding was performed by re-analyzing these open codes to identify major trends and findings related to ambulance accidents.

RESULTS

The initial literature research yielded 870 articles, with an additional 9 articles obtained via manual search for relevant references within the reference lists as well as from Google search engine. Out of these 879 articles, 31 articles were first removed as these were duplicates. After removing another 789 irrelevant articles and an additional 30 articles that did not fulfill the eligibility criteria of this scoping review (i.e., not peer-reviewed articles published in academic journals), we were left with 29 potentially eligible articles. Another 10 articles were mutually agreed to be removed as they did not directly address ambulance accidents. Eventually, 19 full text articles were identified for inclusion in this review. The PRISMA flow diagram is shown in Figure 1.

Most of these articles were published during the decade from 2001 – 2010, i.e., from the year 2001 – 2005 (5 articles, 26.3%)[2-3,10-12] and from year 2006 – 2010 (5 articles, 26.3%).[4, 13-16] Eighteen articles (78.3%) are original articles (18 articles, 78.3%)[1-5,10-15,17-23] and another one article is a review article.15 Majority of the articles that we analyzed originated from the United States of America (15 out of 19 articles, 78.9%). In brief, most of these articles focused on two key trends of research: (1) the types of collisions and (2) the risk factors of ambulance accidents. The detailed study characteristics of these articles is given in Table I.

1. Types of collisions

Compared to non-ambulance vehicles, ambulances were significantly more likely to be involved in four-way intersection crashes, angled collisions and collisions at traffic signals.[12] This was particularly true in an urban setting, as opposed to a rural setting.[13] Similarly, Sanddal et al reported that ambulance accidents in an urban setting was more likely to have occurred at intersections whereas accidents in a rural setting was more likely to be due to non-intersection rollover collisions.[4] Weiss et al reported that rural ambulance accidents were more likely to be front collisions type whereas urban ambulance accidents were more likely to be rear collisions type.[10]

2. Risk factors of ambulance accidents

Urban versus rural settings

According to Weiss et al, although there were more ambulance accidents in an urban setting compared to a rural setting, the severity of injury in rural accidents were greater than those in urban accidents.[10] This trend of higher incidence of accidents in urban setting compared to rural setting was similarly reported by Sanddal et al,[4] Chiu et al[22] and Missikpode et al.[23] In the Turkish study by Eksi et al,[21] although the authors did not detect significant differences in the overall accident rates in rural versus urban setting, the likelihood of accidents that would result in injuries was significantly higher in rural setting than in urban setting ($p < 0.05$). This was in contrast with Ray et al[13] who reported that urban accidents were more likely to result in injuries compared to rural accidents. Ray et al also found that there was no significant difference in term of the severity of injuries sustained in rural versus urban settings.[13]

Road conditions: Dry road versus wet road

Ironically, out of the 6 articles that examined the association between road conditions and ambulance accidents, 5 articles reported that more accidents occurred on dry road condition than on wet road condition.[1,3,10,13,18] The only article that reported no significant difference was Missikpode et al.[23]

Using L&S vs not using L&S

The use of L&S to save travel time is arguably one of the most extensively researched factors of ambulance response.15 L&S use had been shown to increase (1) the total number of ambulance accidents[1,4-5] and (2) the risk of injuries in ambulance accidents.[3,17]

Watanabe et al categorized ambulance accidents into 2 phases, i.e., (1) "response to the scene" and (2) "transport from the scene" phase.5 In both phases, the rates of ambulance accidents were significantly higher when L&S was used. Specifically, in the "response to the scene" phase, the accident rate was 5.4 per 100,000 trips with L&S use vs 4.6 per 100,000 trips without L&S use (adjusted odds ratio of 1.5; 95% CI 1.2 to 1.9). In the "transport from the scene" phase, the accident rate was 17.1 of 100,000 trips with L&S use

Table I: Study Characteristics of the Identified Studies

Study characteristics (N = 19)	Count (%)	References
Publication years		
1986 – 1990	1 (5.3)	17
1991 – 1995	2 (10.5)	1, 18
1996 – 2000	1 (5.3)	19
2001 – 2005	5 (26.3)	2, 3, 10-12
2006 – 2010	5 (26.3)	4, 13-16
2011 – 2015	2 (10.5)	20-21
2016 – 2020	3 (15.8)	5, 22-23
Country of origin		
United States	15 (78.9)	1-5, 10-13, 15-17-19, 23
Turkey	2 (10.5)	20-21
United Kingdom	1 (5.3)	14
Taiwan	1 (5.3)	22
Types of articles		
Original article	18 (94.7)	1-5, 10-14, 16-17-23
Review article	1 (5.3)	15
Journals		
Prehosp Disaster Med	4 (21.1)	1, 16, 18-19
Perhosp Emerg Care	5 (26.3)	2-3, 12-13, 15
Ann Emerg Med	1 (5.3)	5
Accid Anal Prev	2 (10.5)	11,23
Emerg Med J	1 (5.3)	14
Am J Emerg Med	1 (5.3)	10
JAMA	1 (5.3)	17
J Forensic Leg Med	1 (5.3)	20
Emerg Med Int	1 (5.3)	4
J Formos Med Assoc	1 (5.3)	22
Turk J Emerg Med	1 (5.3)	21
Risk factors for ambulance accidents		
Urban vs Rural settings		4, 10, 13, 21-23
Dry road vs wet road		1,3,10, 13, 18, 23
Using light & sirens vs not using light & sirens		1, 3-5, 15, 17
Restrained vs unrestrained passengers		10-11, 17
Emergency use vs non-emergency use		2, 11, 18, 23
Front seat passenger vs back seat passenger		2, 11
At intersection vs not at intersection		2-4, 10, 12-13, 17-18, 22
Previous records of accidents vs no previous records of accidents		2, 11,18, 23
Inter-facilities transfer vs primary response to site		20

versus 7.0 of 100,000 trips without L&S use (adjusted odds ratio 2.9; 95% CI 2.2 to 3.9).

Restrained vs unrestrained passengers

According to Auerbach et al[17], the failure to use restraint is the most important factor associated with injuries in ambulance accidents (relative risk is 0.098 when restraint was used compared to when it was not used; p = 0.007).[17] This risk of accidents with injuries among unrestrained passengers was even more significant in a rural setting compared to an urban setting.[10] Restrained passengers were significantly less likely to suffer death or seriously injured than unrestrained passengers.[11]

Emergency use vs non-emergency use of ambulances

With regards to the use of ambulance for emergency purposes (as opposed to, for non-emergency purposes), the results are equivocal: 2 studies reported that emergency use increased the risk of ambulance accidents[2,18] whilst another 2 studies did not increase the risk of ambulance accidents.[11,23] In fact, Becker et al reported that, ironically, non-emergency uses appeared to be more likely than emergency use to result in fatal accidents (relative risk ratio = 2.62; p< 0.05) or in severe injuries (relative risk ratio = 1.69; p< 0.0001).[11]

Types of seating: Front seat passenger vs back seat passenger

Two articles described the effect of front seating vs back seating on ambulance accident.[2,11] In both articles, it was reported that back seat passengers were more likely to be injured or killed than those in the front seat.

At intersection vs not at intersection

Out of the 9 articles that reported on the effect of "at intersection", 8 articles reported that there were more ambulance accidents occurred at intersections[2-4,12-13,17-18, 22,] particularly in an urban setting.[4,13] Only Weiss et al reported that there was no difference between the number of ambulance accidents at an intersection vs when not at an intersection.[10] Custalow et al[3] reported that ambulance accidents that occurred at an intersection was highly predictive of an injury or fatality.

Previous driver's records of accidents

Two articles reported on the impact of driver's previous records of ambulance accidents on future accidents.[2-3] In both of these articles, it was found that many ambulance drivers who were involved in fatal accidents had poor driving records.

Table II: Detailed Descriptions of Key Findings of Identified Articles

	Author(s)	Year	Objectives/aims	Data source	Key Findings and conclusion
1.	Auerbach PS, Morris JA Jr, Phillips JB Jr, Redlinger SR, Vaughn WK.	1987	to analyze the epidemiology of ambulance crash in the state of Tennessee from 1 Jan 1983 to 1 July 1986.	Ambulance crash incidents reported to the Division of Emergency Medical Services, Tennessee Department of Health and Environment (TDHE-DEMS), Nashville	Twenty-nine accidents (28.4%) contributed to a total of 65 injured victims, with one death. The three variables most strongly associated with the probability of a collision resulting in an injury were (1) use of a passenger restraint device, darkness and occurrence at an intersection. The variable most strongly associated with the probability of an injury-accident was failure to use the passenger restraint device (P = 0.007; relative risk is 0.098 when restraint was used compared to when not used). Darkness (P = .08; relative [high] risk, 3.05) and occurrence at an intersection (P = 0.13; relative [high] risk, 2.25) were variables showing increased risk, but were not statistically significant.
2.	Pirrallo RG, Swor RA.	1994	to analyze the characteristics of fatal ambulance crashes to assist emergency medical services (ems) directors in objectively developing their ems system's policy governing ambulance operations.	Fatal Accident Reporting System (FARS) from 1987 to 1990.	Seventy-five fatal crashes (69%) occurred during EU and 34 fatal crashes (31%) occurred during NEU, the number of fatal EU crashes also lessened while the number of fatal NEU crashes increased progressively (p =0.016). More fatal ambulance crashes occurred during the afternoon (37.6%) than during any other time interval. The lowest number of ambulance crashes resulting in fatalities occurred late at night (15.6%). The percentage of EU crashes was elevated between 1200 h and 1800 h (44.0%), whereas the largest percentage of NEU crashes took place between 0000 h and 0600 h (32.4%). These differences are statistically different (p = 0.009). The increased number of EU crashes during daylight hours could be surmised by the larger volume of cardiac arrest ambulance calls during the daytime. The increased number of NEU crashes that occur during decreased light conditions may be inferred by the relative reduced visibility of the ambulance when lights and siren are not used.
3.	Saunders CE, Heye CJ.	1994	To characterize ambulance collisions and assess the risk of traveling with lights and siren in an urban emergency response setting	Data of all consecutive ambulance collisions of the Paramedic Division of the San Francisco Department of Public Health during a 27-month period.	Overall collision rate for lights and siren (LS) travel was higher than that for non-lights and siren travel, although the difference was not statistically significant (45.9 collisions per 100,000 LS patient travels, 95% CI 29.7-62.1, versus 27.0/100,000 for non-LS travel, 95%CI 18.3-35.7). The rates of resulting injuries displayed a statistically significant difference (22.2 injuries per 100,000 LS patient travel, 95% CI 11.0-33.5, versus 1.5/100,000 for non-LS travel, 95% CI -0.6 - 3.5). Majority of collisions (60.0%) occurred during patient-related travel. Majority of collisions were due to inattention, failure of on-coming traffic to yield, or unsafe parking; unsafe speed was an infrequent cause. Most crashes occurred during daylight, in dry weather, and involved another vehicle.
4.	Biggers WA Jr, Zachariah BS, Pepe PE.	1996	to define the incidence and severity of, and to identify any contributing factors to EMVCs in a large urban system (Houston)	Data from the Fire Academy of the Houston Fire Department for year 1993	Of the 86 EMVCs identified, 74 (86%) files were complete and available for evaluation. Major collisions, determined according to injuries or vehicular damage, accounted for 10.8% of all EMVCs. The majority of collisions (85.1%) occurred at some site other than an intersection. There was no statistical association between occurrence at an intersection and severity, day versus night, weekend versus weekday, presence or absence of precipitation, or use of WL & S versus severity of collision. Drivers with a history of previous EMVCs were involved in 33% of all collisions.

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Table II: Detailed Descriptions of Key Findings of Identified Articles

	Author(s)	Year	Objectives/aims	Data source	Key Findings and conclusion
5.	Kahn CA, Pirrallo RG, Kuhn EM.	2001	To describe fatal ambulance crash characteristics, identifying those that differentiate emergency and nonemergency use crashes	All fatal ambulance crashes on U.S. public roadways reported to the Fatality Analysis Reporting System (FARS) database from 1987 to 1997	Three hundred thirty-nine ambulance crashes resulting in 405 fatalities and 838 injuries. Most crashes (202/339 or 60%) and fatalities (233/405 or 58%) occurred during emergency use. Emergency use was defined as use of lights and siren while traveling. These crashes during emergency use occurred significantly more often at intersections ($p < 0.001$), at an angle ($p < 0.001$), with another vehicle ($p < 0.001$). The most serious and fatal injuries occurred in the rear (OR 2.7, as opposed to front); and to improperly restrained occupants (OR 2.5; as opposed to those properly restrained). 41% of these ambulance drivers had records of previous crashes, suspensions, and/or motor vehicle citations suggesting that previous crash history maybe an indicator or predictor of another crash.
6.	Weiss SJ, Ellis R, Ernst AA, Land RF, Garza A.	2001	to compare urban and rural ambulance crashes in the state of Tennessee	Data from the mandatory reporting forms for all ambulance accidents in the state of Tennessee	Although more crashes occurred in urban setting compared to rural, the rate of injuries sustained were significantly lower in urban crashes compared to rural crashes (OR = 0. 49, 95% CI = 0.24 to 0.98) and fewer of these urban crashes were considered "severe" compared to rural type. The postulation by the authors was that rural travel involved longer distance across the county, travelling at higher speed and frequently with lack of restraints. No significant difference in terms of the number of crashes at intersection in both types of crashes (urban 32%, rural 22%, $p = 0.14$).
7.	Becker LR, Zaloshnja E, Levick N, Li G, Miller TR.	2003	to address the impacts of emergency vehicle (ambulances, police cars and fire trucks) occupant seating position, restraint use and vehicle response status on injuries and fatalities.	Merged data from Fatality Analysis Reporting System (FARS) and the General Estimates System (GES) from 1988 through 1997.	Restrained ambulance occupants involved in a crash were significantly less likely to be killed (3.77 times lower risk, $p < 0.009$) or seriously injured (6.49 times lower risk, $p < 0.0001$) times lower than unrestrained occupants. Ambulance rear occupants were significantly more likely to be killed than front-seat occupants (5.32 times higher risk than for front-seat occupants, $p < 0.0001$). Relative to police cars and fire trucks, ambulances experienced the highest percentage of fatal crashes where occupants are killed and the highest percentage of crashes where occupants are injured.
8.	Custalow CB, Gravitz CS.	2004	to identify factors associated with ambulance accidents that are potentially amenable to preventive intervention	Paramedic Division of the Denver Health and Hospital Authority (DHHA) from 1989 - 1997	Using multiple logistic regression, T-bone mechanism, collision at an intersection, and alcohol intoxication of the civilian drivers were significant predictors of collisions resulting in injury (odds ratios of 29.7, 4.3 and 6.1, respectively, $p<0.05$. Although only 75% of the division's responses are run with warning lights and sirens (WLS), a disproportionate 91% of response mode collisions were during a WLS response.
9.	Ray AF, Kupas DF.	2005	To describe the characteristics and associated occupant injuries of ambulance accidents as compared with accidents involving similar-sized vehicles.	Motor vehicle accidents data collected by the Pennsylvania Department of Transportation from 1997 to 2001	Ambulance accidents occurred with increased frequency on evenings (19% vs 10% respectively from 1801 - 0000 hours) and weekends (15% vs 8% respectively on Saturdays; and 9% vs 4% respectively on Sundays). Ambulances were more likely to be involved in four-way intersection crashes (43% vs. 23%, $p = 0.001$), angled collisions (45% vs. 29%, $p = 0.001$), and collisions at traffic signals (37% vs. 18%, $p = 0.001$). More people were involved in ambulance accidents ($p = 0.001$), with 84% of ambulance accidents involving three or more people and 33% involving five or more people. Injuries were reported in more ambulance accidents (76% vs. 61%, $p = 0.001$).

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Table II: Detailed Descriptions of Key Findings of Identified Articles

	Author(s)	Year	Objectives/aims	Data source	Key Findings and conclusion
10.	Ray AM, Kupas DF.	2007	To describe and compare the characteristics of, and associated injuries caused by, ambulance crashes that occur in rural versus urban areas.	Data from Pennsylvania Crash Outcome Data Evaluation System database from 1997 to 2001	Operator error was the most common cause for both types of crashes (75% for rural; 93% for urban), whereas environmental factors (e.g. darkness, snowy conditions) were more prevalent in rural crashes (25% vs. 7%). Urban crashes were more likely to involve angled collisions with other vehicles (54% vs. 19%), intersections (67% vs. 26%), and occured at a stop sign (53% vs, 14%). Rural crashes often involved striking a fixed object (33% vs. 7%). In terms of the severity of injuries sustained, majority (>50%) of the injuries sustained appeared to be minor in both types of crashes.
11.	Lutman D, Montgomery M, Ramnarayan P, Petros A.	2008	to determine how many deaths and injuries were caused by ambulances and aeromedical accidents	Data for ambulance accidents were obtained from the Department for Transport, Road Statistics whereas data for air ambulance accidents were obtained from Civil Aviation Authority, Aviation Safety Review from 1999 to 2004	The authors concluded that although the numbers of fatalities per year remained small, each death should be considered as a disaster and every attempt needs to be made to reduce the incidence to zero.
12.	Sanddal ND, Albert S, Hansen JD, Kupas DF.	2008	to review the literature and discuss the implications for rural EMS agencies and personnel, and to provide a sample policy or protocol that could be adapted for use in most communities.	literature indexed in MEDLINE (1996–2007). A secondary search was conducted using Academic Search Premier, Comprehensive Index of Nursing, and Allied Health Literature. MeSH search terms used in MEDLINE included "ambulance"; "accident", "traffic"; "emergency medical technician"; "occupational health"; and "rural".	28 out of 32 literature were included. The authors categorized their literature review into 4 sub-headings: 1) description of the problem; 2) safety issues; 3) lights and siren use and 4) legal and ethical risks. The authors concluded that driving an ambulance is a dangerous process. A key factor in ambulance crashes is he use of warning lights and sirens. The authors also highlighted the reluctance of emergency care providers to wear safety restraints in ambulance.
13.	Studnek JR, Fernandez AR.	2008	to explore the hypothesis that demographic and work-related characteristics are associated with involvement in ambulance crashes	2004 Longitudinal Emergency Medical Technician Attributes and Demographics Study	A total of 111 (8.6%) of participants reported being involved in an ambulance crash within the past 12 months. On average, the EMS professionals involved in an ambulance crash were younger than those reporting no involvement in a crash 31.0 ±8.2 vs. 34.8 ±10.0 respectively ($p < 0.01$). Specifically, 14.9% of EMS professionals who reported sleep problems were involved in a crash as compared to only 7.5% of those who did not have sleep problems. Results from this analysis suggest age and sleep problems are associated with involvement in an ambulance crash.
14.	Sanddal TL, Sanddal ND, Ward N, Stanley L.	2010	to analyze the 466 ambulance crashes from May 1, 2007 to April 30, 2009, reported in EMSNetwork, which is a site collecting articles from newspapers and other popular press sources	All ambulance crashes published in newspapers and other popular press and complied on the EMSNetwork website occurring between May 1, 2007 and April 30, 2009 were printed	Seventy-nine (79) crashes resulted in fatalities to persons inside or outside of the ambulance. As a result of the 79 fatal crashes, a total of 99 persons died. Intersections were the most common location (196 (42%) of 466 total) noted for the crash. In 145 cases, the ambulance was responding to an emergency. Out of these 139 cases where the utility of lights and siren were noted, 111 (80%) of these cases had used lights and ambulance at the time of crash. More crashes occurred in urban setting (382 cases, 82%) than in rural setting (84 cases, 18%).

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Table II: Detailed Descriptions of Key Findings of Identified Articles

	Author(s)	Year	Objectives/aims	Data source	Key Findings and conclusion
15.	Ersoy G, Ersoy O, Yuksekbas O, Kurnaz G, Akyildiz EU, Ekemen S.	2012	to investigate traumatic consequences of ambulance accident on patients	Data were collected from the reports issued by the First Board of Council of Forensic Medicine (CFM)	15 cases died on the day of the accident. Skin injuries at head (8 cases) and legs (6 cases) were most common traumatic lesions. In total, only 6 deaths were found to be directly related to ambulance accident. Death of patient after ambulance accidents may not be associated easily to the accident. This is because death of patients after the ambulance accidents could be directly due to these accidents or the medical conditions which cause these patients to be transported in ambulances in the first place. This is not surprising in that most of the patients had a life-threatening condition, severe trauma or chronic disease at the terminal stage. Even if they had not had an ambulance accident, they had a high risk of mortality.
16.	Eksi A, Celikli S, Catak I.	2015	to evaluate the effects of the institutional structural changes and legislative framework on the number of ambulance accidents in Turkey. Institutional changes in the management of ambulance services in Turkey at the time of publication were (1) changing from employing ambulance drivers whose only role and responsibility was to drive ambulances (staffed together with doctors and nurses) to employing paramedics and EMTs to drive the ambulances; (2) the increased number of female drivers; and (3) decreasing the level of overall driving experience of these newly appointed paramedic/EMT drivers.	(1) ambulance accident data from the Ministry of the Interior and (2) data on ambulance numbers was obtained from the Ministry of Health	The effects of changes in the system were all found to have no significant effect on the increased number of ambulance accidents. The number of ambulance accidents increased by 42.5% over five years (2009 - 2013), whereas the area of coverage increased by 57.3% during the same period. The rate of EMS personnel experiencing ambulance accidents was 69.4%.
17.	Chiu PW, Lin CH, Wu CL, Fang PH, Lu CH, Hsu HC, Chi CH.	2018	to analyze the characteristics of ambulance accidents in Taiwan	Ambulance accidents data from the National Fire Agency of Taiwan	715 ambulance accidents resulting in 1852 victims (8 deaths within 24 h and 1844 injured patients; fatality rate 8/1852 = 0.4%). Compared to overall traffic accidents, ambulance accidents were 1.7 times more likely to lead to death and 1.9 times more likely to lead to injuries among patients. On average, there was one ambulance accident for every 8598 ambulance runs. Among the 715 ambulance accidents, 8 (1.1%) ambulance accidents were fatal and 707 (98.9%) were nonfatal. All 8 fatalities were associated with motorcycles. The urban areas were significantly higher than the rural areas in the annual number of ambulance accidents (14.2 ± 7.3 [7.0–26.7] versus 3.1 ± 1.9 [0.5–8.4], p = 0.013), the number of ambulance accident-associated fatalities per year (0.2 ± 0.2 [0.0–0.7] versus 0.1 ± 0.1 [0.0–0.2], p = 0.022), and the annual number of injured patients (who needed urgent hospital visits) in ambulance accidents (19.4 ± 7.3 [10.5–30.9] versus 5.2 ± 3.8 [0.9–15.3], p < 0.001). This 24-h ambulance accident fatality rate in Taiwan (0.4%) is almost four times of the fatality rate in the United States (0.1%) as reported in previous studies. All fatalities and almost half of the injuries in ambulance accidents were associated with motorcycles.

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Table II: Detailed Descriptions of Key Findings of Identified Articles

	Author(s)	Year	Objectives/aims	Data source	Key Findings and conclusion
18.	Missikpode C, Peek-Asa C, Young T, Hamann C.	2018	to estimate relative risks for emergency vehicle crashes driving in emergency mode compared with non-emergency mode, including police, ambulance and fire vehicles	Iowa Crash Database for the period of 2005 through 2013.	Police vehicles had 1.28 (95% CI = 1.07–1.53) times the risk for crashing when in emergency mode. Ambulances and fire vehicles had no increase in crash risk while driving in emergency mode (OR = 1.08; 95% CI = 0.74 – 1.58). Female drivers and driver age under 30 were associated with an increased crash risk for crashing in both the police and ambulance/fire model.
19.	Watanabe BL, Patterson GS, Kempema JM, Magallanes O, Brown LH.	2019	to compare crash rates between ambulance with versus without lights and sirens	transporting patients from an emergency scene	Response phase crash rate was 4.6 of 100,000 without lights and sirens and 5.4 of 100,000 with lights and sirens (AOR 1.5; 95% CI 1.2 to 1.9). Response phase means the ambulance's response to the scene whereas transport phase refers to the phase where the ambulance transport the victim back to the medical center or hospital. For the transport phase, the crash rate was 7.0 of 100,000 without lights and sirens and 17.1 of 100,000 with lights and sirens (AOR 2.9; 95% CI 2.2 to 3.9). Ambulance use of lights and sirens is associated with increased risk of ambulance crashes. The association is greatest during the transport phase. EMS providers should weigh these risks against any potential time savings associated with lights and sirens use.

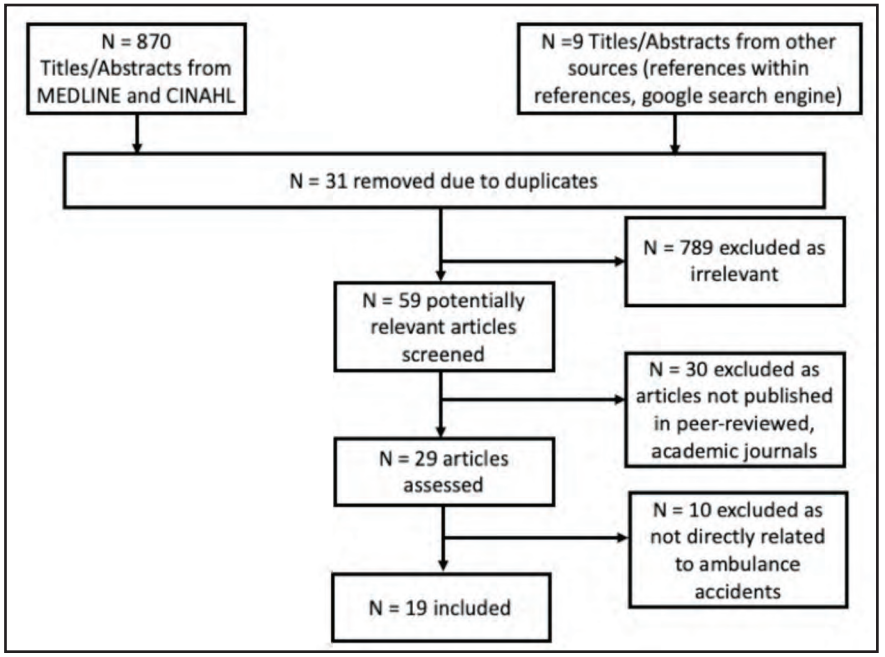

Fig. 1: Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) Flow Diagram for Scoping Review.

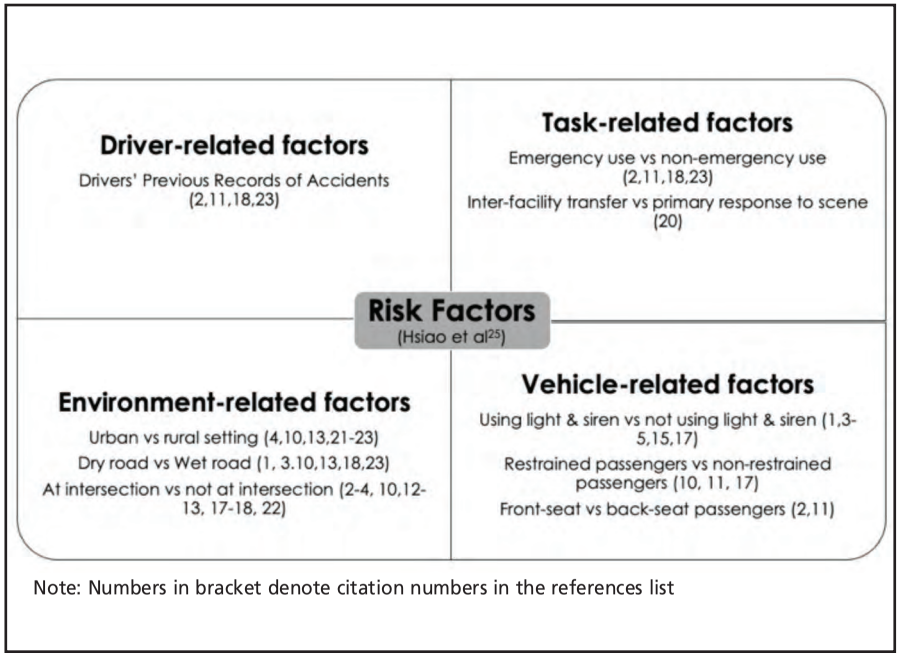

Fig. 2: Framework of Risk Factors for Ambulance Accidents.

Type of transfer- Interfacility vs primary response

Ersoy et al reported that only 6 ambulance accident cases were due to transportation to a healthcare facility (primary response) compared to 15 cases (71%) that were due to transportation from one healthcare facility to another (inter-facility transfer).[20]

The data on the study characteristics (i.e., the country of origin, types of articles, the journals where these articles were published, year of publication, objectives as well as the risk factors for ambulance accidents reported in these articles) are tabulated in Table I. The detailed descriptions of the key findings of these articles are given in Table II.

DISCUSSION

The two most common research areas on ambulance accidents identified in this scoping review are the types of collisions and the risk factors for ambulance accidents. With regards to risk factors, we identified 9 risk factors that contributed to ambulance accidents: (1) driving in urban settings (2) driving on dry roads (3) the use of L&S (4) the failure to use restraints (5) driving for emergency use (6) back seating (7) at road intersection (8) driver's previous records of accidents and (9) inter-facility transfer.

Out of these 9 risk factors, the two most studied risk factors are the use of L&S and when driving at road intersection. L&S is often used by ambulances to herald its arrival and to request the right-of-way from other drivers. To be effective however, the siren sound must be of sufficient loudness and frequency in order to overcome the competing masking noises generated from the road, vehicle engines, sound systems, ventilation system sound, sound insulation system, etc.[24] But with this degree of loudness, it may also limit the ambulance driver's ability to pick up important auditory signal from the radio system or from surrounding vehicles.[24-25] This may predispose the vehicle to ambulance accidents. L&S can also have a number of adverse effects to the surrounding vehicles. For example, the strobe light can trigger a number of bodily reactions such as unusual feeling, involuntary twitch, impede the vision of other drivers, induce the distractions of drivers[25] and can even produce a "wake effect".[26] "Wake effect" refers to the phenomenon of accidents involving surrounding vehicles caused by the passage of an ambulance with L&S when the other vehicles are pulling to the side of the road, running through red lights, slowing down, etc.[26] More importantly, most studies have shown that although the time saved with the use of L&S may be statistically significant, they were often not clinically significant.[27-32] For example, one study showed that even with the amount of time saved using L&S, none of the patients were able to receive any time-critical interventions within that short period of time.[29] For this reason, it is argued that the use of L&S is often unwarranted except in the most pressing clinical circumstances.

In the study by Watanabe et al[5], although L&S use was associated with increased rates of ambulance accidents in both response and transport phases compared to when no L&S was used, this increase was more significant during the transport phase. The authors hypothesized that during the "response to the scene" phase, two healthcare staff were typically seated in the front compartment of the ambulance and they shared the cognitive load required to operate the ambulance (e.g., using the radio, activating the siren, watching for traffic risks). But during "transport from the scene", only the driver was typically seated alone in the front compartment. The other staff would be attending to the victim in the ambulance cabin.[5] The increased cognitive load imposed on the driver predisposes him or her to accidents.

Indeed, ambulance driving is a cognitively demanding task particularly when the driver is driving at high speed. It can also be a highly stressful task[33], as the driver often has to attend to secondary tasks simultaneously such as engaging in radio communication and identifying the victim's location. Often, these secondary tasks may even require eyes to be taken off the road[34] resulting in inattentional driving. The demands for secondary tasks and "eyes-off-road" can significantly delay a driver's response time by 16% and 29% respectively.[34]

Stress by itself has also been shown to result in a surge of adrenaline. Witzel et al had demonstrated increased levels of cortisol and other adrenocortotropic hormones in ambulance drivers during emergency driving compared to during non-emergency driving.[35] This sympathetic response results in more aggressive and risk-taking behaviors among the drivers. The problem of cognitive overload is further compounded when an ambulance driver approaches the dilemma zone of a road intersection.[25] Dilemma zone is the stretch of road before an intersection traffic light where an ambulance driver is faced with the dilemma of whether to apply brake or to run through the red traffic light without stopping.[36] Should an ambulance driver decide to run the red traffic light without stopping, he or she may also face the challenge of other potential red-light runners coming from another direction. This is because the decision to run through the red light is predicated on the trust that other road users would comply with traffic rules and give way to the ambulance. But when this trust is breached, unpredictable traffic conflicts and accident risk may result. On the other hand, should the ambulance driver decide to abruptly apply brake to the fast-moving ambulance, this may create a sudden conflict with the vehicles following behind, leading to risk of rear-end collisions.[37] The ambulance driver often faces a surge of high cognitive load, split-second decisions that must be made at the dilemma zone.[38]

According to a framework on ambulance accidents developed by Hsiao et al[25], risk factors for ambulance accidents can be divided into four broad categories, i.e., (1) driver-related factors (e.g. individual differences, driver experience and driver behavior); (2) task-related factors (e.g. time pressure, secondary-task demands, long shift hours, driving under emotions); (3) vehicle-related factors (e.g. vehicle characteristics, in-vehicle equipment, conspicuity, warning signals) and (4) environment-related factors (e.g. at intersection, traffic signals, speed, light conditions, weather). Using this framework to map out the 9 risk factors we have identified in this scoping review (see Figure 2), it is evident that most of these risk factors concentrated on 3 out of the 4 categories. The least studied category (the knowledge gap) is

the category of driver-related factors. Indeed, the potential risk factors under this category (such as individual driver's traits and personalities) can be just as important as other categories of risk factors. For example, people with Type-A personality have been shown to be linked to rage and aggression. Type-A personality is a personality type with attributes such as high levels of competitiveness and impulsiveness.[39-40] Specifically, in the context of driving, Type-A personality has been shown to be associated with increased risk of accidents, traffic rules violation, impulsive and reckless driving habits and road rage.

One limitation inherent to the methodology of scoping review is that, although we have broadly mapped out the different types of collisions and risk factors, we did not systematically appraise our findings. In this regard, a systematic review is called for. A systematic review is also useful to minimize various research and publication biases as well as to control between-studies and within-studies variability. Secondly, the lack of a standard reporting guideline hampered our endeavor to conclusively identify the most common types of collisions involving ambulances. Lastly, as most of the articles in our review originated from developed countries (in particular, the USA and United Kingdom), the findings reported here might differ should a similar study is conducted in the setting of a developing country. This is because the road conditions, the drivers' behaviors and attitudes, the traffic congestion as well as the ambulance maintenance may be substantially different in a developing country as compared to that in a developed country. Hence, there is a need for more studies on ambulance accidents to be conducted in the setting of a developing country.

CONCLUSIONS

In this scoping review, we have identified 9 major risk factors described in the literature on ambulance accidents. The two most common risk factors studied are (1) the use of L&S and (2) driving at intersection. Most of these risk factors can be mapped into three categories of risk factors: task-related factors, vehicle-related factors and environment-related factors. The category of risk factors least studied is the category of driver-related factors. The lack of standard reporting guideline hampered our quest to identify the main types of ambulance accidents reported in literature. As such, it is hoped that this scoping review may serve as a springboard for more elaborative in-depth systematic reviews of selective risk factors of ambulance accidents or future research in ambulance accidents.

DECLARATIONS

Competing interests:
The authors declare that they have no competing interests

Funding:
None

Authors' contributions:
Both authors were involved in the initial conception of the study design. KSC conducted the initial search for the articles in MEDLINE and CINAHL. Both authors independently screened the eligibility of articles for inclusion. Both authors were involved in the quantitative and qualitative synthesis of the articles. KSC drafted the manuscript and both authors approved the final draft of the manuscript.

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Association between fatty acids and coronary heart disease: A scoping review

Wan Zulaika Wan Musa, BHSc[1], Nur Ain Fatinah Abu Bakar, BHSc[1], Aryati Ahmad, PhD[1], Nyi Nyi Naing, MMedStat[2]

[1]School of Nutrition and Dietetics, Faculty of Health Sciences, Universiti Sultan Zainal Abidin, Gong Badak Campus, Kuala Nerus, Terengganu, Malaysia, [2]Faculty of Medicine, Universiti Sultan Zainal Abidin, Medical Campus, Kuala Terengganu, Terengganu, Malaysia

ABSTRACT

Introduction: High intakes of total fat are long known as a risk factor for coronary heart disease (CHD), but the association between fatty acids and CHD remains unclear. This scoping review aims to collate and analyze the association between types of fatty acid and risk of CHD.

Materials and Methods: This review uses the methodological framework of Arksey and O'Malley. A total of 19 studies were selected from 9456 studies screened from the electronic databases.

Results: Majority of the studies reported no association between saturated fat (SFA) and monounsaturated fat (MUFA) with CHD. Meanwhile, seven out of 12 studies reported inverse association between polyunsaturated fat (PUFA) and risk of CHD whilst 67% of the studies found that trans-fat intake was positively associated with CHD risk.

Conclusions: This review finds that all the types of dietary fat have different effects on the risk of CHD. Nevertheless, intakes of healthy fat such as MUFA and PUFA in controlled amounts are expected to reduce CHD risk. In addition, the divergence of findings found between studies might be due to the methodological inconsistencies. More robust research is needed to determine the actual dietary determinants of CHD as it will provide important information for future development of dietary intervention.

KEYWORDS:
Type of fatty acid, dietary fat, fat intake, coronary heart disease

INTRODUCTION

In recent years, non-communicable diseases (NCDs) have become a global concern. The four main NCDs are cardiovascular diseases (CVDs), cancers, respiratory diseases and diabetes.[1] World Health Organization (WHO) 2017 has estimated that out of the 17 million premature deaths due to NCDs in 2015, 37% were caused by CVDs.[2] In the United States of America (USA), it was estimated that the annual cost of CVD in 2014-2015 was estimated at $351.2 billion.[3] Improved preventions of CVD can help to reduce the number of CVD incidence as well as their treatment cost globally. Of all CVDs, coronary heart disease (CHD) is the most common type of CVDs.

A number of risk factors have been associated with CHD, known as modifiable and non-modifiable risk factors. Apart from the non- modifiable risk factors such as age, sex and family history, the lifestyle risk factors of CHD such as smoking, poor lipid profile, physical inactivity and unhealthy dietary intake are the major contributing factors towards CHD.[4,5] Global clinical practice guidelines still advise that CHD treatments and prevention methods are based on underlying risk factors. Adherence to a healthy diet may reduce the mortality rate of CVD by eight to 45%.[6] Therefore, the main objective of Medical Nutrition Therapy is to reduce the intake of cholesterol, total fat, and saturated fat (SFA). It is believed that high SFA and trans-fat consumption may increase low-density lipoprotein (LDL) cholesterol levels which leads to CVD.[7] High LDL-cholesterol can increase lipids deposition in the arterial wall, leading to the build-up of plaque and narrowing the arteries, known as atherosclerosis process.[8]

However, the recent guidelines from USA Dietary Guidelines and Recommended Nutrient Intake (RNI) for Malaysia removed the cholesterol intake recommendation as there is insufficient evidence to show whether lowering cholesterol intake reduces LDL-cholesterol.[7] Previous studies found that the reduction of SFA consumption together with increased intake of unsaturated fatty acids would reduce the incidence of CHD.[9] Over the years, there are conflicting arguments on the association between fatty acids and CHD that may confuse the public and healthcare practitioners. Therefore, the association between fatty acids and CHD has to be examined continually and extensively using the most current evidence as the type of fatty acids in dietary intake have an important role in determining CHD risk.

Thus, this paper aims to collate, assemble and analyze previous literature on the association between fatty acids and the risk of CHD. The findings are important to provide a basis for the development of dietary intervention, particularly for at-risk patients.

MATERIALS AND METHODS

This review was conducted using the methodology outlined by Arksey & O'Malley.[10] The five stages included in this framework were (1) identification of research questions, (2) identification of related studies, (3) study selection, (4)

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Corresponding Author: Aryati Ahmad
Email: aryatiahmad@unisza.edu.my

charting of data and (5) collating, summarizing, and reporting the results. A flow diagram based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2009) from literature search to its final selection is shown in Figure 1.

Identifying the research questions
The research question to be addressed in this review was 'what is the association of type of fatty acids with the risk of CHD?'

Identifying relevant studies
Two databases were utilized in the search method i.e. Medline (via EBSCOHost) and SCOPUS. The initial selection criteria were broad to ensure that as many studies as possible were assessed according to the criteria of the studies. There was no restriction in the year of publication and this review included studies conducted in any country and published in English. All observational studies such as retrospective, prospective, case-control and cross-sectional studies which report on the association between fatty acids with CHD were included in the search. To be eligible for inclusion in this review, a study had to be conducted in the adult population (≥18 years) and only studies that employed validated dietary assessment (i.e. FFQ, 3-7 days diet diary, 24 hours diet recall, and food records) were included in this review paper. Key search terms used for searching articles are recorded in Table I.

Study selection
The selection of relevant studies was based on the research questions and eligibility criteria. Duplicates were removed, and the remaining titles and abstracts were screened by two independent reviewers following the eligibility criteria. Any abstract that did not meet the study criteria were excluded. Then, full texts were assessed by the reviewer according to inclusion/exclusion criteria independently. In addition, the exclusion was applied to non-relevant articles. Non-duplicated original articles from the review paper were checked and included.

Charting the data
The country(-ies), author(s), year of publication, type(s) and purpose(s) of study, characteristic of participants, dietary assessment method, fat intake, incidence and findings are described in Table II.

Collating, summarizing and reporting the results
Evaluations of the review on the association of type of fatty acids with risk of CHD are summarised in Table II.

RESULTS

Figure 1 illustrates the process of inclusion of the eligible studies for this scoping review. Initially, 9,456 articles were obtained, 1,300 from Scopus and 8,156 from Medline. After removing the duplicates of articles, 9,090 articles remained. Those articles were screened and only 101 full-text articles were assessed for eligibility. Finally, only 19 studies were included in this scoping review after excluding 82 articles with reasons. Out of 19 studies, 16 were observational prospective studies, two were case-control studies and one was cross-sectional study.

Nine studies were conducted in the United State of America (USA), two studies each were conducted in Denmark, Netherlands and Norway, and the remaining studies were from Finland, Italy, United Kingdom and Iran. The total number of participants involved in all studies was 869,608 ranging from 222 to 344,696. The duration of follow-up across the studies ranged from 4 to 30 years. The age range of the participants was eighteen to 86 years old. Three studies involved only female participants, five studies involved male participants, whilst eleven studies involved both sexes. Eleven out of 19 studies used a food frequency questionnaire (FFQ) to assess dietary intake, meanwhile, eight studies used other methods including dietary history interview, 4-day food recording, 7-day weighed food record, cross-check dietary history, and 24-hour diet recall.

The association between fatty acid intakes and CHD were reported in different ways between studies (Table II). Seventy-seven per cent of the studies reported that saturated fat (SFA) was not associated with CHD.[11–20] In contrast, Jakobsen et al. in their cohort study found a positive association between CHD and SFA intake among females with HR = 1.36 (0.98, 1.88).[21] However, no overall association between SFA and CHD was found among males in the same study. Posner et al. found that SFA intake had a marginally significant association with CHD.[22] Conversely, another study by Jakobsen et al. showed that there was a significant inverse association between polyunsaturated fat (PUFA) and risk of coronary events for each 5% substitution of SFA with PUFA with HR = 0.89 (0.50, 1.57) for females and HR = 0.80 (0.55, 1.15) for males.[23]

Six out of nine studies reported no association between monounsaturated fat (MUFA) and CHD.[12,14,15,18,19,21] However, a study by Virtanen et al.[17] showed that MUFA intake was positively associated with increased risk of CHD with HR=1.40 and 95% CI (0.90-2.20) whilst Posner et al.[22] found this association only among 45-55y people. In contrast, a case-control study conducted by Moghadam et al. showed a negative association between MUFA and CHD risk (OR=0.7, 95% CI 0.45-1.08).[20] In terms of PUFA alone, seven out of twelve studies reported an inverse association between PUFA and the risk of CHD.[14,15,17,19–21,24] Jakobsen et al. found that PUFA intake was inversely associated with risk of CHD among females, HR = 0.89 (0.50, 1.57).[21] Conversely, other five studies showed that PUFAs were not linked with CHD protection.[12,18,22,25,26]

Nonetheless, 67% of the studies included in this review found that trans-fat intakes were positively associated with CHD risk with a relative risk or hazard ratio between 1.20 to 3.3.[11,12,14,15,27,28] However, a study done by Smith et al. showed different finding between males and females.[28] The odds of CHD were smaller in the highest intake of total trans fatty acid (OR=0.59, 95% CI 0.35,1.00) among males, but trans fatty acid intake did not appear to influence odds of CHD (OR=1.24, 95% CI 0.64, 2.41) among females. The other three studies showed no association between trans-fat CHD risk.[17,18,29]

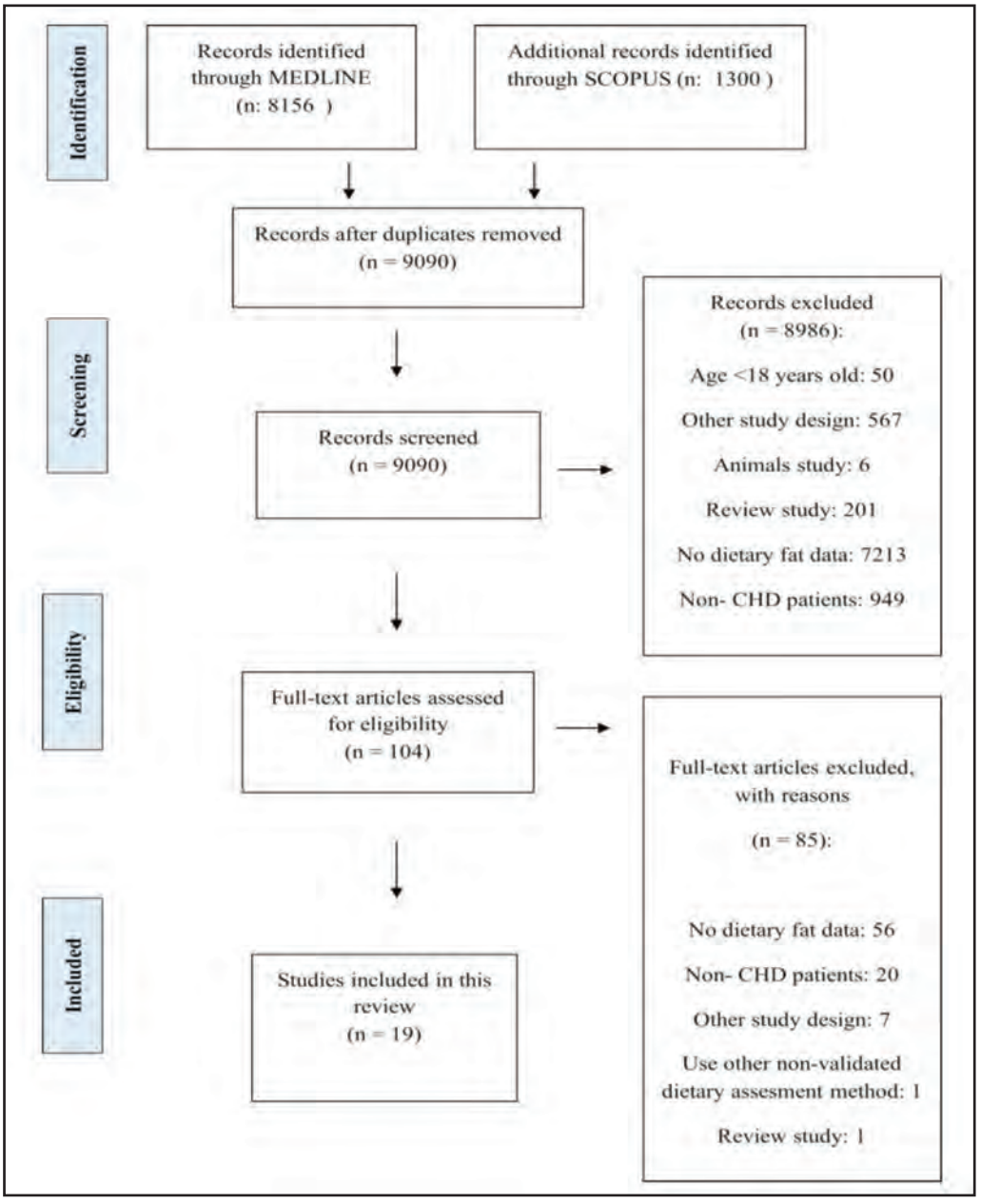

Fig. 1: PRISMA flow diagram of article screening and eligibility.

Table I: Key terms in the scoping review

Key Search Terms
"Dietary Fat" AND "Coronary Heart Disease" OR CHD
"Dietary Fat" AND "Coronary Artery Disease" OR CAD
"Fat Intake" AND "Coronary Heart Disease" OR CHD
"Fat Intake" AND "Coronary Artery Disease" OR CAD

DISCUSSION

Each type of fatty acid gives a different effect on blood cholesterol levels, either beneficial or adverse.[30] Most the dietary guidelines limit the intake of SFA as it has been believed that SFA increases CHD risk due to its potential effect in increasing low-density lipoprotein (LDL) cholesterol. The original American Heart Association (AHA) Step 1 suggested an ideal balance of dietary fat consumption by 1:1:1 for SFA: MUFA: PUFA to maintain a good plasma LDL/HDL level.[31] The current recommendation from the AHA indicates that a lower intake of saturated fat accompanied by higher intake

Table II: General characteristics and important findings of included studies

Country	Author (Year)	Types, Purpose of the study & Duration of follow up (years)	Participants' characteristic	Dietary assessment method	The intake of fat	Findings
Denmark	Jakobsen et al. (2004)	Prospective cohort study -to describe the associations between the energy intake from total dietary fat and the major types of dietary fat and risk of CHD -16 years of follow up	N= 3686 Age: 30-71 years Sex: Both CHD cases: 326	7-day weighed food record or a dietary history interview	Saturated fat Female: 19.5% Male: 19.7%	- A 5% greater energy intake from the consumption of SFA among females will increase the CHD risk by 36% (HR= 1.36, 95% CI 0.98, 1.88) - SFA and CHD was not associated among males, (HR=1.03, 95% CI 0.78, 1.37)
					MUFA Female: 15.2% Male:15.8%	- There was no association between MUFAs intake and the risk of CHD among females (HR= 1.01, 95% CI 0.56, 1.83) and males (HR=0.95, 95% CI 0.65, 1.40)
					PUFA Female: 6.5% Male:6.5%	There was an inverse trend between the percentage of energy derived from PUFA and risk of CHD but not significant among females (HR= = 0.89, 95% CI 0.50, 1.57) and males (HR= 0.80, 95% CI 0.55, 1.15)
US	Jakobsen et al. (2009)	Prospective cohort study - to investigate associations between energy intake from MUFA, PUFA and carbohydrates and risk of CHD and to clarify whether energy from unsaturated fatty acids or carbohydrates should replace energy from SFAs to prevent CHD. - 4-10 years of follow up	N= 344,696 Age: 37-76 years Sex: Both CHD cases: 5249	Dietary history interview/ FFQ	Saturated fat 10.1%	- PUFAs had a significant negative correlation with CHD risk, if replacing SFs with PUFAs by 5 percent, (HR=0.87, 95% CI 0.77-0.97) - Carbohydrates had moderate significant positive correlation with CHD risk, if replacing SFs with carbohydrate by 5 percent, (HR=1.07, 95% CI 1.01-1.14)
US	Posner et al. (1991)	Prospective cohort study -to examine the effect of major dietary lipid components on the longitudinal incidence of CHD in the Framingham cohort population - 16 years of follow up	N= 859 Age: 45-65 years Sex: Male CHD cases: 213	24-hour dietary intake	SFA 45-55y: 15.2% 56-65y: 14.8%	- SFA intake was marginally significant
					MUFA 45-55y: 16.2% 56-65y: 15.5%	- MUFA intake among 45-55y was positively associated with CHD and no association among 56-65y people
					PUFA 45-55y: 5.5% 56-65y: 5.4%	- PUFAs intake was not associated with CHD among 45-55y people and 56-65y people
US	Hu et al. (1999)	Prospective cohort study -to examine the associations between intakes of individual saturated fatty acids and their food sources and risk of CHD - 14 years of follow up	N= 80,082 Age= 34-59 years Sex: Female CHD cases: 939	FFQ	SFA Median intake of 4:0-10:0 (% of energy): 1st quantile: 0.87 5th quantile: 2.00 Median intake of sum of 12:0-18:0 (% of energy): 1st quantile: 9.5 5th quantile: 17.2	- No significant association between consumption of short to medium chain SFAs with CHD risk (RR= 1.07, 95% CI 0.89, 1.30) - Consumption of longer-chain SFAs were each separately correlated with a small risk increment (RR= 1.14, 95% CI 0.93, 1.39)

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Table II: General characteristics and important findings of included studies

Country	Author (Year)	Types, Purpose of the study & Duration of follow up (years)	Participants' characteristic	Dietary assessment method	The intake of fat	Findings
US	Xu et al. (2006)	Prospective cohort study - to examine the associations between intakes of dietary fat and CHD incidence in American Indians - 7.2 years of follow up	N= 2398 Age: 47-79 years Sex: Both CHD events: 436	Cross-check dietary history method	SFA 1st quartile= 7.5% 4th quartile= 16.5%	- No association between SFA and its components with CHD incidence after the variable adjustments (HR= 1.15, 95% CI 0.81, 1.63)
					MUFA 1st quartile= 8.5% 4th quartile= 18.2	- In multivariate analyses, there were no statistically significant interactions for CHD incidence between quartiles of dietary fat intake and sex, diabetes, or age group - Intake of total fat and its components were not associated with CHD incidence after the analysis was controlled for other MUFA: HR (95% CI) = 1.23 (0.86, 1.76) PUFA: HR (95% CI) = 1.18 (0.81, 1.71) Trans fat: HR (95% CI) = 1.21 (0.85, 1.74)
					PUFA 1st quartile= 3.5% 4th quartile= 9.9%	
					Trans fat 1st quartile= 0.9% 4th quartile= 3.9%	
Finland	Virtanen et al. (2014)	Prospective cohort study - to examine the associations between dietary fatty acids with risk of CHD - 21.4 years of follow up	N= 1981 Age: 42-60 years Sex: Male CHD cases: 382	4-day food recording	SFA 1st quantile = 13.4% 4th quantile= 22.8%	- No association between SFA consumption and CHD risk (HR=1.05; 95% CI 0.70-1.57)
					MUFA 1st quantile = 8.6% 4th quantile= 13.4%	- MUFA intake was associated with increased risk (HR= 1.40, 95% CI 0.90-2.20)
					PUFA 1st quantile = 2.9% 4th quantile= 6.3%	- PUFA was associated with decreased risk of fatal CHD (HR= 1.00, 95% CI 0.64-1.56)
					Trans fat 1st quantile = 0.7% 4th quantile= 1.5%	- Trans fat intakes were not associated with CHD risk (HR= 0.94, 95% CI 0.70–1.26)
US	Oh et al. (2005)	Prospective cohort study - to examine the associations between dietary fat and specific types of fat with risk of CHD among US female initially free of CVD and diabetes - 20 years of follow up	N= 78,778 Age: 30-55 years Sex: Female CHD cases: 1766	FFQ	SFA 1st quantile = 10.1% 5th quantile= 17.6%	- No significant association between consumption of SFA with CHD (RR= = 0.97, 95% CI 0.74-1.27)
					MUFA 1st quantile = 10.6% 5th quantile= 18.0%	- MUFA were not statistically significant predictors of CHD after adjustments (RR= 0.82, 95% CI 0.62-1.10)
					PUFA 1st quantile = 4.1% 5th quantile= 7.4%	-PUFA intake was significantly associated with lower risk of CHD (RR= 0.75, 95% CI 0.60-0.92)
					TRANS FAT 1st quantile = 1.3% 5th quantile= 2.8%	- A significant direct association between consumption of trans-fat and CHD risk was found (RR= 1.33, 95% CI 1.07-1.66)

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Table II: General characteristics and important findings of included studies

Country	Author (Year)	Types, Purpose of the study & Duration of follow up (years)	Participants' characteristic	Dietary assessment method	The intake of fat	Findings
US	Hu et al. (1997)	Prospective cohort study - to examine the associations between dietary intake of specific types of fat and risk of CHD - 14 years of follow up	N= 80,082 Age: 34-59 years Sex: Female MI cases: 658	FFQ	SFA 1st quantile= 10.7% 5th quartile= 18.8%	- No association between SFA and CHD risk (RR= 1.07, 95% CI 0.77–1.48)
					MUFA 1st quantile= 11.0% 5th quartile=19.3%	- No association between MUFA and CHD risk (RR= 0.95, 95% CI 0.64–1.39)
					PUFA 1st quantile= 2.9% 5th quartile= 6.4%	- PUFA was not associated with CHD risk (RR= 0.68, 95% CI 0.53–0.88)
					TRANS UNSATURATED FAT 1st quantile= 1.3% 5th quartile= 2.9%	- There is a significant association between trans unsaturated fat and CHD risk (RR= 1.53, 95% CI 1.16–2.02)
US	Ascherio et al. (1996)	Prospective cohort study - to examine the association between fat intake and the incidence of coronary heart disease in men of middle age and older - 6 years of follow up	N= 43,757 Age: 40-75 years Sex: Male CHD cases: 505	FFQ	SFA 1st quantile= 7.2% 5th quartile= 14.8%	- SFA was correlated with increased myocardial infarction risk, but the correlation reduced after fibre intake adjustment (RR= 0.96, 95% CI 0.73 to 1.27)
					Trans Fat 1st quartile= 0.8% 5th quartile= 1.6%	- There was a positive association between trans fatty acids consumption with risk of myocardial infarction after adjustment for age and standard risk factors but reduced after further adjustment for fibre intake (RR= 1.21, 95% CI 0.93 to 1.58)
US	Li et al. (2015)	Prospective cohort study - to study associations between dietary saturated fats compared with unsaturated fats and different sources of carbohydrates in relation to CHD risk - 24-30 years of follow up	N=127,536 Age: 30-75 years Sex: Both CHD cases: 7667	FFQ	SFA Male: 1st quantile = 7.4% 5th quantile= 13.6% Female: 1st quantile= 9.6% 5th quantile=16.9%	- No association between SFAs with CHD among males (HR= 0.93, 95% CI 0.82–1.05)
					MUFA Male: 1st quantile = 9.0% 5th quantile= 15.1% Female: 1st quantile= 10.4% 5th quantile= 17.3%	- MUFAs were not associated with CHD (HR=1.00, 95% CI 0.87–1.13)
					PUFA Male: 1st quantile = 5.2% 5th quantile= 7.5% Female: 1st quantile= 4.9% 5th quantile= 7.4%	- Higher PUFA intake was associated with a lower risk of CHD (HR= 0.80, 95% CI 0.73–0.88)
					Trans fat Male: 1st quantile = 0.7% 5th quantile= 1.9% Female: 1st quantile= 1.1% 5th quantile= 2.6%	- Trans-fat intake was significantly associated with an increased risk of CHD (HR= 1.20, 95% CI 1.09–1.32)

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Table II: General characteristics and important findings of included studies

Country	Author (Year)	Types, Purpose of the study & Duration of follow up (years)	Participants' characteristic	Dietary assessment method	The intake of fat	Findings
Norway	Puaschitz et al. (2015)	Prospective cohort study -to examine the association between self-reported dietary SFA intake and risk of subsequent coronary events and mortality in patients with coronary artery disease - 4.8 years of follow up	N= 2412 Age: 27-86 years Sex: Both CHD cases: 292	FFQ	SFA 1st quartile= 8.4% 4th quartile= 15%	- Consumption of SFA was not significantly associated with coronary risk events (RR= 0.83, 95% CI 0.59, 1.16)
US	Hu et al. (2002)	Prospective cohort study - To examine the association between fish and long-chain omega-3 fatty acid consumption and risk of CHD in women - 16 years of follow up	N= 84,688 Age: 34-59 years Sex: Both CHD cases: 1513	Semi quantitative FFQ	Median intake of Omega-3 Fatty Acid (% of energy) 1st quintile= 0.03 5th quintile= 0.24	- There was a significant inverse association between dietary omega-3 fatty acids consumption and CHD risk. This inverse association stronger for fatal CHD than for nonfatal MI (RR= 0.69, 95% CI 0.57-0.84)
Norway	Manger et al. (2010)	Prospective cohort study - to examine the relation between dietary intake of n–3 LCPUFAs or fish and risk of future coronary events or mortality in patients with well-characterized CAD. - 4.75 years of follow up	N= 2412 Age: >18 years Sex: Both Coronary event: 292	FFQ	n-23 LCPUFAs (g) 1st quartile= 0.58±0.29 4th quartile= 2.64±1.18 * Mean ± SD	- There was no dose-response relation between quartiles of n–3 LCPUFAs (based on intake as percentage of total energy) and coronary events or separate endpoints (HR= 0.95, 95% CI 0.69, 1.31)
Nether-lands	Oomen et al. (2001)	Prospective cohort study - to examine whether dietary alpha-linolenic acid intake was inversely associated with risk of CAD. - 10 years of follow up	N= 667 Age: 64-84 years Sex: Male CHD cases: 98	Cross-check dietary history method	The mean (± SD) daily intake of α-linolenic acid was 1.32 ± 0.47 g	No association between consumption of α-linolenic acid and the CAD risk (RR= 1.68, 95% CI 0.86, 3.29)
Nether-lands	Oomen et al. (2001)	Prospective cohort study - to investigate the association between trans fatty acid intake and risk of CHD in the Zutphen Elderly Study - 10 years of follow up	N= 667 Age: 64-84 years Sex: Male CHD cases: 98	Cross-check dietary history method	Daily mean of trans fat intake, g/day: Year 1985= 10.9±6.3 Year 1995= 4.4±1.7	- Trans fatty acid intake at baseline was positively associated with the 10-year risk of coronary heart disease (RR= 2·00, 95% CI 2·07–3·75)
Denmark	Jakobsen et al. (2008)	Prospective cohort study -to describe the association between R-TFA intake and risk of CHD evaluating both the absolute and the energy-adjusted intake. - 18 years of follow up	N= 3686 Age: 30-71 years Sex: Both	7 day weighed food record	R-TFA intake (g/d) Female Q1= 0.7 (0.3,0.8) Q5= 2.7 (2.3, 3.8) Male Q1= 0.8 (0.4,1.0) Q5= 3.4 (2.8, 4.9)	- There were no overall associations between absolute R-TFA intakes and risk of CHD (HR= 0.98, 95% CI 0.92, 1.05)

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Table II: General characteristics and important findings of included studies

Country	Author (Year)	Types, Purpose of the study & Duration of follow up (years)	Participants' characteristic	Dietary assessment method	The intake of fat	Findings
Italy	Marangoni et al. (2013)	Case-control study -to examine the relationship between MI, whole blood fatty acids and the diet in Italian cohort.	N= 222 Age: 18-70 years Sex: Both Case: 119 Control:103	Semiquantitative FFQ	SFA Mean (SD) Cases: 28.6 (12.6) Control: 28.1(14.6)	- No significant association was detected between SFA and MI risk (OR=2.25, 95% CI 0.96-5.27)
					MUFA Mean (SD) Cases: 38.7(14.5) Control: 38.9(17.4)	- No significant association was detected between MUFA and MI risk (OR=1.95, 95% CI 0.77-4.90)
					PUFA Mean (SD) Cases: 9.3(3.9) Control: 9.2(4.4)	- MI risk significantly and steadily decreased with increasing levels of total PUFA (OR=0.14, 95% CI 0.05-0.40)
Iran	Moghadam et al., (2017)	Case- control study -to evaluate the association between nutrition factors and CHD among Armenians in Yerevan	N= 640 Age: more than 30 years Sex: Both Case: 320 Control: 320	Semiquantitative FFQ	SFA Mean (SD) Cases: 30.1(8) Control: 30.7(8.8)	- No significant association between SFA and CHD risk. (OR=0.84, 95% CI 0.54-1.31)
					MUFA Mean (SD) Cases:21.7(5.1) Control: 22.9(6.4)	- Higher intakes of MUFA were associated with a reduced risk of CHD (OR=0.7, 95% CI 0.45-1.08)
					PUFA Mean(SD) Cases: 13.1(4.5) Control: 15.1(5.6)	- Higher intakes of PUFA were associated with a reduced risk of CHD (OR=0.22, 95% CI 0.14-0.35)

of PUFA and MUFA is associated with a reduced rate of CVD.[9] In this review, only one study showed that gender may influence the association of SFA and risk of CHD. A study showed a positive association between SFA and CHD risk, in which the association was only found among women and no overall association was found among men.[21] There may be due to the production of postprandial hypertriglyceridemia by fat that increases triglycerides. High triglycerides level is one of the CHD mortality risk factors that is stronger in women compared to men.[21] This finding is in line with the study done by Naska et al. which found out that lipoprotein metabolism is faster approximately two-fold in women compared with men, due to the stimulatory effects of estrogen in women and the inhibitory effects of androgen in men, thus, a greater increment in CHD risk is associated with women.[32] However, other study showed no association between SFA and CHD in both sexes.[14] Besides, findings from a study done by Hu et al. showed that intakes of longer-chain SFA are associated with a small increase in CHD risk which may be related to postprandial responses to these fatty acids.[13] On the contrary, this review found an inverse association between SFA intake and risk of CHD, which could be due to the replacement of other macronutrients to maintain energy balance. A recent study also suggests that substituting SFAs with PUFAs instead of MUFAs or carbohydrates prevents CHD over a wide range of intakes.[23]

There were two studies that reported a positive association between MUFA and risk of CHD. Conversely, one study reported a negative association between MUFA and CHD incidence and other prospective studies of MUFA intake and CHD risk had a different conclusion, in which no association with higher intake of MUFA. An analysis by Posner et al. showed that a higher level of MUFA intake was associated with increased CHD mortality and morbidity in the younger male cohort.[22] These findings were contradicting with previous studies which showed a beneficial effect on CHD.[20] This might be due to the different sources of MUFA, in which in Posner et al. study, MUFAs were obtained from animal food products which high in both MUFA and SFA.[22] Meanwhile, it was suggested that previous studies obtained MUFA largely from vegetable sources.[22] Another recent study suggested that MUFAs were associated with an increased risk of CHD which might be due to underlying hepatic de novo lipogenesis activation.[33] However, Virtanen et al. explained that there was a probability that the incorporation of two highly correlated variables (PUFA and MUFA) in the same model has led to the greater CHD death risk.[17] Due to these mixed findings, further research on the impact of MUFA on the risk of CHD is highly required.

The majority studies reported an inverse association between PUFA and the risk of CHD. Virtanen et al. pointed out that PUFA has beneficial effects to reduce CHD risk factors, including blood total/high-density lipoprotein cholesterol ratio, insulin resistance, blood pressure, and vascular function.[17] Besides, higher PUFA intake will reduce the thickness of carotid artery wall. It is in line with the findings of a meta-analysis of randomised clinical trials (RCTs) which showed that each 5% energy greater in PUFA consumption in place of SFA reduced CHD risk by 10%.[34] Omega-3 and omega-6 are the two most biologically important PUFA classes. Several potential mechanisms of omega-3 fatty acids intake in reducing CVD risk are by lowering triglyceride levels, increasing HDL, lower resting blood pressure, decrease aggregation of platelet, reduce atherosclerosis, and reduce inflammation.[35] On the other hand, although many studies suggested that omega-6 fatty acid intakes reduce CHD risk, there was a concern that high omega-6 fatty acids intake might have a bad effect on cardiovascular health. However, the latest meta-analysis claimed that an intake of omega-6 fatty acid within the range as recommended by the AHA was not associated with CVD risk.[36]

In contrast, positive associations between intake of trans fatty acid and risk of CHD were reported in many studies in this review. The highest RR was 2.00 (95% CI 2.07, 3.75) which was related to the 10-year risk of CHD.[27] The findings were consistent with the result of most previous studies.[37] Trans fatty acid can contribute to increased risk of CHD by increasing the ratio of LDL: HDL, increased ratio of apolipoprotein B: apolipoprotein A, increased cholesterol content in both LDL and HDL particles in comparison to SFA, increased plasma triglyceride levels, which adversely affects the essential fatty acid metabolism.[38,39]

Apart from the biological variance such as gender differences, the inconsistency of findings between studies might be due to different methodological approaches. One of the most important reasons could be the self-reported method of dietary assessments. All studies in this review reported dietary intake based on self-reported measurements which are at risk of bias. Participants' inability to accurately recall their food intake could be the source of errors as it might limit the validity of the generated information.[32] Furthermore, the effect of changes in dietary habits could not be assessed if only baseline information regarding dietary habits was available.[21] It was noted that the majority studies in this review used a food frequency questionnaire (FFQ) as it can assess long-term dietary intakes in a relatively simple, cost-effective and time-efficient manner. Although FFQ might produce measurement error related to methodology, however, it is proven to be a valid method to assess dietary intake particularly in a large sample size.[40] Besides dietary factor, variability in lifestyle habits such as physical inactivity, intake of alcohol, cigarette use and waist circumference are well known to be strongly correlated with increased risk of CHD and may confound the results and explain the variation between studies, however, it was not reported in individual study. In addition, the difference in the duration of follow-up might produce inconsistent outcomes among these studies. Moreover, demography differences among different study population will lead to divergence in habitual diet which affect the findings of study.

CONCLUSIONS

In conclusion, this scoping review of nineteen observational studies found conflicting results regarding the association between types of fatty acid with the risk of CHD. The discrepancies of the results among the studies might be due to many factors particularly the inter-studies variability of biological factors such as age and gender of participants. Methodological inconsistencies may also contribute to the

divergence of findings between studies. Nevertheless, more than 50% of the studies suggested no association between SFA and MUFA intake with CHD, whilst 58% suggested an inverse association between PUFA intake with CHD. Sixty-seven percent of the studies showed a positive association between trans-fatty acid with CHD. Overall, this review may provide new insights into current dietary guidelines for CHD prevention. More robust longitudinal prospective research is required to evaluate the association between dietary fat and CHD risk to confirm these findings.

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SHORT COMMUNICATION

Induction of labour survey: A need for standardisation and/or change in practice

Zahar Azuar Zakaria, MMed

Obstetrics & Gynaecology Department, Hospital Kemaman, Chukai, Terengganu, Malaysia

SUMMARY

Induction of labour is one of the most common antepartum intervention. There are numerous methods available but the most commonly used in Malaysian public hospital is the intravaginal dinoprostone. This survey highlighted the various practices of using dinoprostone for different group of pregnant women which are unfortunately, not supported by robust clinical evidence. As such, it calls for futher studies to allow future practice standardization. Alternatively, the use of misoprostol for induction of labour, which has better data profile, should also be considered.

INTRODUCTION

Induction of labour is one of the most common interventions in obstetric practice. The pharmacological agents approved for cervical ripening in the Ministry of Health Malaysia (MOH) hospitals are, the vaginal the prostaglandin E2 (dinoprostone 3mg tablet) and prostaglandin E1 analogue (gemeprost 1mg pessary), where the former is used for term or near-term pregnancy.

The Royal College of Obstetricians and Gynaecologists in 2001 and the National Institute for Health & Care Excellence (NICE) in 2008 recommended a maximum total dose of 6mg of prostaglandin E2 to be used for all women.[1,2] This was; however, a grade C recommendation and it was largely based on the recommendation by the drug manufacturer. However, various protocols are currently being used by different centres including dosing beyond the recommendation. This study was initiated to determine the labour induction methods and protocols use by the obstetric services in public hospitals across the country.

MATERIALS AND METHODS

The hospitals under the MOH Malaysia with specialist obstetric services were identified in June 2019. A questionnaire. accompanied by a cover letter stating the intention of the survey were posted to the Heads of Obstetrics and Gynaecology Department of those hospitals. An empty envelope with a stamp, addressed to the author was also supplied for the respondents to return the completed survey questionnaire. The information sought in this survey were the methods of induction, the starting and maximum dose of dinoprostone tablet for different groups of women; the primiparas, multiparas (2nd till 5th pregnancy), grand multiparas (>5 previous pregnancies) and those with a history of caesarean section (CS). The respondents were also asked about the preferred induction method for women with previous CS.

RESULTS

The questionnaire was posted to 48 hospitals, out of which 36 completed survey forms were returned. These involved nine state hospitals, 22 major and 5 minor specialist hospitals including those from Sabah and Sarawak.

All centres used Prostin® (Pfizer, NY, USA), a form of prostaglandin E2 or dinosprostone tablet 3mg and one also add dinoprostone gel in its induction of labour protocol. Twenty-six centres also used non-pharmacological methods such as laminaria tent osmotic dilator, Dilapan® (Gel-Med International, Prague, Czech Republic), and membrane sweeping.

All hospitals, except one, used 3mg tablet for cervical ripening in primiparous women, but the dosage for multiparas, grand multiparas and women with previous history of CS varied. Some did not use PGE2 in grand multiparas and women previous CS but opted for non-pharmacological method only (Table I).

In primiparas, the most common maximum dose use was 9 and 12mg. One centre used only a single dose of 3mg while another was in the opposite end of the spectrum, applying up to 15mg (5 tablets). In multiparous women the maximum PGE2 dose was more varied with 9mg being the most commonly used (27.7%). More than two-third of the surveyed hospitals used no more than 6mg of PGE2 for grandmultiparous women with only two went beyond this (Table II). Due to the risk of uterine scar dehiscent occurring, two-third of the hospitals used half-tablet for women with previous CS, and 30% used non-pharmacological methods only (mechanical or membrane sweeping) (Table II).

In total, about 80% of the surveyed hospitals used >6mg of prostaglandin in primiparous women. Among those that used the 3mg tablet for multiparas and grand multiparas, 70.8% and 50.0% respectively, exceeded the total of 6mg. While majority of the hospitals preferred either the mechanical methods or half tablet of dinoprostone for women with previous CS, seven used the 3mg tablet including one centre using up to a total of 9mg (Table II).

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Corresponding Author: Zahar Azuar Zakaria
Email: zazuarz@yahoo.co.uk

Table I: Number of hospitals (n) and labour induction method used according to the parity and past history of caesarean delivery

Method	Primipara (n)	Multipara (n)	Grand multipara (n)	Previous CS (n)
Dinoprostone 1.5 mg	1	12	26	22
Dinoprostone 3.0 mg	35	24	4	3
Other methods only	0	0	6	11

Table II: Number of hospital (n) and maximum dinoprostone dose used according to the parity and past history of caesarean delivery

Dose	Primiparous (n)	Multipara (n)	Grand multipara (n)	Previous CS (n)
1.5	-	-	1	6
3.0	1	1	-	-
3.0 (2 X 1.5 mg)	-	2	5	-
4.5 (3 X 1.5 mg)	-	7	14	12
6.0 (2 X 3.0 mg)	6	6	8	6
6.0 (4 X 1.5 mg)	-	3	-	-
9.0 (3 X 3.0 mg)	17	10	1	1
12.0 (4 X 3.0 mg)	11	6	1	-
15.0 (5 X 3.0 mg)	1	1	-	-
Total	36	36	30	25

DISCUSSION

A survey conducted in the United Kingdom had shown that 84.6% of the obstetrics units exceeded the recommended maximum dose.[3] This survey found a similar figure, where 83.3% of the local public hospitals used more than 6 mg dinoprostone, or 77%, 70% and 50% for primiparas, multiparas and grand multiparas respectively, for labour induction.

The use of half tablet in women of high parity or with uterine scar derived from the presumed increased the risk of uterine rupture. Studies showed that dinoprostone at 1.5mg even for grand multiparas is safe, but the efficacy and safety of 3mg dosing are not clear.[4] In women with uterine scar from previous CS, the recommendations on labour induction with vaginal prostaglandin are conflicting. A French and NICE guideline add a caution for such practice while a Canadian document advised against it.[2,5,6] Yet the above data showed that 70% of the hospitals were using dinoprostone, singly or in combination with non-pharmacological methods, at full or half dose for this group of women.

In general, this survey highlights the diversity in the protocols of induction of labour among public hospitals in Malaysia especially the dinoprostone dosage, reflecting the inadequacy of data. Thus, this calls for further studies especially of Malaysian population to enable a standard to be drawn.

On another aspect, the dinoprostone is now largely being superseded by another prostaglandin preparation, misoprostol, which has the advantage of being cheaper, easier to store, having various routes of administrations and multiple peripartum indications. Meta analysis had shown that misoprostol is indeed superior to dinoprostone for labour induction.[7,8] Unfortunately, in Malaysia, it is not approved to be used in pregnancy. But with the latest evidence, including a recommendation by an international body, considerations should be given to review the obstetrics use of misoprostol in the country.[9]

CONCLUSIONS

The marked difference in the practices of labour induction among the public hospitals in Malaysia exposes the lack of data especially the efficacy and safety of using different dosage of vaginal dinoprostone. More evidence on dinoprostone dosing should be sought, or the use of misoprostol, which has more robust data profile, should be considered.

CONFLICT OF INTEREST

The author reports no conflict of interest.

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Potential of smartphone enabled otoscopy for teleconsultation and teaching

Krishnan Rajam, FRCP[1], Shivali Shamsher, MD[2], Narayanan Prepageran, FRCP[3]

[1]Family Medicine, Unit, Faculty of Medicine, Asian Institute of Medicine, Science and Technology (AIMST) University, Bedong, Kedah, Malaysia, [2]Anaesthesia Unit, Faculty of Medicine, Asian Institute of Medicine, Science and Technology (AIMST) University, Bedong, Kedah, Malaysia, [3]Department of Otorhinolagyngology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur

SUMMARY

The smartphone enabled otoscope (SEO) provides an opportunity for telemedicine and enhancing teaching of otoscopy. We describe our preliminary experience with the use of one such inexpensive device bought from an online store. It is a simple and feasible procedure which patients can perform on themselves (or guardians on their wards) after minimal training. The resolution of the image is adequate for follow up through teleconsultation. It is also a good teaching tool as it enables the sharing of views.

Medical technology has come a long way since the invention of stethoscope and the current pandemic has accelerated the widespread use of telemedicine and ever-advancing medical innovation. One such innovation is the smartphone enabled otoscope (SEO) which provides an accessible and cost-effective way of ear examinations. Meng et al reported a series of patients who performed otoscopy on themselves and relayed the images / video to the doctors who successfully monitored them.[1] We describe our preliminary experience with one such device.

Fig. 1: Patient pulls the ear backwards while inserting the otoscope and monitors the image on the smartphone.

The SEO is a small camera with LEDs and is available from online stores as "boroscope", "endoscope" or "otoscope". They are advertised for use in pipelines, small holes, industries, etc. where direct visual access is difficult or not possible. The diameter of the cameras varies from 5 to 8 mm. The SEOs come in various price ranges (from USD 5-25 each), camera resolution and lengths. Some of them are deemed waterproof. The images (photos or video) are seen or stored on a smart phone with appropriate software. The brightness of the light can be adjusted. Some of them are equipped with a small hook and magnet to enable removal of small objects. Power supply is 5V via the USB from the smartphone.

After reviewing many models, the first author obtained one SEO made of composite material based on the diameter of the camera. The camera properties were as follows: diameter 5.5 mm, resolution 640 x 480 pixels, frame rate 30/second, focal length of 2 cm, JPEG photo image and AVI video format, 6 LEDs with adjustable brightness.

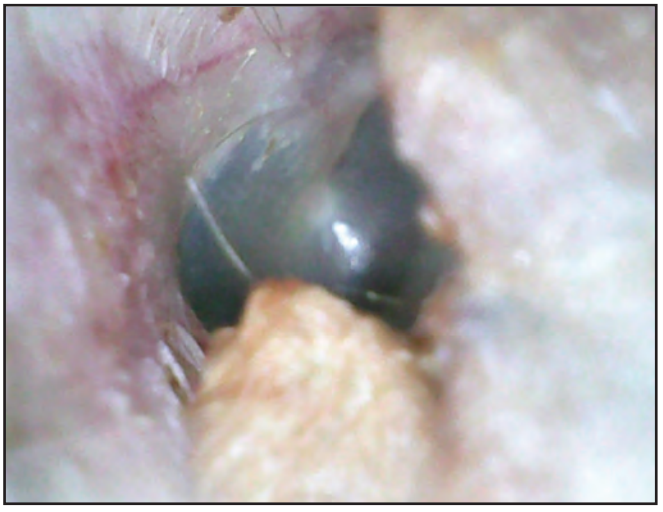

Fig. 2: Image of an ear with wax.

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Corresponding Author: Shivali Shamsher
Email: shivalibernard@gmail.com

Patients with common ear conditions requiring otoscopy were selected in a general practice setting. Approval was obtained from the institution's ethics committee.

The first author ensured that the device was not flimsy and that the small parts at the end of the tube were fused well. He practised inserting the device on himself on many occasions. In order to convince patients, he demonstrated the procedure on himself. Patients who consented to this procedure were instructed to slowly and carefully insert the device while pulling the ear with the other hand (Figure 1). The author and the patient monitored the image on the smartphone throughout the procedure. The resolution of the image was sufficient for initial screening for common abnormalities (Figure 2). The device was cleaned with spirit after use. The author also attempted to cover the tip of the device with a transparent finger glove for safety and hygiene purposes. The quality of the image was not affected. When needed a regular otoscope was used for further examination.

The major advantage of this device is that teleconsultation is facilitated by training patients to perform the procedure at home and transfer the images to their doctors. They can also be reassured visualizing the images themselves. Patients suitable for teleconsultation could include those requiring follow up after procedures like tympanoplasty as shown by Don et al in their study.[2]

An earlier study reported the sensitivity and specificity of the SEO to be 87.8% and 80%, respectively.[3] Parents can also be taught to carry out the procedure on their children and the images can be relayed to their doctors.[2]

The smartphone enabled otoscopy enables sharing of views and was shown to be a better teaching tool than conventional otoscopy.[4] Hence, it can be used to teach initial approaches to otoscopy. We emphasize that the quality and safety of the device should be ensured. Wireless SEO models with higher resolution cameras offer better pictures but may be more expensive.

In summary, the SEO is a feasible system which facilitates teleconsultation and teaching of otoscopy. Further studies of feasibility of use of SEO for mass screening in remote areas through teleconsultation should be carried out.

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Adjuvant breast radiotherapy outcome in older women: A Malaysian experience

Jasmin Munchar Elias, MBBS[1], Nur Fadhlina Abdul Satar, FRCR[1], Koi Yung Chean, MBBS[1], Rizma Mohd Zaid, MBBS[1], Nurul Atiqah Mat Nasukhat, MBBS[1], Diana Abdul Wahab, PhD[2]

[1]Department of Clinical Oncology, University Malaya Medical Centre, Kuala Lumpur, Malaysia, [2]Department of Applied Statistics, University of Malaya, Kuala Lumpur, Malaysia

SUMMARY

Adjuvant breast radiotherapy is offered to patients with localized breast cancer. We performed a retrospective review of older women receiving adjuvant breast radiotherapy in University Malaya Medical Centre, Malaysia (UMMC) in 2014. Out of 191 women, 23% (43) were 60 years old and above. At a median follow up of 6.6 years, 4.6% (2) had local recurrence and 19% (8) distant metastasis. In a subgroup of low risk older patients with hormone-sensitive, HER2 negative, T1N0 disease, all (3/43) are still alive with no local recurrence. We propose further research for treatment de-escalation in low risk elderly patients.

INTRODUCTION

World Health Organization (WHO) defines the older population as being 60 years old and above.[1] In Malaysia, older women (>60) represent almost 50% of breast cancer patients.[2] Our study investigates University Malaya Medical Centre, Malaysia (UMMC) practice of adjuvant radiotherapy in older women. The use of adjuvant radiotherapy has been shown to reduce locoregional recurrences, halving cancer relapse.[3,4] However, the absolute benefit of radiotherapy in older low-risk women is low. UK PRIME's 5-year local relapse rate was 1.3% post radiotherapy compared with 4.1% without radiotherapy.[4] This article dissects the impact of radiotherapy further on Malaysian population, comparing outcomes with pivotal studies.

MATERIALS AND METHODS

Retrospective review of Electronic Medical Records of patients receiving adjuvant breast radiotherapy in UMMC for the year 2014, aged 60 years old and above. Patients who received palliative radiotherapy for stage IV cancers, or patients with carcinoma in situ were excluded. Median overall survival and local recurrence free survival (LRFS) were calculated. LRFS is defined as the time interval between date of diagnosis and date of local relapse. Overall survival is defined as the time interval from date of diagnosis to date of death, or when censored. The analysis was carried out using SPSS, and Kaplan-Meier survival analysis was used to estimate survival. This study was approved by the Medical Ethics Committee of UMMC (MECID. NO.: 2021511-10131).

RESULTS

In 2014, 191 women underwent adjuvant breast radiotherapy and 23% (43) were over 60 years old;(86%) (37) aged 60-70, 14% (6) 70-80 years old. In this group, most (60%, 26) were Chinese, 23% (10) were Malay and 16% (7) were Indian. At a median follow-up of 6.6 years, 4.6% (2) had local recurrence; both had aggressive disease; stage 3, HER 2 positive, one with grade 3 and another with high Ki-67 index (Table 1). They both represent patients with higher risk locally advanced breast cancer at presentation. The median local recurrence-free survival was 79 months (95% CI 62-76 months) (Figure 1). Of note, all (3/43) low-risk T1N0, ER +, HER 2 - older patients are still alive, with no local recurrence. All patients completed their course of 40Gy in 15 fractions. 18% recorded radiation-induced dermatitis. 19% (8) developed distant metastasis, with aggressive subtypes (Triple Negative, Her2+, Luminal B) and advanced stage at presentation (Stage 3, Luminal A subtype) (Table I). 79% (34) patients are still alive and 21% (9) died at median follow-up of 6.6 years. The median overall survival for this cohort was 80 months (95% CI 65-78 months) (Figure 2). The log-rank test showed no significant difference in overall survival when comparing subtypes of breast cancer, but this is most likely due to small sample size ($p = 0.87$).

DISCUSSION

In 2014, a meta-analysis of 5 randomized trials, whereby 39%were elderly (>70 years old) with T1N0 hormone receptor-positive cancers.[5] It showed the absolute benefit was modest (4.3%) with no overal survival benefit. Our study's results aligned with the meta-analysis. We showed regional recurrence of 4.6% (n=43) which is similar to the pivotal START-A trial (3.5% after 41.6Gy, n=2236).[6]

The limitation of our study is the retrospective study design. Our study defined older women using the age cut off of 60 years old. However, international studies use 65 and 70 years old. According to Department of Statistics Malaysia, average life expectancy for Malaysian women in 2020 is 77.6 years old.[7] In the United Kingdom, average life expectancy for women in 2020 is 82.7 years old.[8] Therefore, higher life expectancy in the UK compared to Malaysia justifies our choice of a slightly lower age cut-off.

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Corresponding Author: Jasmin – Munchar
Email: jasminelias91@gmail.com

Table I: The patient's age, stage at diagnosis and tumor biology.

	Number of patients	Age at diagnosis	Staging (AJCC 7th edition)	Subtype
Local recurrence	1	71	Stage 3	HER 2+
	1	62	Stage 3	HER 2+
Distant metastasis	1	61	Stage 1	Triple-negative
	1	67	Stage 2	Luminal B
	1	61	Stage 2	Luminal B
	1	65	Stage 3	Luminal A
	1	62	Stage 3	HER 2+
	1	61	Stage 3	Luminal B
	1	67	Stage 2	Triple negative
	1	71	Stage 3	Luminal A

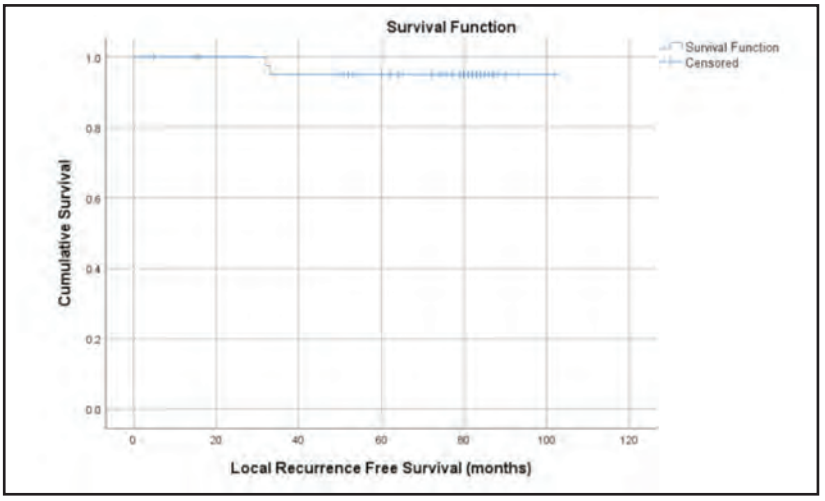

Fig. 1: Local recurrence-free survival in elderly breast cancer patients.

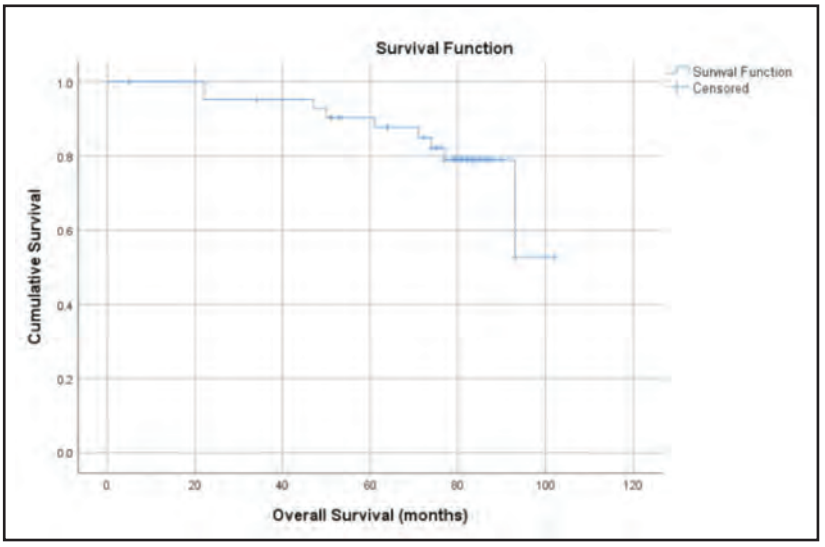

Fig. 2: The overall survival in elderly breast cancer patients.

The PRIME trial looked at the impact of radiotherapy in low-risk elderly patients, their quality of life and health economics.[4] Over 15 months' median follow up, they have concluded that radiotherapy for this population is not a cost-effective treatment, associated with increased breast symptoms and fatigue. Our rates of dermatitis (18%) were lower than the rates in START-B trial (23% in arm 40Gy in 15 fractions).6 This is most likely due to under-reporting in the medical record system.

Subsequent PRIME II trial studied the survival outcome and LRFS in this low-risk population.[9] In this trial, 1326 women aged 65 years or older with early low-risk breast cancer were assigned to either whole-breast radiotherapy or no radiotherapy. A 5-year follow-up analysis showed no differences in regional recurrence or distant metastases. Furthermore, hormone-positive patients only had a 2.4% absolute gain in local relapse.

The PRIMETIME trial investigates the safe omission of radiotherapy following breast-conserving surgery in elderly patients at low risk of recurrence.[10] In this prospective cohort, local recurrence rate for the low-risk cohort was <4% at 5 years. Similarly, our cohort showed a local recurrence rate of 4.6% at 6.6 years of follow up. No recurrence in the low-risk group.

Conversely, we recognize the side effects of radiotherapy. Therefore, an important strategy for the future is de-escalation of treatment in low-risk older women. Intraoperative radiotherapy (IORT) / Accelerated Partial Breast Irradiation (APBI), is a good alternative to external beam radiotherapy in our group of interest, recognized by international guidelines.

In summary, previous studies show a fairly similar local recurrence rate to our study. Due to excellent local control, there is growing evidence to de-escalate treatment by omitting radiotherapy in low-risk elderly patients.

CONCLUSION

Our study shows real-time treatment efficacy of adjuvant radiotherapy with low (4.6%) local recurrence rate, and median overall survival of 80 months. In low risk older women with T1N0 hormone positive breast cancer, the local recurrence rate is 0%. Further work in identifying low risk older women for treatment de-escalation is needed, especially in a resource-limited country such as ours.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The results of this paper have not been published previously, except in abstract format.

AUTHORS' CONTRIBUTIONS

All authors were involved in conception or design, or analysis and interpretation of data, or both. All authors approved the final version of the manuscript.

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COMMENTARY

The ethics of a work strike

Zhong Ning Leonard Goh, MBBS[1], Alexis Ching Wong, MBBS[1], Sean Chern Choong Thum, MB BCh BAO[2], Nor Adriana Muhammad Ridzuan Tan, MBBS[3], Timothy Tsin Jien Cheng, MSOrth[4], Vijay Ganasan, MPM[1], SCoRe Investigators[5]

[1]Sarawak General Hospital, Kuching, Sarawak, Malaysia, [2]Universiti Putra Malaysia Teaching Hospital, Serdang, Selangor, Malaysia, [3]Queen Elizabeth Hospital, Kota Kinabalu, Sabah, Malaysia, [4]Duchess of Kent Hospital, Sandakan, Sabah, Malaysia, [5]SCHOMOS Committee for Research (SCoRe), Kuala Lumpur, Malaysia

The old English saying goes, strike while the iron is hot. The current situation in Malaysia as of writing is as heated as it gets. Faced with the onslaught of the Delta strain of the SARS-CoV-2 virus, coupled with years of underfunding and understaffing of our public healthcare system, Malaysian hospitals are buckling under the immense pressure. Complicating things is the fact that the vanguard of the country's COVID-19 response teams is mainly comprised of junior doctors. Being employed on a contract basis, these junior doctors face job insecurity, a lack of career prospects, and unequal welfare benefits despite their unwavering service and sacrifice for Malaysia.[1]

The Section Concerning House Officers, Medical Officers, and Specialists (SCHOMOS) of the Malaysian Medical Association (MMA) has been actively engaging various governmental bodies and representatives to work towards the resolution of these issues, though progress was admittedly slow. Dissatisfaction with contract employment terms and plummeting morale consequently grew rampant among the ranks, against the backdrop of a rising COVID-19 daily death toll.

To show solidarity with contract doctors, SCHOMOS organised a 12-day Code Black movement from the 1st July 2021, which culminated in Black Monday on 12th July 2021. Participants were encouraged to change their profile pictures on social media to monochrome for the duration of Code Black and wear black clothes to work on Black Monday. The colour black was chosen to symbolise the mourning of the bright young talents whom Malaysia had already lost to other countries, in addition to mourning the slow death of hope for contract doctors in Malaysia.[1,2]

Two weeks later, a group of contract doctors operating independently from SCHOMOS staged a symbolic walkout from the wards on 26th July 2021 to protest the longstanding maltreatment by the Government of Malaysia. The walkout garnered coverage from international and national media outlets, heavily publicising the plight of contract junior doctors in Malaysia. Its organisers have since issued a statement after the event expressing hope that these issues would be resolved soon, failing which there would potentially be a second demonstration sometime in December 2021.

The walkout on 26th July cannot be considered an actual strike despite the initial characterisation as such; it would be better categorised as a peaceful demonstration. Nevertheless, with the promise of a work strike on the horizon, it is perhaps timely for the Malaysian medical fraternity to ponder upon the ethics of the strike – is it ethical for doctors to strike, especially during a pandemic?

Ethics of a strike

Industrial action and strikes are not new to the medical profession and have occurred around the world for various reasons.[3] However, industrial actions are rarely undertaken in Malaysia. The last industrial action organised in the Malaysian healthcare sector would be the work-to-rule led by SCHOMOS in 1983, which successfully pushed the government to recognise HOs as civil servants.[4] This resulted in better remuneration and welfare benefits for the HOs.

The umbrella term of industrial action encompasses several types – from a slowdown at work to an all-out strike. Such movements are generally organised to mount pressure on the authorities and force them to capitulate to stated demands.[5] It usually requires that a third party be adversely affected, so that they act as a proxy in the standoff between the authorities and the workers and increase pressure on the former. In the medical fraternity, this third party would invariably be our patients.[3]

At first glance, conducting an industrial action would appear to directly contravene our code of ethics. *Primum non nocere*, or do no harm, is the oft-repeated mantra drilled into medical students from their first day of medical school. Any form of industrial action would require doctors to impose major inconveniences on their patients. In the case of work strikes, skeleton crews would be severely limited in their capability to respond to medical emergencies. Such industrial actions would therefore, in theory, result in spikes in patient mortality and morbidity rates. It would then seem that going on strike is morally wrong. Studies into healthcare workers' strikes in other countries have however demonstrated the contrary – there were no significant differences in mortality rates as a consequence of the strikes.[3,6]

Nevertheless, strikes in the aforementioned studies did not occur during crises such as the current COVID-19 pandemic. At present time in Malaysia, even after roping in doctors at all levels of training (including house officers), hospitals in the latest pandemic epicentre of the Greater Klang Valley are still finding themselves severely shorthanded.[7] A work strike

This article was accepted: 19 September 2021
Corresponding Author: Zhong Ning Leonard Goh
Email: LGZN92@gmail.com

by doctors in our Malaysian public hospitals at this critical juncture would be catastrophic.

Proponents of a strike argue that it is precisely because of the expected devastating consequences that an industrial action conducted now would have the greatest chance of success. Their supporters go on further to argue that in the long run, the failure to act now is equivalent to allowing our public healthcare system to be undermined further by the ongoing political squabbling, doing more harm cumulatively. Only something as drastic as a strike, they opine, would be able to force the authorities to focus on urgent rehabilitation of our healthcare system. As advocates of our citizens who depend on public hospitals to receive medical care, the organisers and supporters perhaps view it as their duty to strike.[8] The sensationalism of a strike in the Malaysian setting also aids in dramatically increasing public awareness and discourse regarding our healthcare system.[9]

The ethics of a strike therefore seem to boil down to a cost-benefit analysis – will the benefits outweigh the immediate dire repercussions of a strike during this pandemic? If the evaluation is limited to the short-term, a strike would be unethical. Yet from the long-term perspective, if the strike provides an impetus for extensive reform in our healthcare system, then it may be viewed to be ethical.[6] We would only be able to comment definitively on hindsight, with the benefit of the 20/20 vision it affords.

That said, strikes are almost always executed as a last resort after diplomatic talks have failed or come to an impasse.[3] SCHOMOS and MMA remain steadfast in their attempts to engage the government in moving towards swift resolution of these matters. It is the fervent hope of the authors that these attempts prove successful, to avoid the need for a strike by this independent group.

What remains undiscussed are the legal considerations and ramifications of a strike. The authors feel that these aspects are best left to the advice of legal experts.

The need for urgent healthcare reform

Regardless of the individual's stance on a work strike, it remains uncontentious that our healthcare system needs major reform urgently. Our specialist-to-population ratio of 3.23:10,000 is drastically lower than that of 22.4:10,000 in member countries of the Organisation for Economic Co-operation and Development.[2] At the same time, we can expect increasing reliance on the public healthcare system for specialist care, with more Malaysians slipping below the poverty line.

The first step towards increasing that ratio would be to retain our talents and prevent brain drain. That can only be achieved via revising our healthcare financing policies to ensure adequate funding of our public hospitals and better treatment of the backbone of the entire system – our healthcare workers.[10]

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CASE SERIES

Case series of COVID-19 with spontaneous pneumomediastinum

Nur Munirah Ibrahim, MRCP, Suresh Kumar Chidambaram, MRCP

Infectious diseases Unit, Department of Medicine, Hospital Sungai Buloh, Malaysia

SUMMARY

Spontaneous pneumomediastinum is a rare condition in viral pneumonia. However, it can arise spontaneously in COVID-19 patients with no other risk factors. Here we present four cases of spontaneous pneumomediastinum in patients with COVID-19 pneumonia with no other precipitating factors.

INTRODUCTION

Pneumomediastinum describes the presence of free air in the mediastinum. They usually occur due to presence of underlying risk factors such as direct trauma, airway mucosal disruption or use of positive pressure ventilatory support. In COVID-19 pneumonitis they can arise without any underlying risk factors. Most of the time they resolve with conservative management. Rarely, propagation and accumulation of air within the enclosed mediastinum, can progress to tension pneumomediastinum, with cardiorespiratory compromise. In COVID-19, presence of pneumomediastinum may signify worsening of disease and indicates closer monitoring of the patients.

CASE REPORTS

Case 1

A 45-year-old male non-smoker with underlying hypertension and obesity (BMI 34.3) presented with fever, dry cough and anosmia. At day 5 of illness his COVID-19 PCR turns positive. Due to increasing cough and shortness of breath he presented to the covid-19 assessment centre and was noted to have respiratory rate of 26 with oxygen saturation of 90% at rest, saturation improved to 98% on facemask oxygen 5L/min which then reduced further to nasal prongs oxygen 3Lmin upon admission to ward. His CXR showed infiltrates at peripheral of the lungs and CRP was 7 mg/dL. He was started on steroids and thromboprophylaxis and remained stable on oxygen supplementation. On day 6 of admission patient remained comfortable on nasal prongs oxygen 2L/min but complained of tightness over his neck upon coughing. On examination there was crepitus over bilateral supraclavicular regions. Repeated CXR showed surgical emphysema above the clavicles, however, the view was limited. It also showed worsening ground glass opacities at peripheral and basal regions of the lungs and D-dimer was markedly raised. CT pulmonary angiogram (CTPA) done showed right segmental pulmonary embolism, ground-glass opacities predominantly in peripheral distribution and perilobular densities of both lungs. There was also pneumomediastinum and pneumopericardium which extended into soft tissue of the anterior neck region. Linear lucency was seen at the posterior wall of the trachea at T1/T2 vertebral level, suspicious of tracheal wall defect.

A cardiothoracic specialist was consulted, in view of patient was not in respiratory distress and saturating well on nasal prongs oxygen, conservative treatment with oxygen supplementation and observation was suggested. Antibiotics was commenced in view of rising CRP and NLR ratio, treatment dose of anticoagulants for pulmonary embolism given and steroids were continued. Patient was observed for another 5 days in ward. Surgical emphysema over neck reduced, inflammatory markers came down and patient remained comfortable. He was then discharged with oral anticoagulants to complete for 3 months. Repeat CT Thorax one week after discharge showed healing tracheal defect with resolved pneumomediastinum and pneumopericardium.

Case 2

A 38-year-old man, non-smoker with BMI of 30 presented on day 9 of illness with fever and cough. His COVID-19 PCR was positive on day 2 of symptoms. On admission he was noted to have oxygen saturation of 93% under room air which picked up to 98% under nasal prongs oxygen 3L/min. CXR on admission shows minimal left basal ground glass opacities and CRP was 8.3 mg/dL. He was started on steroids and thromboprophylaxis. On day 4 of admission he deteriorated needing facemask oxygen 10L/min. Repeated CXR showed worsening opacities especially over right basal region. CTPA done showed extensive surgical emphysema involving the subcutaneous and intermuscular layer of the anterior and posterior chest wall and presence of pneumomediastinum and pneumopericardium. Scattered ground glass densities with peripheral and basal predominance seen and perilobular densities with arch-like patterns was noted in both lungs. There was no pulmonary embolism or pneumothorax seen.

During the next 5 days in the ward, patient improved with medical treatment: steroids, anticoagulations and oxygen support. There was reducing oxygen requirement, reducing inflammatory markers and improving chest radiograph. No repeat CT thorax done prior to discharge and the patient was seen in clinic 3 weeks later feeling better with improving CXR.

Case 3

A 33-year-old man with no known co-morbidities came in at day 7 of illness with fever, cough and shortness of breath. His COVID-PCR turns positive at day 3 of illness. He is a non-smoker and had a BMI of 27.4. Upon assessment his

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Corresponding Author: Nur Munirah Ibrahim
Email: munirah_ibrahim@yahoo.com

Table I: Blood parameters and oxygen requirements of case 1 according to day of admission

DOA	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Date	10/6/21	11/6/21	12/6/21	13/6/21	14/6/21	15/6/21	16/6/21	17/6/21	18/6/21	19/6/21
CRP (mg/dL)	7	6.8	4.4	3.9	3.8	8.1	19.0	12.7	7.1	3.6
Ferritin (ng/mL)							1210	1278		
D-dimer (ng/mL)							21213			
PCT(ng/mL)							0.18			
WCC	3.97	3.69	4.28	6.94	6.6	5.4	4.97	7.13	11.46	7.35
ALC	0.7	0.72	0.91	0.86	0.69	0.79	0.53	0.64	0.93	0.87
NLR	4.5	3.7	3.2	6.4	8.1	5.5	7.5	9.2	10.6	6.9
*O2	FM 5L	NP 3L	NP 3L	NP 3L	NP 3L	NP 3L	NP 3L	NP 3L	NP 3L	NP 3L

*Oxygen requirement: NP: Nasal prongs, FM: Facemask, RA: Room air
DOA: Day of admission, CRP: C-reactive protein, PCT: Procalcitonin, ALC: Absolute Lymphocyte counts, NLR: Neutrophils to Lymphocyte ratio, WCC: White Cell Counts

Table II: Blood parameters and oxygen requirements of case 2 according to day of admission

DOA	Day 1	Day 3	Day 4	Day 5	Day 6	Day 7
Date	14/6/21	16/6/21	17/6/21	18/6/21	19/6/21	20/6/21
CRP (mg/dL)	8.3	3.8	6.0	3.2	1.3	1.0
Ferritin (ng/mL)		1441				
D-dimer (ng/mL)						561
PCT (ng/mL)		0.12				
WCC	4.73	12.9	16.73	17.3	17	17.49
ALC	0.57	0.75	0.81	1.07	1.23	0.99
NLR	7	15.4	18.9	14.5	12.3	15.7
*O2	NP	NP	FM 10L	FM 10L	FM 8L	FM 8L

*Oxygen requirement: NP: Nasal prongs, FM: Facemask, RA: Room air
DOA: Day of admission, CRP: C-reactive protein, PCT: Procalcitonin, ALC: Absolute Lymphocyte counts, NLR: Neutrophils to Lymphocyte ratio, WCC: White Cell Counts

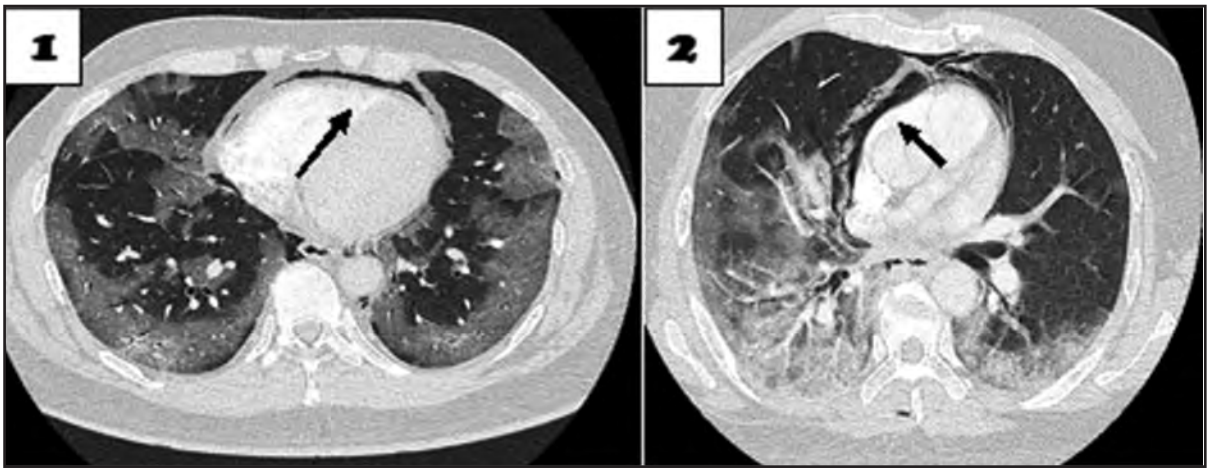

Fig. 1&2: CT pulmonary angiogram of case 1 and 2 respectively showing pneumomediastinum and pneumopericardium.

respiratory rate was 28/min and saturation under room air was 88% which picked up to 95% under nasal prongs oxygen 3L/min. In the ward he was started on steroids and anticoagulants and stable on oxygen supplementation.

On day 6 of admission, patient was getting slightly more tachypnoiec, increasing oxygen requirement with worsening inflammatory markers and CXR. High resolution CT thorax (HRCT) was done and it showed diffused ground glass opacities in central and peripheral distribution bilaterally, scattered consolidation in bilateral lower lobes and minimal perilobular densities with arch like pattern in bilateral lower lobes. Antibiotic was started, steroids was continued and thromboprophylaxis was increased to treatment dose. Supportive treatment with oxygen was continued. Patient subsequently improved clinically with reducing oxygen

requirement over the next few days. However, after 12 days of admission, although clinically improving, the patient had difficulty weaning off oxygen and d-dimer noted be raised. CTPA was done to rule out pulmonary embolism, which was reported as patchy ground glass opacities in central and peripheral in distribution in both lungs, patchy consolidation in both lungs mainly at the peripheries and a few perilobular densities with arch like pattern seen in both lung peripheries. Pneumomediastinum was seen extending to the superior, anterior and posterior mediastinum. No tracheal defect was seen. Bilateral subsegmental pulmonary embolism seen.

Although ground opacities on CT thorax was worsening with presence of pulmonary embolism and pneumomediastinum, patient was clinically stable with low oxygen requirement. Anticoagulant and conservative supplemental oxygen continued. Patient eventually was able to saturate under room air and was discharged home with oral anticoagulant. He was seen in clinic 2 weeks later feeling better with improving chest x-ray.

Case 4

A 33-year-old gentleman, non-smoker with BMI of 29 presented with fever, cough, diarrhoea and anosmia started 12 days before admission. His COVID-19 PCR was positive on day 6 of symptoms. Upon assessment, his respiratory rate was 27/min, saturation of 89% on room air, picked up to 98% on facemask oxygen 5L/min. His initial CXR shows peripheral and basal opacities especially over left lung and CRP was 10 mg/dL. He was started on steroids and thromboprophylaxis and only required nasal prongs oxygen 2L/min in the ward. On day 5 of admission patient continued to cough and noticed crepitus over his neck and chest region. Upon examination he was noted to have respiratory rate of 32 with saturation of 89% on NPO2 3L. He was then supplemented with high flow mask 15L/min and upon examination he had surgical emphysema over neck extending to bilateral jaws. Repeated CXR shows emphysema over his neck and worsening chest infiltrates. CTPA done showed pneumomediastinum and subcutaneous emphysema at the anterior chest wall extending up to bilateral axilla. There were minimal air pockets at the upper back. Scattered ground glass densities seen in confluence and consolidation in bilateral lungs in central and peripheral distribution with minimal perilobular densities in bilateral lungs. There was no pneumothorax, no obvious tracheal defects and no pulmonary embolism seen on the CTPA. He was commenced on antibiotics. Steroids and thromboprophylaxis were continued, oxygen requirement subsequently reduced to 10L/min. Four days later patient got more tachypnoiec with desaturations, a repeat CTPA shows worsening bilateral ground glass densities and consolidations in both central and peripheral distribution. There were more conspicuous perilobular densities in periphery of bilateral lungs. Previously seen subcutaneous emphysema had resolved. Minimal residual pneumomediastinum up to lower cervical region present. No pneumothorax, no obvious tracheal defects and no pulmonary embolism were seen in the CTPA. Immunomodulators and steroids were given for worsening inflammatory changes in the lungs with increasing oxygen requirement. Antibiotics to cover for hospital acquired infection was given. Patient was eventually intubated and ventilated and sent to Intensive Care Unit (ICU) for care. In ICU his CXR was worsening with infiltrates and fungal cover was initiated. His tracheal aspirate and blood cultures for bacterial and fungal had no growth and MTB gene expert for tuberculosis was negative.

Unfortunately, 5 days later while in ICU the patient eventually died due to worsening of the pneumonia with multiorgan failures.

DISCUSSION

In pneumomediastinum, there is unusual presence of air in the mediastinum. It is usually seen in mechanical or barotrauma that leads to air escape from the lungs, airways or esophagus into the chest cavity. Symptoms are usually chest pain, shortness of breath and subcutaneous emphysema. The diagnosis can usually be confirmed by CXR or CT of the thorax.

Respiratory diseases, tobacco smoking, use of recreational drugs and vigorous Valsalva manoeuvre have been associated to pneumomediastinum.[1] In all our four patients, there were no history of pulmonary disease, pneumothorax, or tobacco use. They developed spontaneous surgical emphysema and pneumomediastinum without any history of intubation or invasive medical procedures.

It was noted in all our patients that the presence of surgical emphysema and pneumomediastinum are accompanied with worsening COVID-19 disease as evidenced by worsening symptoms as well as worsening chest infiltrates due to COVID-19 pneumonitis. One of the possible mechanisms could be a result of diffuse alveolar injury in severe COVID-19 disease, in which the alveoli may be prone to rupture followed by air dissection through the bronchovascular sheath into the mediastinum.[2,3] Worsening cough, may also contribute to alveolar rupture. In all the cases pneumomediastinum resolved spontaneously without any intervention. However, in all the four cases presence of pneumomediastinum resulted in longer hospital stay, which may eventually increase the overall morbidity and mortality.

CONCLUSION

Pneumomediastinum in COVID-19 is not uncommon and its presence in COVID-19 patients should alert clinicians regarding possibilities of worsening of COVID-19 disease. It may lead to prolonged hospital stay and increased morbidity and mortality in COVID-19 patients.

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Clinical and laboratory observation on immunoglobulin replacement therapy switching from an intravenous to a subcutaneous route in a Malaysian X-linked agammaglobulinemia patient

Adli Ali, DPhil(Oxon)[1], Asrul Abdul Wahab, MPath(UKM)[2], Amir Hamzah Abdul Latiff, MRCP(Ire)[3], Intan Hakimah Ismail, PhD(Melbourne)[4], Faizah Mohd Zaki, MMed(UKM)[5], Boekhren Karyostyko Borhanuddin, MMed(UKM)[6], Lokman Mohd Noh, FRCPE[7]

[1]Department of Paediatrics, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia, [2]Department of Medical Microbiology & Immunology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia, [3]Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia, [4]Department of Paediatrics, Faculty of Medicine and Health Science, University Putra Malaysia, Serdang, Malaysia, [5]Department of Radiology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia, [6]National Heart Institute, Kuala Lumpur, Malaysia, [7]Tunku Azizah Hospital for Women & Children Kuala Lumpur

SUMMARY

We report a clinical and laboratory observation in a boy with X-linked agammaglobulinemia (XLA) who underwent an immunoglobulin replacement therapy (IRT) via the subcutaneous route (IGSC) seven years after his IRT via intravenous route (IGIV). He was free of invasive infections when on IGIV but not the troublesome coughs a week before the next infusion. A switch to a subcutaneous route resulted in significant improvement of symptoms with good weight gain. When on 2-weekly IGSC cycle, adjusting dose for weight resulted in an IgG trough level of > 600 mg/dl.

INTRODUCTION

Immunoglobulin replacement therapy (IRT) is mandatory for primary antibody deficiency to prevent infection.[1] The IRT has been administered via intravenous route until the 1990's after which the subcutaneous (SC) route became an optional route for children and adults.[2] Among the advantages of IGSC (immunoglobulin administered via subcutaneous route] are: a) obviate the need of intravenous route for difficult venous access; b) achieve stable serum IgG level instead of initial peak and lower trough level associated with IGIV (immunoglobulin administered via intravenous route) cycles; c) fewer systemic side effect than IGIV route; and d) more amenable towards home therapy for patients.[3,4] A common complication is a temporary subcutaneous tissue swelling at site of SC administration.

CASE REPORT

A 12-year-old boy was diagnosed as X Linked Agammaglobulinemia (XLA) at the age of 4.5 years old. He began to have yearly episodes of pneumonia from the age of 1 year until 4.5 years at which time he suffered a lung empyema. Laboratory investigations showed the following: low serum immunoglobulins (mg/dL) IgG: 30 (504-1474), IgA: 5 (27-195), IgM: 5 (15-259). The lymphocytes subsets count (cells/µL) were: CD19 (B cells) 9 (normal range: 500-1200), CD3(T cells) 7756 (1500-2900). A genetic study revealed a missense mutation at BTK gene loci with A>T substitution in exon 18 at nucleotide position 2020 of X-chromosome, confirming a diagnosis of X Linked Agammaglobulinemia.

He required IGIV since age of 4.75 years on a 4-weekly cycle. His episodes of pneumonia became less often until it stopped at the age of 6 years old. However, he continued to be unwell with wet coughs towards the end of each IRT cycle when trough serum IgG level depreciated to <400mg/dL; the 4 weekly cycle was reduced to 3 weeklies, increasing Immunoglobulin dose from 400 mg/kg to 500 mg/kg resulting in a trough serum levels IgG of > 500 mg/dL. Despite the dose increment (500mg/kg) he remained unwell with continuing episodes of coughs and a further episode of gastroenteritis including an adverse event while on IGIV administration. With an ongoing difficulty of venous access, a switch to an IGSC was inevitable.

His initial starting dose on IGSC was 7.5 gram of immunoglobulin weekly which was a bioequivalent of 5 grams intravenous weekly with washout period of 6 months, with dose adjustments to avoid excessive high serum IgG level. Once the patient maintained a stable serum IgG pre -infusion trough level of 600 mg to 1000 mg /dL on weekly IGSC, it was opportune to convert to longer 2-weekly subcutaneous dosing. The mean trough serum IgG level has been well above 600mg/L for the IGSC phase. The average IgG trough for each immunoglobulin dose level was 950-1080 mg/dL on weekly IGSC reducing to 600-800 mg/dL on 2 -weekly IGSC cycle adjusted immunoglobulin dose with weight increment (Fig 1). While on IGIV average weight increased of 1.6 kg yearly was observed increasing to 3.5 kg yearly on IGSC. He was free of respiratory symptoms, a

This article was accepted: 18 October 2021
Corresponding Author: Lokman M Noh
Email: lokman.m.noh@gmail.com

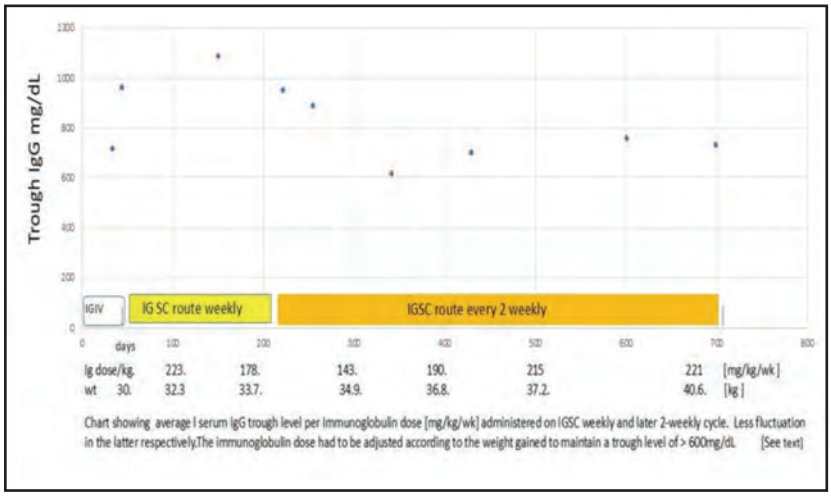

Fig. 1: Mean IgG trough levels for doses of immunoglobulin in an IRT switch from intravenous to subcutaneous in an XLA child.

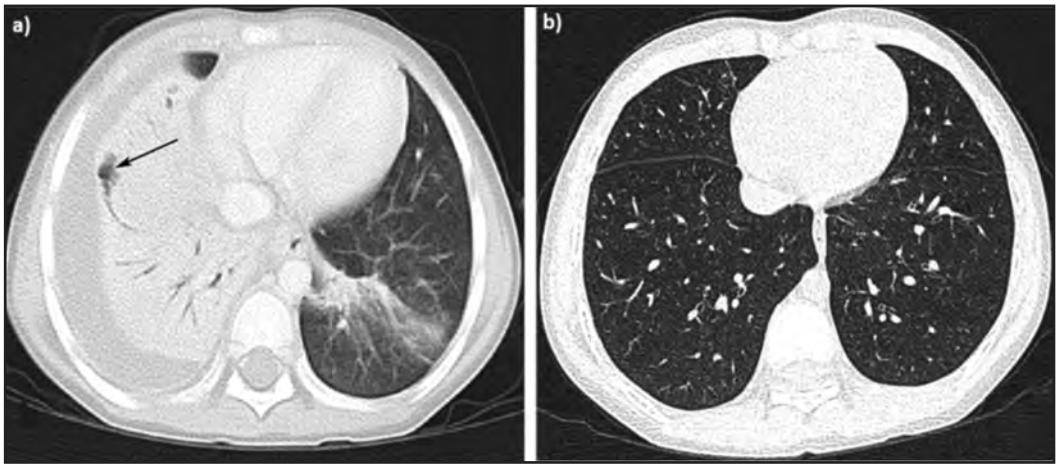

Fig. 2: CT-scan of the thorax at a) age of 5 years shows a collapsed consolidation with pleural effusion of the right lower lobe with a focal bronchiectatic changes at the periphery (black arrow), b) 3 months after the start of subcutaneous immunoglobulin therapy shows complete resolution of the consolidation, bronchiectasis and pleural effusion. The lung parenchyma is normal.

positive sense of well-being with no recorded adverse event while on IGSC.

The patient was noted to have bronchiectasis on chest CT-Scan imaging at age of 5 years, 3 months after IGIV commencement (Fig 2a). He had frequent upper respiratory infections cough at the end of each IRT cycle persisting even after dose modification reaching a trough IgG level above 500mg/dL. However, after commencement of IGSC weekly for 3 months, his repeated CT-Scan imaging showed resolution of bronchiectasis (Fig 2b). Although, this change could not be solely attributed to IGSC as no CT-Scan was done immediately prior to IGSC, it is conceivable that IGSC facilitate its resolution further, having been free of symptoms.

DISCUSSION

IGSC as a replacement therapy is a safe and efficacious to prevent serious bacterial infections while maximising patient satisfaction and quality of life.[5,6] Among the advantages of IGSC over IGIV are the fewer associated systemic effects especially anaphylactic reaction that may occur with IGIV, however, the risk is reduced when converted to IGSC.[5] The first Scandinavian study with 33,000 SC infusions in 1995 recorded no anaphylactoid reaction.[5,6]

A trough IgG level of > 500mg /dL for both IGSC & IGIV to sufficient to prevent recurring infections in antibody deficiencies.[3,7] Titrating the dose towards a higher IgG trough level up to 960mg/dL progressively reduces the rate of infections beyond which it will not have further benefit.[8] To reduce the progression of bronchiectasis in XLA and CVID a trough level of > 500mg/dL is recommended, while a higher level of 800mg/dL is shown to prevent pulmonary changes.[3,9] Indeed our patient when on IGSC showed reduction in infections and complications, with resolution of bronchiectasis and good weight gain. This is highly remarkable as reports of improvement of bronchiectasis on IGIV is scarce although there was one report of changes on HRCT in more than 50% of patients receiving high dose intravenous immunoglobulin of 600-800 mg/kg/month with trough IgG levels of ≥600mg/dL.[4]

IGSC leads to a higher serum IgG with less fluctuating levels overall. With IGIV, the immunoglobulin is introduced directly into the veins, which will be redistributed in the intravascular and interstitial space. This leads to a high peak level in the early phase but with a heightened IgG catabolism, the level is decreased towards the end of the cycle, with an average half- life of 21-28 days. In comparison, IGSC administered weekly or biweekly resulted in the accumulation of IgG in subcutaneous tissue with a slower absorption into the circulatory system over 2-3 days producing a less fluctuating and a higher and stable serum IgG trough levels.[10] Every attempt should be made to switch to IGSC when venous access becomes difficult, obviating a need for the use of a fixed implantable venous device, a perpetual source of extraneous infections.

CONFLICT OF INTEREST

Nil as declared by the authors.

ACKNOWLEDGEMENT

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CASE REPORT

A case report of Carnitine Palmitoyltransferase deficiency type II

Roshan Singh, DCH , Rabi`atul-Adawiyah Mohamad, MD

Hospital Sultan Abdul Halim, Sungai Petani, Kedah

SUMMARY

Carnitine Palmitoyltransferase deficiency type II (CPT II) is a rare metabolic disorder of fatty acid oxidation with an autosomal recessive mode of inheritance. The outcome is usually severe with most of the patients typically passing away in the newborn period. In this report, we share our experience in managing a case of CPT II in a one-day-old term female baby who was delivered at Hospital Sultan Abdul Halim.

INTRODUCTION

Carnitine enzyme is required for the transport of long-chain fatty acids into the mitochondria for the β-oxidation cycle. Four types of carnitine defects have been detected. The four defects are; Carnitine transport defect, Carnitine Palmitoyltransferase deficiency type IA (CPT I), Carnitine Acylcarnitine translocase deficiency (CACT), and Carnitine Palmitoyltransferase deficiency type II (CPT II).[1]

The CPT II enzyme converts long-chain acylcarnitine to long-chain acylCoAs for β-oxidation. This CPT II deficiency is an autosomal recessive disorder and there are 3 main phenotypes in this deficiency: lethal neonatal form, severe infantile hepatocardiomuscular form, and the myopathic form.[1]

We present a one-day-old term female infant, admitted at NICU, Hospital Sultan Abdul Halim for lethargy, low sugars, and cyanosis. The presence, as well as persistent non-ketotic hypoglycemia, hyperammonemia, and cardiomyopathy, led to the suspicion of fatty acid oxidation defect.

CASE REPORT

A term female baby was delivered at Hospital Sultan Abdul Halim with a birth weight of 2760 grams via spontaneous vaginal delivery with an APGAR score of 9 in 1 minute and 10 in 5 minutes. At 25 hours of life, she was referred for unresponsiveness and hypoglycemia (0.8mmol/L). On examination, we noted a non-dysmorphic baby girl, encephalopathic with poor breathing effort and bradycardic. The hypoglycemia was treated accordingly, and she was transferred to neonatal intensive care (NICU) for further management.

She was ventilated, and the initial blood investigation showed a slightly raised leukocyte count (20,800), a respiratory alkalosis blood gas with an anion gap of 21.3. Given the above clinical findings and investigations, she was initially treated for meningitis. However, the cerebral spinal fluid (CSF) biochemistry was normal, and the CSF culture did not yield any growth. In addition to the above investigation, an Inborn Errors of Metabolism (IEM) panel was sent which resulted in a raised ammonia (144mmol/L), raised lactate (3mmol/L), and raised creatinine kinase (3414 units/L). The plasma amino acid resulted in an elevation of methionine and tyrosine levels, suggesting liver dysfunction and urine organic acid was non-diagnostic. The blood spot resulted in an elevation of the C16 with moderate elevation of C18 with mild to moderate elevation of C12, C14, C16:1, and CIB:1. The free carnitine levels were lowish (C0) with a moderate elevation of C16+CLB:11C2 ratio. This profile is very suggestive of long-chain fatty acid oxidation either CACT or CPT 2 deficiency.

Bedside echocardiography revealed cardiomyopathy with both the ultrasonography brain and abdomen resulting in a normal study. Given the cardiomyopathy and a general edematous appearance, she was started on oral furosemide.

Feeding was introduced slowly, and she achieved full feeds by day 5 of life. Unfortunately, the following day she went into metabolic crisis. An Anti-hyperammonemia cocktail was administered and the refractory hypoglycemia was stabilized with GIR ranging between 18 – 20 mg/kg/min. We aimed to maintain a calorie intake of 120kcal/kg/day.

The case was discussed with the metabolic team and based on the clinical findings and the initial IEM panel a differential diagnosis of CPT II and CALT was put forward. We also repeated the IEM blood spot and urine organic acid test. In addition, serum carnitine and parents' DNA extraction were also sent. The IEM blood spot test resulted in elevated C12, C160H, and C1b with persistently raised C16+C18:1/C2 ratio with lowish free carnitine and C2. The serum carnitine levels resulted in a mildly increased acyl: free carnitine ratio. The urine organic acid resulted in a non-diagnostic profile. The parents' DNA extraction revealed in both parents were carriers of the mutation in the patient.

We increased her calorie intake to 140 – 190kcal/kg/day initially with a mixture of IV maintenance and fortified expressed breast milk. As she showed improvement in both her dexterity as well as her ammonia levels (75 – 140 umol/L) we were able to shift all her calorie intake to oral feeds.

During the following 3 weeks, she had a stormy course. Unfortunately, she contracted nosocomial pneumonia subsequently followed with MRSA sepsis. In both conditions,

This article was accepted: 17 December 2021
Corresponding Author: Roshan Singh
Email: roshansingh9a@gmail.com

the inflammatory markers were raised, and she was covered with IV antibiotics. Despite our best efforts, on day 29th she developed respiratory failure secondary to sepsis and cardiomyopathy and succumbed to her illness.

DISCUSSION

CPT II is a fatty acid oxidation (FAODs) group. These groups are a rare inherited disorder in which the body is unable to oxidize fats for energy. A definitive diagnosis is usually made by detection of reduced CPT II enzyme activity and molecular genetic testing. As stated earlier the 3 clinical presentations are the lethal neonatal form, severe infantile hepatocardiomuscular form, and the myopathic form.[2] Among the 3 forms, the myopathic form is the most encountered with the highest numbers seen in males.

Clinically, the presentation of lethal neonatal form and severe infantile hepatocardiomuscular have almost similar systemic involvement. The lethal neonatal form presents with liver failure, hypoketotic hypoglycemia, cardiomyopathy, respiratory distress, and/or cardiac arrhythmias. It has been reported that in this form there is a neuronal migration defect leading to cystic dysplasia of the basal ganglia. Patients with lethal neonatal form can have nervous system involvement; hydrocephalus, cerebellar vermian hypoplasia, polymicrogyria, pachygyria, cerebral calcification, cystic dysplasia of the brain, and agenesis of the corpus callosum. Some cases have also reported the presence of polycystic kidneys.[2]

The severe infantile hepatocardiomuscular form is characterized by hypoketotic hypoglycemia, liver failure, cardiomyopathy, and peripheral myopathy. The myopathic form is due to lipid metabolism affecting skeletal muscle and is the most frequent cause of hereditary myoglobinuria.[2]

In our patient, the clinical manifestations, as well as the investigations, led to a diagnosis of CPT II with the lethal neonatal form variant. In this form, the presentations are seen within the first few days of life and invariably lead to early infantile death. Certain red flag signs raised suspicion of inborn error of metabolisms such as persistent/unexplained lethargy, vomiting, poor feeding, seizure, altered sensorium, and failure to gain weight should be familiar with health care providers particularly those in a NICU setup. Acylcarnitine analysis using tandem mass spectrometry helps in the diagnosis of CPT II deficiency. The activity of the CPT II enzyme can be demonstrated by carnitine levels, serum creatinine kinase levels, and transaminase levels. However, a definitive diagnosis can be obtained by sequencing the CPT II gene for mutation analysis.[1]

Prenatal diagnosis for risky pregnancies is possible either by molecular genetic testing of CPT II or CPT II enzyme activity assay in cultured amniocytes. Radiological evidence of brain or renal abnormalities in the mid-trimester of pregnancy can be supportive.[1]

Management of CPT II is by reducing dietary fat intake and at the same time increasing carbohydrate mainly to reduce the abnormal accumulation of both long-chain acyl-coenzyme A (CoA) and acylcarnitine intermediates. In acute cases, glucose infusion has been suggested to reduce lipid mobilization and a large volume of fluid alkalinization to enhance renal excretions of myoglobin.[3]

The current treatment approach to a case of CPT II is avoidance of known triggers and reduction in the amount of long-chain dietary fat while covering essential fatty acids. Patients should also be given carnitine to convert potentially long-chain acyl-CoAs to acylcarnitine. A large portion of the patient's calories should be obtained from carbohydrates which in turn reduces body fat utilization and prevents hypoglycemia. At least 1/3 of the calories should be obtained from even-chain medium-chain triglycerides (MCT). Metabolism of the eight to ten carbon fatty acids in medium-chain triglycerides oil, for example, is independent of CPT I, carnitine/acylcarnitine translocase, CPT II, very-long-chain-acyl-CoA dehydrogenase (VLCAD), trifunctional protein, and long-chain hydroxyl-acyl-CoA dehydrogenase deficiency (LCHAD) enzyme activities.[3]

The anaplerotic diet with triheptanoin provides an alternate route to produce acetyl-CoA and oxaloacetate to allow for citrate synthesis which in turn results in increased ATP formation via the respiratory chain. The trihepatonin is readily taken up by the mitochondria of the liver without needing the transport via CPT I, carnitine-acylcarnitine translocase, or CPT II. Once within the liver mitochondria, the trihepatonin undergoes β-oxidation leading to the formation of acetyl-CoA and pentanoyl-CoA.[3]

Oxidation of Pentanoyl-CoA leads to the formation of acetyl-CoA and propionyl-CoA. The propionyl-CoA enters the citric acid cycle forming oxaloacetate. The acetyl-CoA along with β-ketopentanoyl-CoA (BKP-CoA) forms the ketone bodies via the β-hydroxy- β-methylglutaryl-CoA pathway. This ketone body is used by the peripheral organs, more importantly, the brain.3The presence of acetyl-CoA and oxaloacetate allows for citrate synthesis resulting in increased ATP formation via the respiratory chain.

Triheptanoin is available as over a counter product. The recommended total daily dose is administered in milliliters (ml) using the formula:

- Patient DCL (kcal) x target % dose of DCL divided by 8.3kcal/mL
- The total dose is then given at least 4 times per day in equal doses
- When initiating, begin with 10% of the calculated dose in 4 individual doses
- The dosage is slowly titrated up to the maximum dose over a 2-to-3-week period

For patients switching from another medium-chain triglycerides product

- Discontinue previous medium-chain triglycerides before therapy initiation
- Initiate at last tolerated medium-chain triglycerides dose divided into at least 4 individual doses
- Increase total daily dosage by approximately 5% DCI every 2 to 3 days until target dosage is achieved

Certain appropriate measures to prevent primary manifestations include:

- Infusion of glucose during intercurrent infection to prevent catabolism
- High-carbohydrate (70%) and low-fat (<20%) diet to provide fuel for glycolysis
- Frequent meals and avoidance of extended fasting
- Avoidance of prolonged exercise

The most important complication that tends to arise in individuals with CPT II deficiency is renal failure which usually is secondary to an episode of rhabdomyolysis and myoglobinuria. To avoid this, sufficient hydration and if necessary dialysis must be performed immediately.

CONCLUSIONS

There has not been any case report published regarding CPT II deficiency in Malaysia. The initiation of investigation towards a case of CPT II deficiency requires a high degree of suspicion. In this publication, we intend to highlight persistent and unexplained lethargy, vomiting, poor feeding, seizure, altered sensorium, and failure to gain weight are some red flags for CPT II deficiency.

The diagnosis, investigation, and management in the case of CPT II deficiency have not been fully established. We share our limited experience in the management and treatment of such a case.

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Left aorto-ventricular tunnel: A differential diagnosis to aortic regurgitation

Abdul Rahim Wong, FNHAM[1], Amelia Alias, MRCPCH[2], Mohd Rizal Mohd Zain, MMed Paediatrics[3], Khairil Amir Sayuti, MMed Radiology[4]

[1]Dept of Pediatrics, Faculty of Medicine, Universiti Sultan Zainal Abidin, Malaysia, [2]Dept of Pediatrics, Hospital Raja Perempuan Zainab II, Ministry of Health, Malaysia, [3]Dept of Pediatrics, School of Medical Sciences, Universiti Sains Malaysia, Malaysia, [4]Dept of Radiology, School of Medical Sciences, Universiti Sains Malaysia, Malaysia

SUMMARY

Left aorto-ventricular tunnel is a rare congenital heart disorder. A then 19-year-old young lady was referred to our clinic for chronic rheumatic heart disease with aortic regurgitation. However, because of an almost continuous murmur, and an unusual transthoracic echo, she underwent various investigations, finally revealing a rare type 2 left aorto-ventricular tunnel. She had been variously diagnosed as chronic rheumatic heart disease with aortic regurgitation, bicuspid aortic valve with aortic regurgitation, and then possibly coronary arterial (cameral) fistula (based on 2D transthoracic echo) and finally left aorto-ventricular tunnel. This is the first case described in South East Asia who is asymptomatic, apart from a murmur, and her long journey to this final diagnosis illustrates the need to "chase shadows" on echoes, to come to a proper conclusion for the patient.

INTRODUCTION

Aorto-ventricular tunnel (AVT) is a rare congenital heart disorder. It is an anomalous tract that connects the ascending aorta usually just above the sinotubular junction to either the right or left ventricle, with the left being more common. This is different from a fistula which forms following the rupture of a dilated sinus of Valsalva and hence below the level of the coronary ostia.[1] This anomalous tract has normal aortic vessel like media structurally[1] and most likely arises because of an abnormal separation of the great vessels and possibly valve leaflets (conotruncal region).[2] There are cases reported 2 where there are even rudimentary valve leaflets in these tunnels, hence making it likely that this is at least one of the possible ways that this rare anomaly arises.

CASE REPORT

Miss N, then a 19-year-old lady was referred to us from our adult cardiology colleagues with a diagnosis of chronic rheumatic heart disease with aortic regurgitation (AR). This was because of a murmur picked up during a routine school examination in her secondary school years. During clinical examination, we noted the presence of an almost continuous murmur. Our initial transthoracic echo (TTE) performed by one of us, detailed a bicuspid aortic valve (BAV) with an aberrant jet that did not look like AR. At the time, we thought of possibilities of coronary artery (cameral) fistula (CAF) with exit to the left ventricle or unlikely a left aortic-ventricle tunnel (LAVT). We referred her to a large tertiary centre in Malaysia, but she was told that the diagnosis was BAV with AR, after a TTE performed there. She was then referred back to us for continuation of care. However, because of our initial echoes, we managed to persuade her family to agree for further investigations with the view of percutaneous closure from interventional catheterization. A repeat TTE performed, by another of the authors, was unusual (Fig. 1a) and clinically the agreed upon auscultation was that the murmur was continuous. The transoesophageal echo (TEE) showed clearly a LAVT (Fig. 1b). An angiogram performed in the right oblique view at 30o also revealed LAVT (Fig 2a). Because of that, the procedure was abandoned as none among the authors had experience with AVT, nor had read on possible percutaneous closure of LAVT. A CT angiogram scan (with contrast) was arranged, in the likelihood that the patient required surgery, and confirmed our diagnosis (Fig. 2b and c).

DISCUSSION

AVT is a rare congenital cardiac disorder that was first described in 1963 by Levy and colleagues.[1] It describes the lesion of a channel that connects the aorta (usually above the artic sinuses) to the right, or more commonly left ventricle.[3] A classification scheme based on the local anatomic findings of the AVT was proposed in 1988 by Hovaguiman and colleagues[4] with:

Type I: A slit like aortic orifice without valvular distortion.
Type II: A larger, oval shaped aortic orifice with an extracardiac aneurysmal tunnel.
Type III: An oval aortic orifice with a septal (intracardiac) aneurysmal tunnel.
Type IV: A combination of type II and III.

This rare condition, has had various incidences reported ranging from 0.03% to 0.46% of all congenital heart defects.[5] The clinical presentations can be varied, ranging from usually heart failure in infancy to the mildly symptomatic case. In our patient apart from the murmur, she was not in heart failure and was asymptomatic, even beyond her second decade of life. And it had been variously diagnosed as AR due to rheumatic fever or BAV with AR, and CAF. We believe this is the first reported case in South East Asia, and although rare, the abnormal colour Doppler image should pique interest in the possibility of other conditions. In reality, one of

This article was accepted: 10 October 2021
Corresponding Author: Abdul Rahim Wong
Email: arahimwong@unisza.edu.my

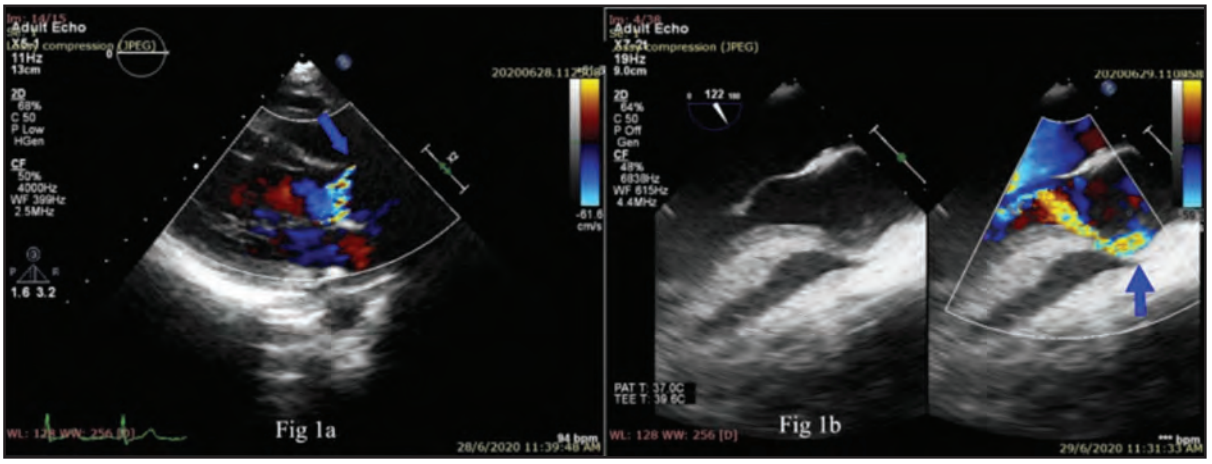

Fig. 1: Echocardiogram of the patient on long axis view (1a) showing skewed jet from patient with continuous murmur variously diagnosed as BAV and AR, AR secondary to rheumatic fever. Transoesophageal echo revealing left AVT (1b), which can be seen especially with colour Doppler, appearing above the coronary sinus and then coursing beside it before entering the left ventricle just below the aortic valve (arrow). AVT=aorto-ventricular tunnel, AR=aortic regurgitation, BAV=bicuspid aortic valve.

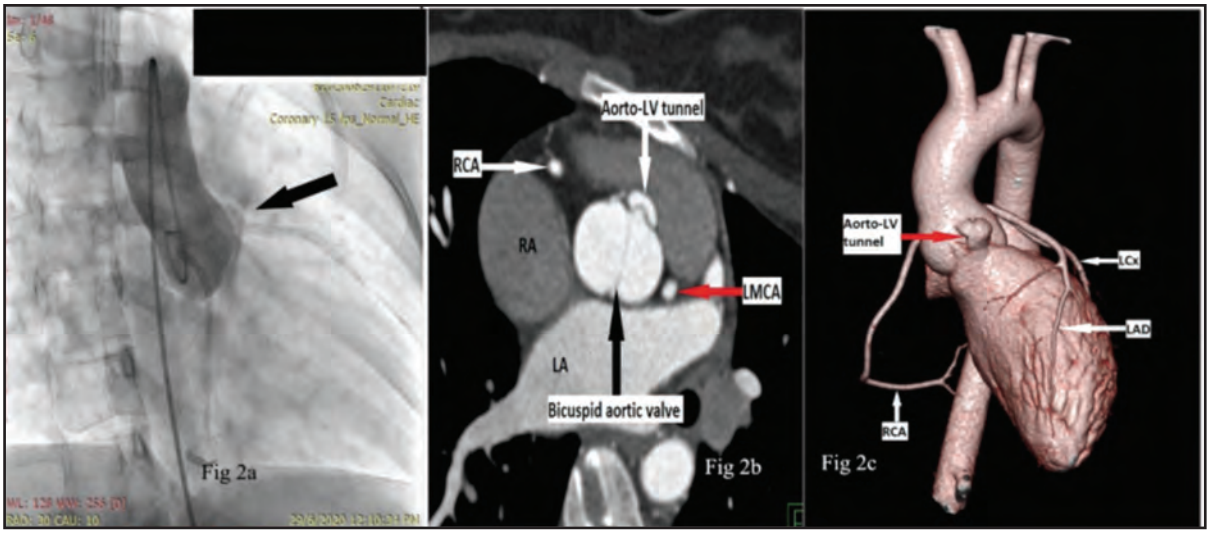

Fig. 2: An angiogram of the patient from the RAO 30o view (Fig 2a) revealing the left AVT (arrow). The top right corner was blacked out to remove the patient's details. AVT=aorto-ventricular tunnel. RAO (right anterior oblique) CT angiogram of the patient at the level of the aortic valve (Fig 2b). Left AVT is labelled (fine arrow). Reconstructed 3D CT image (Fig 2c) showing mainly the left ventricle, aorta and coronary vessels and left AVT (labelled). LA=left atrium, LAD=left anterior descending artery, LCX=left circumflex artery, LMCA=left main coronary artery, RA=right atrium, RCA=right coronary artery.

us tried tracking that jet and traced it back to a vascular-like structure, hence CAF was considered, and also LAVT. Because we thought the large centre was better equipped to deal with such situations, hence, the patient was initially referred there. After her return, we managed to persuade her and her family of the need for a proper diagnosis, hence we proceeded with TEE and also catheterization.

We did not proceed with any intervention, due to our lack of experience in LAVT, and upon perusing the literature, most discussed surgery and the importance of closing both ends of the track. Percutaneous closure results were also discouraging compared to surgery.[6] This is understandable, considering that the echo and angiography are two dimensional images displaying a rather small track above the aortic sinus, and traversing to a region below the aortic valve. However, the 3D reconstruction on CT (Fig 2 b and c) showed that although narrow in 1 dimension, the LAVT was wide in another with a curved extramural course (Type II), hence making percutaneous intervention difficult with many devices, unless one was specifically designed for it. Little to nothing is known of the natural history of asymptomatic cases, with one case of "spontaneous closure"[7] and some reporting symptomatic individuals presenting at 45 years of age.[6] But recommendations for LAVT are for closure due to the possible progression of heart failure and also possible progressive aortic regurgitation and dilation of the aorta.[6,7]

CONCLUSION

LAVT should be considered as part of the differential diagnosis to AR, when there is an abnormal colour Doppler image, and when clinically, an almost continuous murmur can be heard.

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CASE REPORT

First toddler mesenteric lymphatic malformation in Malaysia - A case report

Soh Chai Hoon, MD[1], John Emmanuel, MPaedSurg[1], Mohamad Ikhwan Rahizan, MBBS[1], Muhamad Asyraf Azmi, MD[1], Sakti Devi, MPaedSurg[1], Nurdaliza Mohd Badarudin, MPaedSurg[1], Nurashikin Jamaluddin, MMed Radiology[2]

[1]Department of Surgery (Paediatric Surgical Unit), Hospital Raja Permaisuri Bainun, Ministry of Health, Malaysia, [2]Department of Radiology, Hospital Raja Permaisuri Bainun, Ministry of Health, Malaysia

SUMMARY

This is the first reported case of a mesenteric lymphatic malformation in a toddler in Malaysia. It is a rare benign condition with incidence of 1 in 250,000 populations. Our patient presented to us at 2 years 11months old complaining of abdominal distension for 6 months without obstructive symptoms. Clinically there was a vague soft central abdominal mass. CT abdomen done revealed a large multiloculated intraperitoneal mesentery cystic mass within the central abdomen extending to pelvis. A semi-emergency laparotomy was performed. Intra-operatively the multiloculated mesenteric cyst measured 20cm x 30cm, adherent to the small bowel beginning at 12cm from duodeno-jejunal junction. Resection of the mesenteric cyst with adherent small bowel and primary anastomosis was done. Histopathological examination revealed multiple large lymphatic channels of various sizes in the mucosa and submucosa. Our patient has no signs of recurrence and remains symptom-free after 1 year since his surgery. Surgery with clear margins of resection is the recommended gold standard based on available literature. Type of surgical resection required will depend on the type of mesenteric lymphatic malformation. An awareness of this rare pathology is required to ensure proper management is given to these patients.

INTRODUCTION

Mesenteric lymphatic malformations are a rare benign condition which represent less than 1% of all lymphatic malformations. Its incidence is estimated to be 1 in 250,000 population.[1] To date this is only the third case of mesenteric lymphatic malformation reported in Malaysia, but the first one in toddlers.[2]

CASE REPORT

Our patient presented to the emergency department when he was 2 years 11 months baby boy with a complain of abdominal distension for 6 months but was able to have normal bowel openings without obstructive symptoms. Abdominal radiography performed showed no dilated bowels, however there was paucity of bowel gas centrally. On examination the abdomen appeared slightly distended with a central vaguely palpable soft mass. He was reviewed at the outpatient clinic and admitted. Sonography revealed a large intra-abdominal mixed solid cystic mass extending to pelvis with multiple thick septae and thick debris within the mass, likely lymphatic malformation of the mesentery. We proceeded with a CT of the abdomen (Figure 1) which showed a large multiloculated intraperitoneal mesentery cystic mass within the central abdomen extending to pelvis, multiple mesentery vessels insinuating the cystic lesion, no solid lesion with cystic mass, no bowel dilatation; likely mesenteric cyst. Alpha fetoprotein and beta-Hcg were normal. Patient underwent a semi-emergency midline laparotomy and excision of mesenteric cyst. Intra-operatively (Figure 2) there was a large multiloculated mesenteric cyst measuring 20cm x 30cm. The cyst was adherent to the small bowel beginning at 12cm from duodeno-jejunal junction. The 24cm of small bowel was resected along with the cyst with a remaining small bowel length of 211cm. Patient was discharged home well on post-operative day 5.

Histopathological examination (HPE) reported multiple cystic lesions at mesentery measuring 180mm x 70mm x 50mm with cysts sizes ranging from 5mm to 8mm. Sections from the bowel showed multiple large lymphatic channels of various sizes in the mucosa and predominantly in the submucosa. Similar cysts were also seen in the mesentery surrounded by loose connective tissue stroma. These cysts were lined by fairly uniform flattened to cuboidal epithelium and containing eosinophilic secretions. The lining epithelium were positive for CD31, focally for CD 34 and Factor VIII. They were negative for Calretinin. Focally disorganised smooth muscle are also noted within larger cyst wall. Lymphoid aggregates with some foreign body granuloma and cholesterol clefts were present at the periphery. No communication between the mesenteric cyst and the small intestinal segment was noted. No evidence of nuclear atypia or malignancy was seen. The surgical margins resected were adequate.

During the post-operative review at 1 month, 4 months and 1 year, the patient was well and did not have any complications or symptoms recurrence. No follow-up imaging was done.

DISCUSSION

Cystic mesenteric lymphatic malformations previously known as mesenteric lymphagiomas are divided into

This article was accepted: 18 October 2021
Corresponding Author: Soh Chai Hoon
Email: yvonnesohch@gmail.com

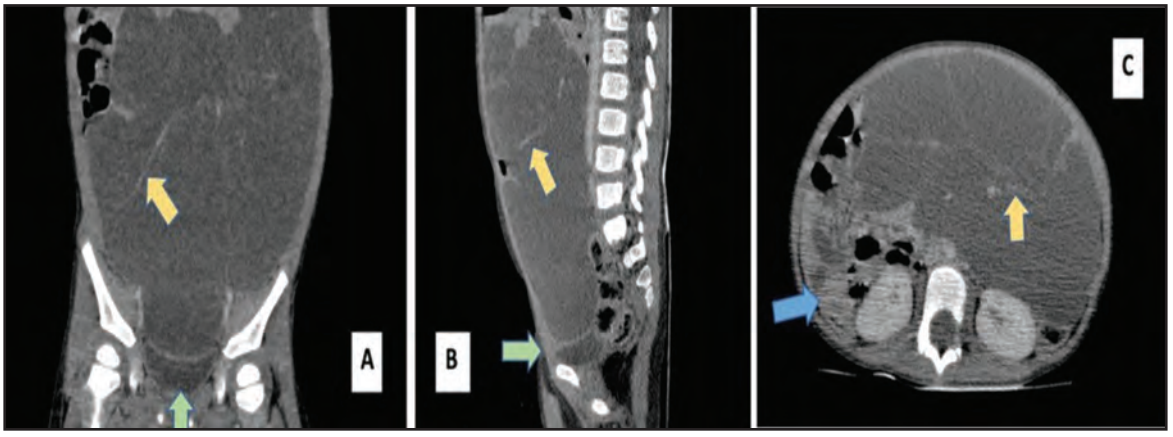

Fig. 1: Computerized tomography contrasted computed tomography (CT) scan images in coronal.
(a) sagittal (b) and axial (c) images shows large multiloculated intraperitoneal mesentery cystic mass within the abdomen (which is centrally located), below the subhepatic region and extends inferiorly until the pelvis (superior to the urinary bladder- green arrow). Bowel (blue arrow) is displaced postero- laterally by the large cystic mass. No extension of the mass into the spinal canal. Presence of multiple thin enhancing septa (yellow arrow) within the mass. No solid lesion seen within the cystic component.

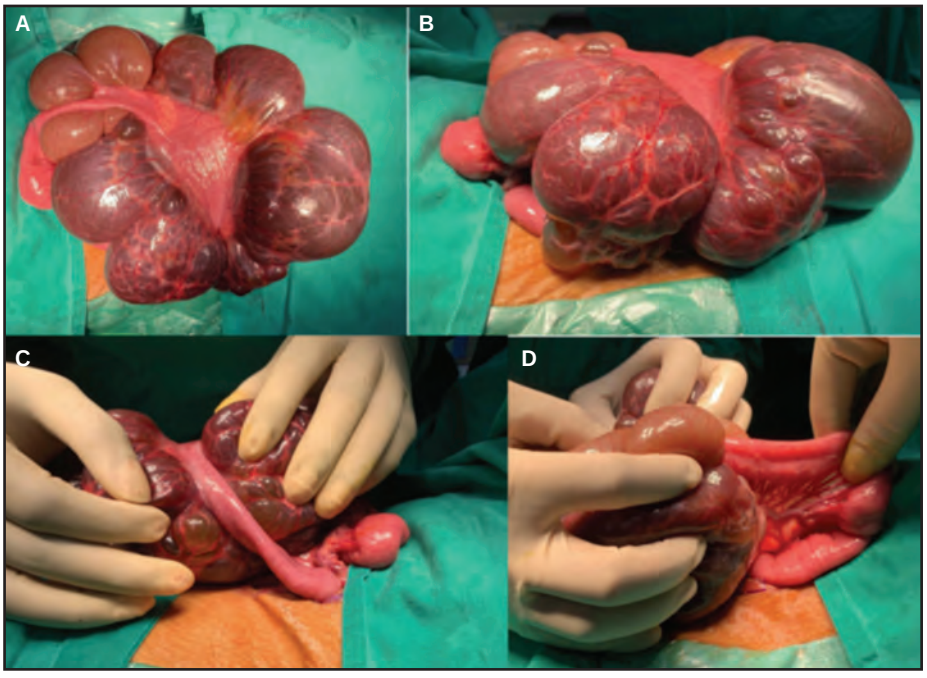

Fig. 2: Intra-operative findings revealed a large multiloculated mesenteric cystic lesion measuring 20cm x 30cm, a part of the small bowel adherent to cyst proximally 12cm from duodenojejunal junction. 24cm of small bowel was resected along with the cyst with a remaining small bowel length of 211cm. [Image A: Anteroposterior view. Image B: Lateral view. Image C: Inferior view. Image D: Caudal view.]

macrocystic, microcystic and mixed lymphatic malformations according to the latest ISSVA 2018 classification.[3] Lymphangiomas were previously classified histologically into capillary (simple), cavernous and cystic.[4]

The typical location for lymphatic malformations are head, neck and axillary region. Abdominal lymphatic malformations are rare and consist of only 5% of all lymphatic malformations, majority being diagnosed in childhood with 88% having symptoms such as abdominal distension, abdominal pain, abdominal mass, altered bowel habits, nausea or vomiting.[5] Abdominal lymphatic malformations may arise from the mesentery, solid organs (liver, spleen, pancreas), retroperitoneum and the gastrointestinal tract. Lymphatic malformations specifically of the small bowel mesentery has been described with an incidence of less than 1%.[4]

The aetiology of mesenteric lymphatic malformations were proposed to be due to congenital sequestration of lymphatic vessels during the embryonic period instead of a true lymphatic tumor. This is evidenced by majority of cases

presenting in childhood. In the older age groups, there are other etiologies proposed such as abdominal trauma, inflammation, radiation, abdominal surgery and lymphatic obstruction.[4]

In the literature there are two available gross anatomical classifications for mesenteric lymphatic malformations. The latest was proposed by Kim et al in 2016.[6] According to this classification, our patient would be of Type 1. The pathology in our patient is not clearly classified according to the previous classification proposed by Losanoff et al in 2003.[7]

Mesenteric lymphatic malformations appear as multiloculated cystic lesions on sonography, usually anechoic but may contain debris. Sometimes the lesions may appear as predominantly solid such as in our case where a solid component was seen on the ultrasound.[8] However, bearing in mind that ultrasounds are operator dependent, a CT scan or MRI will help to better delineate the anatomical structure of the malformation. The CT scan for our patient revealed a large multiloculated intraperitoneal mesentery cystic mass with no solid component.

The treatment for mesenteric lymphatic malformations are different from lymphatic malformations located in the common regions like head, neck and axilla. When originating from the mesentery, surgery with clear margins of resection remain the gold standard especially in symptomatic patients in which the lymphatic malformations has caused complications such as haemorrhagic infarction, intestinal obstruction, small bowel volvulus and infection. Surgery is also recommended even though the patient may be asymptomatic as there is a risk of progressive infiltration into retroperitoneal structures which will make future resection more difficult. The classifications of mesenteric lymphatic malformations are important to assist in surgical decision making of these patients. Based on the classification by Kim et al6, patients with Type 1 and 3 will need resection to include the bowel as blood supply will be affected. Those with Type 2 can have bowel sparing surgery as the malformation is pedicled and not affecting the blood supply of the bowel. Patients with Type 4 may not have adequate resected margins due to the extensive spread and may benefit from medical therapy such as propranolol, sirolimus or sclerotherapy.[1,6]

When mesenteric lymphatic malformations are located in the head, neck and axilla, surgery is avoided if the child is asymptomatic, not increasing in size and not affecting mobility or function. It is very important to restore and preserve the function and aesthetics of these regions. Other treatment modalities like OK-432, sirolimus, propranolol and sclerotherapy (using agents such as bleomycin, lauromacrogol, doxycycline, ethanol, etc.) would be the initial choice of therapy to reduce the size of these lymphatic malformations in order to achieve clear margins if surgical intervention is needed. Sclerotherapy is currently the gold standard of treatment for macrocystic or mixed lymphatic malformations in these regions.[9,10]

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Milk-alkali syndrome: The forgotten diagnosis for altered sensorium

Yap Wai Leong, MD[1], Andey Rahman, MMed[1,2], Kamarul Aryffin Baharuddin, MMed[1,2]

[1]Department of Emergency Medicine, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia,
[2]Hospital Universiti Sains Malaysia, Jalan Raja Perempuan Zainab 2, Kubang Kerian, Kelantan, Malaysia

SUMMARY

Milk-alkali syndrome (MAS) is one of the causes of hypercalcaemia. We report a case of a 75-year-old lady with a history of thyroidectomy, presented with an altered mental state and had an extremely high calcium concentration of 4.96mmol/L. The hypercalcemia was attributed to the ingestion of large doses of calcium supplements, including calcium carbonate and calcium lactate, leading to MAS. She was managed with intravenous fluids, diuretics and withdrawal of calcium supplements. The patient responded well to treatment and regained consciousness. Details of the case including clinical presentations, electrocardiogram (ECG) findings and treatment plan, are discussed in this article.

INTRODUCTION

Altered sensorium (AS) is one of the commonest presentations in the Emergency Department (ED) and is always a diagnostic challenge for ED residents. Most cases of AS are related to neurological causes and a thorough neurological examination is essential. In addition, electrolyte imbalance like hypercalcemia may be a cause of AS. Milk-alkali syndrome (MAS), once among the commonest cause of hypercalcemia, is now considered rare.[1] Failure or forgotten to diagnose is not uncommon[1] and may lead to continuing excess intake of calcium carbonate. Recently, the incidence has resurgent secondary to the use of calcium carbonate to prevent and treat osteoporosis. We report a case of AS secondary to MAS in a 75-year-old lady following ingestion of the calcium supplements.

CASE REPORT

A 75-year-old lady was brought to ED of the Hospital Universiti Sains Malaysia, Malaysia with AS for one day. She had had a total thyroidectomy done in June 2021 for thyroid cancer and was recently admitted for hypocalcaemia with corrected calcium level of 1.89mmol/L. She was discharged a few days later with calcium and vitamin D supplements (calcium carbonate 1.5g BD, calcium lactate 1.2g TDS, and calcitriol 0.5mcg BD), antihypertensive medications (amlodipine 10mg OD and hydrochlorothiazide 12.5mg BD) and thyroid hormone supplement (L-thyroxine 100mcg OD). However, she had not been eating much and appeared tired and lethargic at home.

Two days prior to the presentation at the ED, her condition worsened, and she required assistance for ambulation. On the day of presentation, which was a week post-discharged, a family member noticed that she was less responsive, had no eye response, and did not answer upon call. There was no history of head injury or fall. No seizure or abnormal movements were noticed by the family member. No chest pain or angina symptoms were told by her to the family member.

Upon arrival, she was pink but severely lethargic and dehydrated. She was drowsy with GCS 9/15 (E3V1M5) and her pupils were 2mm reactive bilaterally. She had shown minimal movements of her limbs upon call. Her initial vital signs were blood pressure of 100/68mmHg, heart rate of 99 beats per minute, the temperature of 36.4°C, respiratory rate of 10 breaths per min, oxygen saturation of 99% under room air and capillary blood sugar of 5.5mmol/L. Neurological examination showed generalized muscle weakness and symmetrical hyporeflexia involving all 4 limbs. There were no focal signs or meningeal signs. Other systems were unremarkable.

Results from the point-of-care test (POCT) in ED showed hemoglobin (Hb) level of 13.6g/dL, white cell count (WCC) of 18.8x103µL, and platelet of 804x103µL. Her venous blood gas (VBG) confirmed metabolic alkalosis with pH 7.560, pCO2 56.3 mmHg, pO2 51.9 mmHg, and HCO3 44.5 mmol/L. Her electrolytes values from the VBG showed hypercalcemia, hyponatremia and hypokalemia with ionized calcium (Ca) of 2.60 mmol/L, sodium (Na) of 127 mmol/L, potassium (K) of 2.7 mmol/L. An electrocardiogram (ECG) showed ventricular bigeminy with R-on-T phenomenon, Osborn waves and prolonged QT interval (Figure 1).

Even though her electrolytes values from the VBG were abnormal and no focal signs, a computerized tomographic (CT) scan of the brain was done due to sudden history of AS. The finding of the CT scan was normal. Her chest radiograph showed left lower zone haziness.

Formal the laboratory investigation results came back four hours later and showed severe hypercalcemia, hyponatremia, hypomagnesemia, and hypokalemia with renal impairment (Na 126mmol/L, K 3.0mmol/L, Urea 9.0mmol/L, Creatinine 120µmol/L, Ca 4.96mmol/L

This article was accepted: 27 October 2021
Corresponding Author: Andey Rahman
Email: andey@usm.my

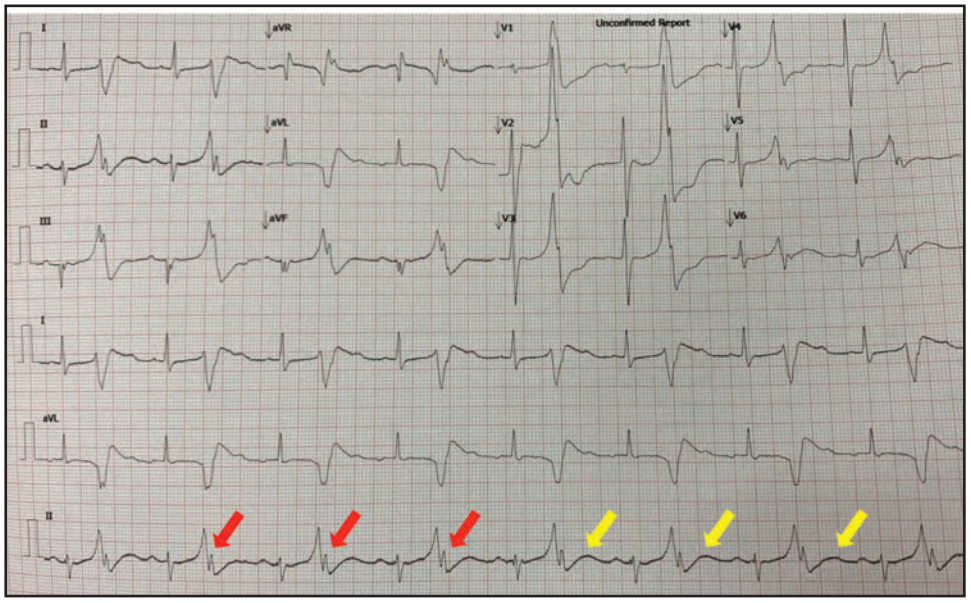

Fig. 1: ECG upon presentation. It appeared as ventricular bigeminy with prolonged QT interval along the sinus beats. Each premature ventricular complex (PVC) was very close to the T wave, represents R-on-T phenomenon. There was prolonged PR interval. Along the PVCs we could appreciate an upstroke of J point (red arrows), representing the Osborn wave. There was upright wave after the PVCs, which represents U wave (yellow arrow).

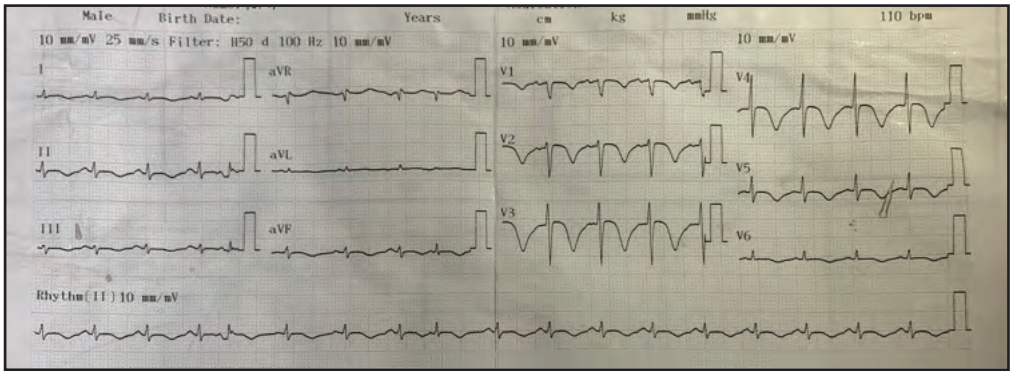

Fig. 2: ECG in ward. There were T inversions in all the leads (except lead aVR) with prolonged QT interval, which was due to the low levels of magnesium and potassium. Previously seen ventricular bigeminy, R-on-T phenomenon, U waves and Osborn J waves had resolved.

(corrected), phosphate (PO4-) 1.14mmol/L, and magnesium (Mg) 0.48mmol/L). Troponin T result came back to be normal (5ng/L).

She was diagnosed with AS secondary to symptomatic hypercalcemia attributed to ingestion of calcium supplements, complicated by hospital acquired pneumonia. She was given aggressive intravenous fluid administration, a single bolus dose of diuretic and withdrawal of calcium supplements. Antibiotic was started and she was admitted to the general medical ward for further management.

During the admission, her conscious level had improved and calcium levels normalized. Her magnesium (0.52mmol/L) and potassium (2.8mmol/L) levels were slowly corrected. ECG done in the ward revealed changes caused by the electrolyte imbalances (Figure 2) prior to complete correction. Parathyroid hormone (PTH) level was low at < 0.127pg/ml. She was not treated with bisphosphonates during the admission.

DISCUSSION

MAS was first described in 1920s as a complication of excessive use of milk and alkali to treat gastric ulcers. However, the incidence has greatly diminished with the introduction of acid reducing drugs like H2-receptor antagonists or proton pump inhibitors.[2] However, since over-the-counter use of calcium for the supplement has increased and complicated with MAS, some authors suggested changing the name to calcium-alkali syndrome.[1,3,4]

The triad of MAS includes hypercalcaemia, metabolic alkalosis, and renal insufficiency. Our patient had profound symptomatic hypercalcaemia, which caused lethargy, cognitive disturbance, and muscle weakness. Life-threatening

central nervous system manifestations may also occur like encephalopathy and seizure.[5] In this case, she was initially treated for hypocalcaemia post thyroidectomy, and she was discharged with high doses of calcium with thiazides. Thiazides are known to reduce calcium excretion, promote intravascular depletion and alkalemia.[2] Moreover, hypercalcaemia is well-known to have natriuretic and diuretic effects that eventually worsen the intravascular status.[2]

Hypercalcaemia usually becomes symptomatic at a concentration of 3 to 3.5mmol/L.[6] The symptoms are predominantly related to gastrointestinal, genitourinary, musculoskeletal and central nervous system. These include abdominal pain, reduced appetite, nephrolithiasis, depressed mood, headache, confusion, lethargy, and muscle weakness. Studies have found that the mean of calcium level among 78 MAS patients was 4.30mmol/L (range, 2.78-6.88mmol/L).[7] In this patient, her calcium was 4.96mmol/L with moderate hypomagnesemia and hyponatremia with mild hypokalaemia. Concurrent electrolyte abnormalities are common in MAS like hypomagnesemia, hyponatremia and hypokalemia.[1] Her serum creatinine (120µmol/L) was slightly high compared to the mean of serum creatinine (106.1µmol/L) in MAS patients.[1]

ECG changes are very important for a high index of suspicious cases, particularly to look for QT/QTc interval shortening and often non-hypothermic J waves.[4] During the initial presentation (Figure 1), there were normothermic Osborn J wave, prominent U waves, PR prolongation, QT interval prolongation, ventricular bigeminy, and R-on-T phenomenon. The presence of normothermic Osborn J wave in a hypercalcaemic patient is not considered as arrhythmogenic that lead to ventricular fibrillation[8] compared to R-on-T phenomenon. R-on-T phenomenon occurs as a result of the increment of T wave duration and therefore, it increases the chance of premature ventricular contraction (PVC) to fall on the T wave. It is well known that hypercalcaemia causes decreased in ventricular conduction velocity and shortening of the refractory period that trigger PVC.[9] Prominent U waves and prolonged PR interval can occur in patients with severe hypercalcaemia.

Our patient had a rapid resolution of hypercalcaemia and metabolic alkalosis after aggressive intravenous normal saline and single bolus dose of diuretic were administered. Withdrawal of the offending agent and treatment with isotonic saline usually produces clinical improvement and rapid resolution of the hypercalcaemia and metabolic alkalosis.10 These combinations are adequate for initial management in ED, but severe cases may require regular diuretics, bisphosphonate and calcitriol.[10] Biphosphonate takes more than 24 hours to take effect and may cause prolonged suppression of serum calcium.[1] Unless clearly indicated, bisphosphonate should be avoided as the emergent treatment in ED. Once the patient's calcium level returned to normal, the Osborn J wave, R-on-T phenomenon, ventricular bigeminy, and prominent U waves in the ECG recording were resolved (Figure 2).

Generally, MAS has a good prognosis if properly treated.[6] Complicated MAS cases associated with posterior reversible encephalopathy syndrome may also have a good recovery if adequately managed.[5] However, a significant number of patients may be left with permanent renal impairment if the diagnosis is forgotten.[6]

CONCLUSION

AS, seizure or encephalopathy may be a presentation for MAS. A high index of suspicion is important in hypercalcaemic patients with metabolic alkalosis and acute kidney injury. A history of taking high doses of calcium supplements should trigger the diagnosis of MAS. Detailed history taking, a complete physical examination and ECG changes are essential for a better diagnosis.

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CASE REPORT

Complicated urinary tract infection caused by *Corynebacterium urealyticum* – A pathogen that should not be forgotten

Mohd Khairul Izzati Omar, MBBCHBAO[1,2], Nurzam Suhaila Che Hussin, MPath[2], Rukman Awang Hamat, MPath[1]

[1]Department of Medical Microbiology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia, [2]Microbiology Unit, Pathology Department, Hospital Kuala Lumpur, Jalan Pahang, Kuala Lumpur, Malaysia

SUMMARY

Although *Corynebacterium urealyticum* has rarely been isolated in diagnostic laboratories, this bacterium can be a significant uropathogen causing significant complications. It causes cystitis and alkaline encrusted cystitis, commonly involved in patients who need prolonged hospitalization and bladder catheterisation. We report here a case of a 19-year-old young man who was diagnosed with N-Methyl D-aspartate receptor (NMDAR) encephalitis that requires hospitalization for optimization of rehabilitation treatment in Hospital Kuala Lumpur, Malaysia. His urine culture isolated slow growing gram-positive pleomorphic rods subsequently identified as *C. urealyticum*. Based on the risk factors, the isolation of *C. urealyticum* could not be simply dismissed as contaminants. The patient was treated successfully with vancomycin for two weeks.

INTRODUCTION

Corynebacterium urealyticum is a recognised pathogen causing urinary tract infection (UTI). This bacterium is commonly seen in people with co-morbidities such as tumour and inflammation, and favour for colonization of urinary catheters that often lead to ascending infection of the bladder mucosa.[1] *C. urealyticum*, formerly known as *Corynebacterium* CDC group D2, is an opportunistic nosocomial pathogen frequently reported to cause cystitis, alkaline encrusted cystitis, pyelonephritis and encrusted pyelitis.[2] This organism had been implicated with human infections since 1935, when it was first discovered. To our knowledge, data on *C. urealyticum* as an uropathogen is limited in Malaysia. The bacterium has a diphtheroid morphology that grows slowly on the culture plates and therefore can be frequently disregarded in routine urine cultures. The identification process can be challenging as *C. urealyticum* has a strong ability to split urea, to distinguish itself from other nonlipophilic *Corynebacterium* species.[1,2] *C. urealyticum* is mostly resistant to a large number of antibiotics such as aminoglycosides and macrolides.[3] However, it is generally still susceptible to vancomycin and teicoplanin. Therefore, accurate identification and appropriate therapy may reduce the avoidable complications of the infection. We report here a case of complicated *C. urealyticum* UTI in a young gentleman as a platform to bridge the clinico-microbiological gap in the care of the patient.

CASE REPORT

A 19 years old young man was recently diagnosed with N-Methyl D-aspartate receptor (NMDAR) encephalitis at Hospital Kuala Lumpur, Malaysia that required hospitalization for optimization of rehabilitation treatment. He lost his bladder control and was put on continuous bladder catheterization (CBD). After two weeks of admission, his urine was noted to be cloudy and stained with blood. He did not have any fever or dysuria. Urine analysis and blood investigations showed features of UTI with alkaline urine (Table I). He went for kidney, ureter and bladder (KUB) ultrasound scan that showed mild right hydronephrosis with proximal hydroureter and thickening of the right ureter wall.

Grossly, the urine was turbid. The urine culture revealed pure growth of tiny colonies on blood agar (BA) and CLED agar after 24 hours incubation. No growth was seen on MacConkey agar. After 48 hours of incubation, the BA showed pure growth of small, pinpoint, whitish to translucent colonies with no haemolysis (Fig. 1). The colony count on CLED agar also revealed similar colony morphology with significant colony count of >25 colonies based on a filter paper method (>10^5 colony forming units per millilitre of urine). Gram stain of the colony revealed gram positive pleomorphic rods resembling diphtheroids (photo was not taken). Rapid urease test was positive. After 72 hours of incubation, enough colonies were available and the isolate was successfully identified as *C. urealyticum* by Vitek ANC (BioMerieux) with 99% confidence level.

Antibiotic susceptibility was performed, and the organism was susceptible to vancomycin but resistant to cotrimoxazole. The patient responded well to vancomycin and the treatment was given for two weeks. Repeat urine culture and sensitivity test showed no isolation of *C. urealyticum*. Ultrasound KUB was repeated following completion of treatment and results revealed that the resolution of the thickening of the right ureter wall. No calculi were seen.

DISCUSSION

C. urealyticum is rarely isolated in Malaysia therefore a high index of suspicions based on the clinical history is of paramount importance. Unfortunately, not all requests for urine culture and sensitivity are completed with significant

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Corresponding Author: Rukman Awang Hamat
Email: rukman@upm.edu.my

Table I: Blood and urine investigations are suggestive of urinary tract infection

Blood investigations	Admission day	Day diagnosed for UTI
Total White Cell count (x 10^9)	7.5	14.4
Haemoglobulin (g/dL)	13.4	13.7
Platelet (x 10^9)	257	178
Urea (mmol/L)	3.9	10.0
Sodium, Na (mmol/L)	139	138
Potassium, K (mmol/L)	2.7	4.5
Creatinine (umol/L)	82	68
Total protein	70	104
Albumin	42	39
Alanine Transaminase	34	58
Alkaline Phosphatase	49	86
Urine FEME		
pH		9.0
Protein		4+
Leucocytes		3+
White blood cell		541/uL
Appearance		Turbid

Fig. 1: Small, whitish to translucent pinpoint colonies (black arrow) of C. urealyticum on BA that can easily be regarded as contaminants after gram stain showed gram-positive pleomorphic rods resembling diphtheroids.

clinical history. Besides prolonged catheterisation and hospitalisation as observed in our patient, other risk factors for *C. urealyticum* infection include immunocompromised status, presence of chronic debilitating disease, recent urologic procedures, kidney transplant and usage of broad-spectrum antibiotics and cytotoxic drugs.[2] This pathogen can be easily missed in routine culture plate as the bacterium takes 48 hours to grow. In addition, the early appearance on the culture plate resembles a non-pathogenic colony; whitish, smooth, opaque and non-haemolytic.[4] Further consideration for investigations is needed when the gram stain of the colony shows gram positive pleomorphic rods and should not merely be regarded as skin contaminants or urethral flora.[2]

The urine FEME will show alkaline features that may have cellular casts or presence of struvite stones but these features are not specific to *C. urealyticum*. Another supportive test such as the urease test is needed. *C. urealyticum* is the only of the *Corynebacterium* species that displays the strongest urease activity.[1,2] This organism is also lipophilic and asaccharolytic, hence could be further differentiated as *C. urealyticum* from other *Corynebacterium* sp. by the production of acid from glucose except for *C. pseudodiphtheriticum*. The latter is an asaccharolytic organism but non-lipophilic and has weak urease activity 2. In addition to the biochemical test, Vitek ANC and API Coryne by BioMerieux are able to identify *C. urealyticum* correctly. Vitek ANC requires smaller inoculums compared to API Coryne that had enabled us to identify the colony correctly after 48 hours. Other parameters such as an increase in white cell count could signify an ongoing infection.

The pathogenicity of *C. urealyticum* is related to its strong urease activity. When the organism invades the uroepithelium, its growth is stimulated by the urea that is present in the urine.[1,2] The urea is hydrolysed, forming hyperammonuria and alkalinisation of urine. This condition leads to hypersaturation and favours for struvite and calcium phosphate crystallization. The crystal formation and its complications are best visualised by an ultrasound graph (USG) which was fortunately not present in our patient. This condition will lead to various clinical complications.

C. urealyticum is also a known multi-drug resistant organism (MDRO).[2,3] It mostly shows resistance to aminoglycosides due to the presence of *aph*(3′)-Ia gene that encodes aminoglycoside 3′-phosphotransferase [3]. This organism also has an *erm* (X) resistance gene that confers resistance towards macrolides [3]. Other antibiotic groups that have been increasingly reported for resistance include quinolones, chloramphenicol and tetracyclines. Vancomycin and teicoplanin are the main stay of treatment and have been shown to have great success in treating *C. urealyticum* UTI.[2] As this is a rare organism, no specific antibiotic susceptibility panel is available. Selected antibiotics were chosen following the consultation from our microbiologist, and the organism was tested susceptible to vancomycin and resistant to cotrimoxazole. The patient was successfully treated with intravenous vancomycin for two weeks.

Urinary tract infection caused by *C. urealyticum* is a nosocomial in origin as it is associated with prolonged catheterisation in our case. Good catheter care will reduce the recovery time from such infection.[2] Infection control measures have a special role in dealing with multi drug resistant organisms. These include standard precautions such as hand hygiene and contact precautions such as single room care patient and proper Personal Protective Equipment (PPE). These important measures will prevent the direct or indirect transmission of *C. urealyticum* when in contact with a patient or with the patient's environment.

CONCLUSION

C. urealyticum is a gram-positive rod that is easily missed in routine urine cultures as it takes 48 hours to grow, and it is commonly regarded as a contaminant or normal urethral flora. A high index of suspicion is warranted in patients with history of prolonged hospitalization and catheterisation, and this will help in isolating the pathogen. Thus, provision of a good clinical history to the laboratory is essential. *C. urealyticum* has a distinct strong urease activity and correctly identified by Vitek ANC. Prompt identification is vital as this is an MDRO and correct choice of antibiotic may prevent complications such as encrusted cystitis and recurrence. The treatment of choice is a course of vancomycin for two weeks. Good catheter care and strict infection control measure will increase the success rate of treatment and also prevent potential outbreak.

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A child with unique skin pattern: A case report of Tinea imbricata

Siti Ruziana Roslan, MD, Azwanis Abdul Hadi, MBChB

Department of Family Medicine, International Islamic University Malaysia, Jalan Sultan Haji Ahmad Shah, Kuantan Pahang Malaysia

SUMMARY

This paper reports a case of Tinea imbricata in a young Orang Asli boy which was noted during his admission for severe symptomatic anemia. Upon discharge, he was started on syrup Griseofulvin 10mg/kg daily and Whitfield cream for 4 weeks. The Department of Orang Asli Development (JAKOA) and the local Health Clinic were contacted before discharge to facilitate patient's follow-up and monitoring. Outbreaks of Tinea imbricata among the Orang Asli have been known to happen from time to time. Although this dermatophyte infection is rare in the urban population, transmission among travelers has been reported. This case report highlights its unique presentation and treatment approach.

INTRODUCTION

Orang Asli or the native aboriginal people in Malaysia makes up only 0.6 percent of the total Malaysian population. Their population is small and they are predisposed to many health problems such as malnutrition, worm infestations, malaria, and skin infections. Tinea Imbricata is common among Orang Asli in Malaysia and infection among visitors to the endemic area has also been reported. Thus, health practitioner in both rural and urban areas should be familiar with common skin conditions among the Orang Asli population for proper diagnosis and treatment.

CASE REPORT

A 4-years old Orang Asli child who was admitted for severe anemia was noted to have a widespread skin rash. His mother had noticed the rash for few months, which started over his abdomen initially and spread to his limbs and face. It was very itchy, especially during hot weather. Apart from lethargy due to the anemia, he had no other symptoms.

He was from the Bateq tribe, which practices a nomadic lifestyle, frequently moving from place to place. He was the elder out of 2 children. Both children had home birth with no formal antenatal follow-up. The patient lived together in a small hut with his parents, younger sister, and his grandparents. His mother said that other family members did not have the same skin condition; however, she was unsure regarding the other villagers.

On examination, conjunctiva of the patient was pale. His height was 94 cm and weight 12kg (Z score between -1 to -2 SD) according to Z score chart (weight for height) for Orang Asli. There were generalized concentric, annular skin lesions with scaly borders mainly over the abdomen, all four limbs, and both cheeks. There were no pedal edema or ascites. His mother and younger sister were examined and noted not to have similar skin lesion. Other systemic examinations were unremarkable. Full blood count (FBC) showed microcytic hypochromic anemia with a hemoglobin of 5.1 g/dl. Anemia workup was taken during admission (Table I).

He was transfused during the admission and was discharged after 6 days of admission. Diagnosis of Tinea imbricata was made clinically based on the typical skin presentation and empirical treatment with syrup Griseofulvin 10mg/kg/day and Whitfield cream (Benzoic acid 6%+ Salicylic acid 3%) for local application for 4 weeks was given. Upon discharge, the JAKOA and the local health clinic were contacted to ensure follow-up. The plan was to screen other family members and villagers for the similar skin condition as well as for weight monitoring, immunization and anemia follow up. During follow up by the local health clinic, the skin lesion has improved, and the child was planned to continue follow up for immunization and weight monitoring. The team from the local health clinic also screened other villagers and found several with similar skin lesion and they were all treated.

DISCUSSION

The 3 main tribes of Orang Asli in Malaysia are the Semang (Negrito), Senoi, and Proto Malay (Aboriginal Malay) with the highest population in Pahang and Perak. The Bateq tribe is one of the sub-group of Negrito found mainly in the Northwest of Terengganu, Northeast Pahang, and South Kelantan.[1]

In Malaysia, there are no established statistics on Tinea imbricata. However, there have been outbreaks among the Orang Asli reported in the news from time to time. Some of them claimed to have had the skin disease for many years, untreated due to poor recognition of the skin disease by the attending healthcare physician, with poor compliance to medications and follow up.[2] Two large outbreaks were reported in year 2018 and 2019, involving Orang Asli in Kampung Kuala Koh, Gua Musang involving 30 and 120 people respectively.[2,3] Even though it was uncommon, there have been reports of Tinea imbricata acquired among non-natives, due to tourism or work-related. Infection among visitors to endemic areas has been reported in Tahiti, Samoa and Solomon Island, whereby an Italian lady who had a close contact with the island's native for 3 months had

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Corresponding Author: Siti Ruziana Roslan
Email: che.seat@gmail.com

Table I: Anemia workup of the patient

Investigations		Result	Normal value
Full blood count	Hemoglobin	5.1 g/dL	10.5-14.0 g/dL
	MCV	54.6 fl	70.0-74.0 fl
	MCH	13.8 pg	25.0-31.0 pg
	WBC	7.6 x 10^9/L	6.0-15.0 x 10^9/L
	Platelet	375 x 10^9/L	150-400 x 10^9/L
Iron study	Serum Ferritin	4.1 umol/L	>12 umol/L
	Serum Iron	3.80 umol/L	5.83-34 umol/L
		TIBC	77.20 umol/L
Stool ova and cyst		Negative	
Hb Analysis		Findings are consistent with iron deficiency anemia however beta thalassemia trait cannot be excluded	
Full blood picture		Moderate hypochromic microcytic RBCs with cigar cells.	

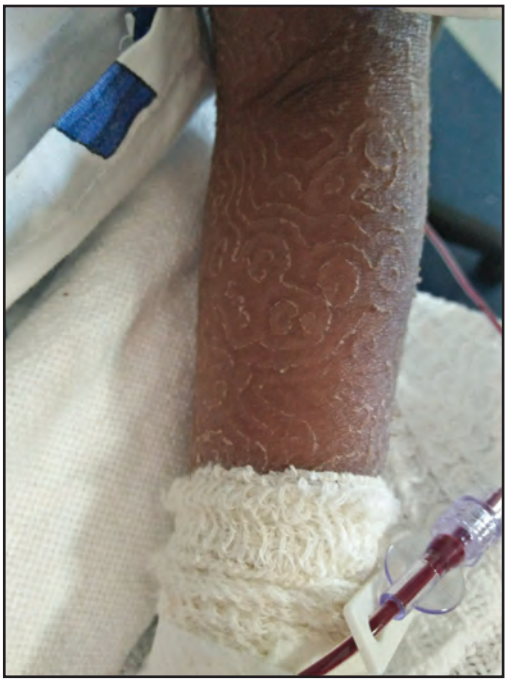

Fig. 1: Concentric, annular skin lesion with scaly borders over the left forearm.

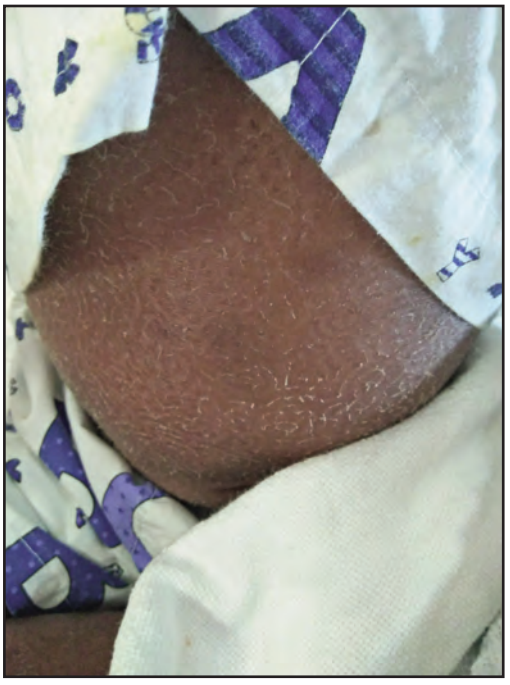

Fig. 2: Concentric, annular skin lesion with scaly border over the left side of abdomen.

contracted the disease. She was initially diagnosed as contact dermatitis for 7 months before treated as Tinea imbricata.[4]

Tinea imbricata is caused by *Trichophyton concentricum*. It has been described as early as 1919 and was also sometimes known as *Kurap Losong* by the locals. It is also known as Tokelau, concentric tinea, Indian or Chinese tinea, scaly tinea, elegant tinea, lace tinea, and chimberé. It is commonly seen in the Southwest Pacific, Central and South America, and Southeast Asia.[5] The disease is mainly seen among the aboriginal people. There is a mix of predisposing factors including the damp and hot climate, poor hygiene, malnutrition as well as genetic predisposition.[5,6] In this case, poor nutrition was one of the predisposing factors for him acquiring this disease. Outbreaks of Tinea imbricata are common since it spreads by close contact especially among households.[7] Genetic susceptibility (autosomal inheritance pattern) towards acquiring Tinea imbricata could also explain the outbreaks among the native aboriginal population.[5]

Diagnosis is made clinically by its typical skin manifestation of generalized concentric, annular or lamellar plaque, with scaly borders, giving rise to appearance of lace, fish scales, or overlapping roof tiles.[5,6] It usually affects the skin over the trunk, limbs, and face. It rarely affects the scalp, nails, soles, and palms and usually spares the hair. It can occur with or without itchiness and topical corticosteroids can obscure the diagnosis.

If needed, diagnosis can be confirmed by examination of skin scrapings of the active border of the lesion by potassium hydroxide (KOH) wet mount, and typical microscopic findings are short, septate hyphae, with no arthroconidia, and numerous spores of *T. concentricum*.[7] *Trichophyton* is characterized morphologically by the development of both smooth-walled macro- and microconidia. The presence of microconidia differentiates this genus from Epidermophyton and Microsporum. For species without conidia, culture characteristics and clinical information such as, lesion morphology, location, travel history, animal contacts and occupation are important.[8]

The lesion can become chronic and lichenified with post-inflammatory hyper/hypopigmentation. Intense itching can impair sleep quality and predispose to secondary bacterial infection. Re-infection is common.[5-7]

Oral antifungal is the treatment of choice. It can be treated effectively by oral antifungal either oral Griseofulvin or Terbinafine.[9] Wingfield AB et al. reported a randomized clinical trial which included 59 patients with tinea imbricata for efficacy analysis showing griseofulvin and terbinafine to be effective with no adverse events. Terbinafine has longer efficacy with additional advantage of daily dosing which can improve compliance, but it is not available in our Health Clinics. The effective dose is oral Terbinafine 250mg once daily or oral Griseofulvin 500mg twice daily for 4 weeks for adults.[9] For children, the dose for Syrup Griseofulvin is 10mg-20mg/kg/day in single or 2 divided doses. Combination with a topical keratolytic agent such as Whitfield's ointment as adjunctive therapy may improve therapeutic response.[10] Oral Griseofulvin and Whitfield's ointment are widely available in Health Clinics across Malaysia.

Despite the effective treatment available, there are many challenges in treating the Orang Asli people. Many of them still practice a nomadic lifestyle. This complicates the local health care to approach them and provide adequate treatment. Language barriers, poor hygiene, low educational background, and unique beliefs, affect their compliance towards health care services by the government. Nowadays, with the help of JAKOA, 'Pasukan Bergerak Orang Asli' (PBOA), and the local health clinic can gain access to the Orang Asli population and provide the basic medical attention they needed.

CONCLUSIONS

Tinea imbricata has a typical skin pattern that facilitates clinical diagnosis and can be treated effectively with oral Griseofulvin which is effective and is readily available in local health clinics in Malaysia. It is important for health practitioners, especially those who work in rural areas to be able to identify this skin infection. However, with the rise of traveling and tourism, it is also important for urban health care physicians to be aware of this skin fungal infection as well. Issues in treating Orang Asli such as non-compliance with treatment can be overcome with the help from the JAKOA.

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CASE REPORT

Intravascular ultrasound guided treatment of severe coronary artery calcification with Shockwave Intravascular Lithotripsy

Yap Lok Bin, FRCP[1], Choy Chun Ngok, MRCP[1], Balachandran Kandasamy, MRCP[2]

[1]Department of Cardiology, Subang Jaya Medical Centre, Malaysia, [2]Department of Cardiology, Institut Jantung Negara, Malaysia

SUMMARY

Coronary artery calcification is a pathological deposition of calcium in the intimal and medial layer of the arterial wall. Shockwave intravascular lithotripsy (IVL) has evolved as a new modality to treat heavily calcified coronary arteries. IVL involves using a percutaneous device to produce acoustic pressure waves resulting in the delivery of sufficient energy to break up superficial and deep calcium deposits. We present a case where highly dense coronary calcium was successfully treated with intravascular ultrasound (IVUS) guided coronary angioplasty and IVL treatment. IVUS demonstrated heavy calcification at the proximal LAD with a 360 ° calcium arc. Post procedure, IVUS demonstrated multiple fractures of coronary calcium. Stent deployment was done successfully with good stent strut apposition. There was no procedure related complication. The case demonstrates an example where IVL is an important adjunctive tool in the cardiac catheterization laboratory for lesion preparation and optimal percutaneous coronary intervention.

INTRODUCTION

Coronary artery calcification is due to deposited calcium in the intimal and medial layers of the arterial wall. Heavily calcified plaques in coronary arteries is a risk factor for major adverse cardiac events and mortality.[1] Coronary intervention in calcified coronary arteries is challenging as it may be difficult to dilate the calcified segment with semi-compliant balloons. Coronary calcium can often be treated successfully with different therapeutic calcium debulking techniques, including orbital or rotational atherectomy, excimer lasers as well as cutting and scoring balloons.[2] However, these techniques can be associated with serious complications, such as coronary artery dissection and perforation. There has thus been a need for alternative treatment modalities, especially those which are associated with a minimal degree of complications. Shockwave intravascular lithotripsy (IVL), a technique similar to the one used in nephrolithiasis, has evolved as a new modality to treat heavily calcified coronary arteries. IVL involves using a percutaneous device to produce acoustic pressure waves resulting in the delivery of sufficient energy to break up superficial and deep calcium deposits.[3] Intracoronary artery imaging techniques such as intravascular ultrasound (IVUS) and optical coherent tomography (OCT) are often performed pre IVL treatment to evaluate the extent of calcification and post procedure as well to demonstrate calcium fractures and evaluate procedural success.

We present a case where highly dense coronary calcium was successfully treated with IVUS guided coronary angioplasty and IVL treatment.

CASE REPORT

A 70-year-old male had presented with angina on exertion for 1 week to Subang Jaya Medical Centre, Malaysia, with ongoing chest pain. He had associated exertional shortness of breath for 1 month. He had a history of dyslipidemia and was on simvastatin 20mg once daily.

On examination, he had a blood pressure of 120/80 mm Hg and a pulse rate of 80 beats per minute. Echocardiography showed good left ventricular systolic function (Ejection Fraction of 55%). Electrocardiogram showed sinus rhythm and blood tests showed normal full blood count and renal function. Cardiac enzymes including troponin were normal. Treadmill stress testing with a Bruce protocol was performed to stage II, the patient developed angina and ST depression in the infero-lateral leads. The patient gave consent to proceed for invasive coronary angiogram.

A coronary angiogram via femoral approach showed densely calcified 70-80% stenosis of the proximal left anterior descending (LAD) and 90% stenosis at the mid-LAD coronary artery (Figure 1). The left circumflex coronary artery was non dominant and unobstructed. The right coronary artery had a proximal moderate 40-50% stenosis. Further evaluation was done with IVUS. This showed extensive circumferential calcium with a 360 degree arc at proximal LAD close to the ostium (Figure 1). The minimal lumen area (MLA) of the LAD vessel was 2.80 mm^2.

We planned for intravascular lithotripsy for densely calcified coronary segments and subsequent coronary stenting. The left main coronary artery was engaged with a 6 french sized guiding catheter (EBU) with diameter 3.5 mm and the lesion in LAD was crossed with 0.014" hydrophilic guidewire. The lesion was predilated with 2.5 mm × 10 mm and 3.0 mm x 10 mm non-compliant (NC) balloons up to 16 atm pressure. Then, the IVL balloon was prepared with negative suction

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Corresponding Author: Yap Lok Bin
Email: dryaplokbin@gmail.com

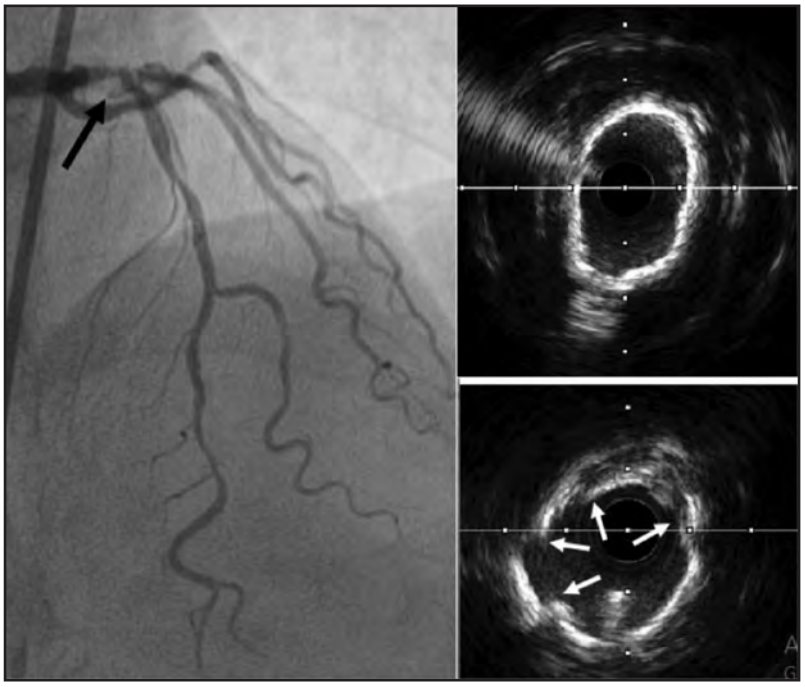

Fig. 1: Pre procedure angiogram (left) showing severely calcified stenosis at the LAD (arrow) and tight stenosis at the mid LAD. IVUS Image shows surrounding a 360 calcium arc (above). Post IVL and calcium fractures (arrows) in the vessel (below).

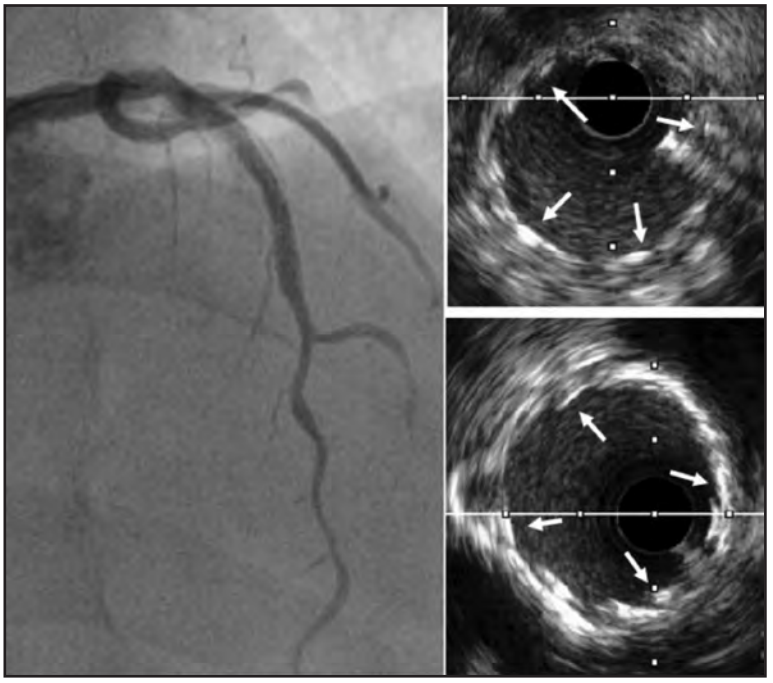

Fig. 2: Postprocedure angiogram after IVL and stenting of the lesion (left). IVUS images of the distal LAD (above) and proximal LAD (below) showing good stent struts apposition (arrows).

with a 20 cc syringe and connected to the IVL pulse generator. A 2.5 × 12 mm IVL balloon (Shockwave C2 IVL, Shockwave Medical) was placed across the proximal LAD calcified lesion, dilated up to 8 atm pressure. Five balloon inflations with 10 shockwave pulses each were delivered to the lesion at the proximal LAD. Following IVL treatment, blood flow in the coronary artery remained good. Repeat IVUS images showed multiple fractures of calcified plaque at the proximal LAD (Figure 1).

A 2.75 × 19 mm Drug-Eluting Stent (DES) was deployed at the mid LAD and a second 3.0 x 14 mm DES was deployed at the proximal LAD close to the LAD ostium, with both stents overlapping. The stents with post dilated with a 3.0 x 10 NC balloon. Repeat IVUS was performed following LAD stenting. IVUS showed an improvement in MLA from pre angioplasty of 2.80 mm^2 to post angioplasty MLA of 5.60 mm^2. The stent struts were well opposed to the LAD vessel wall (Figure 2). The patient was hemodynamically stable post-procedure and was

discharged the following day. He was put on dual anti-platelet treatment with aspirin and clopidogrel for 1 year. The patient was seen for follow-up in clinic after 1 month was stable with no further angina.

DISCUSSION

Shockwave IVL has evolved over recent years as a device which can successfully treat both superficial and deep calcium and aid in effective deployment of the coronary stent. IVL utilizes 2 shockwave ultrasound emitters positioned inside an expandable balloon. The IVL balloon comes in a constant length of 12 mm with various diameters ranging between 2.5 to 4.0 mm. The treatment is delivered by placing the balloon catheter within the coronary artery at the site of stenosis, and inflating it up to 4 atm pressure.[4] On activation, the battery- powered generator delivers a series of electrical pulses into the lithotripsy emitters which convert it into mechanical energy (sonic pressure waves). The combined solution of saline and contrast within the balloon allows transmission of sonic pressure waves into the vessel calcium deposits. These acoustic waves create micro-fractures within calcium deposits in the vessel wall. Since severe calcification is an important predictor of restenosis after PCI, treatment with IVL can potentially increase the vessel diameter and ensure better stent placement.

Trial Evidence for IVL

The Disrupt Coronary Artery Disease (Disrupt CAD) I and II trials demonstrated initial safety and feasibility of IVL in calcified coronary lesions. The first multicentre prospective study, Disrupt CAD I, enrolled 60 patients with severely calcified vessels.[5] There was successful stent implantation following IVL in all patients. The second prospective trial, Disrupt CAD II, studied 120 cases with extensive coronary artery calcification.[6] There was similarly successful delivery and use of the IVL catheter was achieved in all patients. Furthermore, there was no complication of slow coronary flow or coronary artery perforation.

The largest study so far was the Disrupt CAD III study, which was a prospective, single-arm multicenter study including 431 patients with calcified coronary arteries.[7] The primary safety endpoint of the 30-day freedom from major adverse cardiovascular events was 92.2%, procedural success was 92.4%. OCT demonstrated multiplane and longitudinal calcium fractures after IVL in 67.4% of lesions. This study showed that coronary IVL had high procedural success in angioplasty of severely calcified lesions with low complication rate.

Another multicentre registry studied 78 patients with calcified coronaries where the lesion was treated with the Shockwave C2 balloon.[8] The study demonstrated a significant reduction in mean diameter stenosis of up to 26.7 ± 4.3% after IVL therapy. In all the cases, the primary endpoint of adequate stent expansion with < 20% in-stent residual stenosis was achieved. There was no major adverse cardiovascular event, thus demonstrating good success rate with low procedural risk.

Complications of IVL

The procedural complications of IVL may include slow coronary blood flow, lack of reflow, distal embolization, coronary artery perforation, and arterial dissection. Coronary artery perforation is a rare phenomenon secondary to high energy acoustic wave emission. There were four cases of coronary artery dissection in Disrupt CAD I trial [5] whilst only two patients experienced Type B and C dissection in Disrupt CAD II study.[6]

CONCLUSIONS

Coronary calcium hinders adequate stent expansion which is a predisposing factor for complications of acute stent thrombosis and subsequent in-stent restenosis. The Shockwave IVL is a safe and effective treatment approach to disrupt the coronary calcification through localized, circumferential sonic pressure waves. Adequate fracture of coronary calcium by IVL allows successful coronary stent deployment with good stent strut apposition, thus reducing the risk of acute stent thrombosis and further In-stent restenosis. IVL is an important adjunctive tool in the cardiac catheterization laboratory for lesion preparation and optimal percutaneous coronary intervention.

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An exposed Cardiovascular Implantable Electronic Device (CIED) complicated with infection: A case report of unconventional experience with 'Sealed CIED'

Mohd Ridzuan Mohd Said, MMED[1], Sathvinder Singh Gian Singh, MMED[2], Chin Yung Chea, MRCP[2], Mohd Al-Baqlish Mohd Firdaus, MMED[1], Kantha Rao Narasamuloo, MRCP[2], Saravanan Krishinan, MRCP[2]

[1]Department of Medicine, International Islamic University of Malaysia, Pahang, Malaysia, [2]Department of Cardiology, Hospital Sultanah Bahiyah, Kedah, Malaysia

SUMMARY

The rate of infected Cardiovascular Implantable Electronic Device is alarming and causes substantial socio-economic burden. A common approach involves immediate extraction of the infected device. Here, we report an unorthodox approach to this problem by 'sealing' the generator inside a sterile container as a temporary permanent pacemaker while waiting for implantation of another device.

We report a 66 years old emaciated lady with underlying Sick Sinus Syndrome, who had an implanted single chamber pacemaker and presented with partial protrusion of her device. She underwent sub-pectoral implantation of the new device but subsequently re-presented with pocket site infection after a month. A decision was made to extract the infected generator from the sub-pectoral pocket and it was sealed inside a sterile container as 'bridging therapy' while awaiting arrival of a leadless pacemaker for implantation together with total extraction of the old infected device.

Our clinical vignette demonstrated the difficulties we encountered and influenced on our decision for this unconventional approach despite limited supporting evidence.

INTRODUCTION

More than one million of Cardiovascular Implantable Electronic Device (CIED) are implanted on a yearly basis and contributed to the increasing prevalence of infected CIED.[1,2] A common approach involves immediate extraction of the infected device and new implantation placed at a different site. We report here an unorthodox approach and possibly the first to describe 'sealing' the device inside a sterile container for a temporary permanent pacemaker (TPPM).

CASE REPORT

A 66 years old lady with underlying Sick Sinus Syndrome and atrial fibrillation presented to the emergency department of the Hospital Sultanah Bahiyah, Kedah, Malaysia with partial protrusion of her CIED. She was diagnosed with Sick Sinus Syndrome in 2008 and a single chamber pacemaker (Verity ADx XL SC, St Jude Medical, Sylmar, CA, USA) was implanted.

She presented with gradual partial protrusion of the device in 2020 (Figure 1A) and underwent creation of a sub-pectoral pocket under general anesthesia by a plastic surgeon. The previous right ventricular lead was connected to a new generator (Endurity PM1162, Abbot, Sylmar, CA, USA) and implanted into the sub-pectoral pocket. Her recovery was uneventful, and she was discharged with regular follow-up.

Unfortunately, she re-presented with unhealthy discoloration of her skin (Figure 1B) and intravenous Ampicillin / Sulbactam was commenced. White cell count was normal (9 x 10^3/uL) and repeated blood cultures remained negative with no vegetations seen on transthoracic echocardiography. Hence, she underwent further wound exploration under general anesthesia.

Intraoperatively, unhealthy granulation tissue was observed confined only to the inside of the sub-pectoral pocket and this was excised, and a proper debridement was performed. Result of tissue culture demonstrated no growth of organism. Subsequently, the proximal part of the right ventricular lead and pacemaker generator were inserted into a sterile bag and sealed onto anterior chest (Figure 1C). The open wound was sutured and covered with a sterile dressing. Once financial approval was obtained, the Micra™ (MC1VR01, Medtronic, Minneapolis, USA) was implanted (Figure 1D) three days later via a transvenous right femoral approach while simultaneous explantation of the old generator. Decision for immediate implantation of Micra™ (MC1VR01, Medtronic, Minneapolis, USA) was made considering contained infection within sub-pectoral pocket, negative tissue culture and unremarkable septic parameters. Consequently, her recovery was uneventful and she was discharged with close monitoring.

DISCUSSION

Implantation of CIED has increased substantially due to growing evidence on indications plus heightened awareness amongst practitioners.[1] Unfortunately, complication rates remain elevated highest at 12%[1] and the reported rate of infection between 0.13% to 19.9%.[2] In addition, CIED infection is associated with substantial socio-economic burden due to prolonged hospital stays and expensive treatments.

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Corresponding Author: Mohd Ridzuan Mohd Said
Email: ridzuan.said85@gmail.com

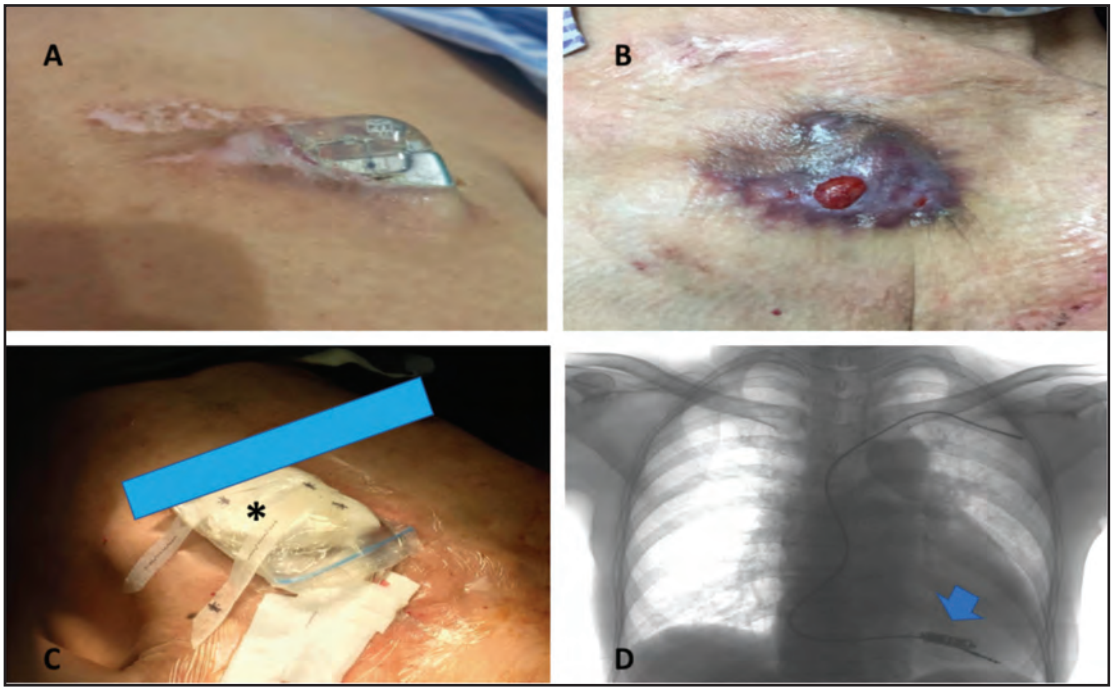

Fig. 1: Images of patients' CIED, A; Protrusion of CIED device on left pectoral, B; Unhealthy discoloration and granulation tissue post sub-pectoral implantation, C; CIED (marked *) was secured inside sterile container during second operation, D; Chest X-Ray post Micra™ (Arrow) insertion and extraction of pacemaker, previous lead was left in situ.

Current practice for CIED implantation is via a pre-pectoral approach for accessibility and better tolerability among patients but a sub-pectoral approach offers an alternative window with its own advantages.[3] Apart from providing aesthetic comfort with undetectable CIED, a sub-pectoral approach is advantageous for the underweight and ageing population with a deep seated CIED.[3]

For our patient, we opted for a sub-pectoral approach at the same site during the initial event because firstly, we noted a sterile healthy pocket and secondly, the patient's small body habitus (BMI 16.7 kg/m^2) favored a sub-pectoral approach as recurrent device erosion was anticipated even with a right - sided pre-pectoral approach.

Subsequently, our decision for packaging the CIED within a sterile container as a functioning TPPM was made as the patient was dependent on the device and had low blood septic parameters. Secondly, the whole procedure was performed in the operation theatre with thorough debridement and a fully aseptic approach. Thirdly, a conventional approach of inserting a temporary pacing system as bridging therapy is preferred but increases the risk of device-related infection by two-fold,[4] especially via femoral approach.[5] In addition, safety and feasibility of TPPM has been demonstrated with minimal complications even for extended periods of months.[5] Collectively, these factors influenced our decision for externalization of the temporary permanent pacemaker as a bridging therapy. In addition, we also left the previous transvenous lead in situ to avoid any complication mainly right ventricular (RV) perforation.

Presently, reports on a similar approach is limited and we believe this to be the first case of 'sealing a CIED' inside sterile packaging as bridging therapy.

CONCLUSION

In conclusion, our clinical vignette demonstrates the difficulties that can be encountered in dealing with CIED infection and highlights an unorthodox management by sealing the CIED outside the patient's body as bridging therapy.

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A case of Multisystem Inflammatory Syndrome in adults in Malaysia

Seow Chee Keong, MBBS[1], Gan Wee Fu, MRCP[2], Nor Zaila Zaidan, MMed[2]

[1]Internal Medicine Department, Hospital Melaka, Malaysia, [2]Infectious Disease Unit, Hospital Melaka, Malaysia.

SUMMARY

Multisystem Inflammatory Syndrome in Adults (MIS-A) is a rare but potentially life-threatening complication following SARS-CoV-2 infection. We present a Malaysian case of MIS-A in a 45 year old gentleman who developed cardiogenic shock following a mild SARS-CoV-2 infection.

INTRODUCTION

Multisystem Inflammatory Syndrome in Children (MIS-C) was first described in April 2020 as a hyperinflammatory syndrome with features resembling Kawasaki disease. Since June 2020, a similar syndrome for adults, Multisystem Inflammatory Syndrome in Adults, (MIS-A) has been increasingly reported worldwide. The Center for Disease Control and Prevention (CDC) published a report with a collection of 21 patients of MIS-A in the Morbidity and Mortality Weekly Report (MMWR) on 20 Oct 2020.[1] In this report we describe a local case of MIS-A in a 45-year-old gentleman who recently had COVID-19 infection. To the best of our knowledge this is the first case described in Malaysia.

CASE REPORT

A 45 years old gentleman who was diagnosed with asymptomatic COVID-19 through contact screening and yielded a positive combined nasopharyngeal (NPS) and oropharyngeal (OPS) swab rt-PCR for SARS-CoV-2. He is an active smoker with no known medical illness or previous admission. He was not vaccinated with SARS-CoV-2 vaccine previously.

He was initially quarantined in a low risk COVID-19 quarantine centre as per the Malaysian protocol at that time and was subsequently discharged well on day 12 of illness. His quarantine was uneventful for he did not require any oxygen therapy or medication.

Soon after discharge, at day 13 of illness based from PCR, he developed intermittent low grade fever, non-productive cough, sore throat, abdominal bloating and diarrhoea. Otherwise, he denied shortness of breath, chest pain, skin rashes, red eyes or haematuria. He consulted a general practitioner who prescribed him a course of empirical antibiotics for presumed infective diarrhoea. However, his symptoms persisted and he sought medical attention from the emergency department of Hospital Melaka, Malaysia six days later (day 19 from PCR).

Upon arrival in the emergency department, he was febrile (39 degrees Celsius), hypotensive (blood pressure 96/50mmHg) and tachycardia (heart rate 125 beats per minute). Otherwise, there was no hypoxia (pulse oximetry reading 98% under room air), with unremarkable examination including no rashes, mucositis or palpable lymphadenopathy except for appearing malaise.

Fluid resuscitation with crystalloid did not improve his haemodynamic status and intravenous infusion of noradrenaline was started. Blood investigations drawn on initial presentation revealed leukocytosis, thrombocytopenia, raised inflammatory markers, acute kidney injury, and mild hepatitis (as shown in Table I). Cardiac dysfunction was evident by raised cardiac biomarkers and echocardiogram findings. Repeated NPS SARS-CoV2 PCR during this admission was negative. No SARS-CoV-2 antibody taken during this admission.

He was admitted to the intensive care unit (ICU) for close monitoring and was started on empirical broad-spectrum antibiotics and venous thromboembolism chemoprophylaxis. However, there was no positive culture and the antibiotic was subsequently stopped. In view of the recent diagnosis of COVID-19 with unexplained multi-organ dysfunction and elevated inflammatory markers in shock, a diagnosis of MIS-A was considered and he was given a dose of intravenous immunoglobulin (IVIG) 2g/kg. There was a remarkable response post IVIG clinically. He felt better with improved blood parameters and we were able to wean off the inotropic support. He continued to improve and was discharged from ICU within 24 hours after IVIG. He was given diuretics for his failure symptoms and was well during his clinic appointment. His repeated transthoracic echocardiogram 2 months later revealed normal ejection fraction with resolved regional wall motion abnormality.

DISCUSSION

MIS-A is a rare yet life-threatening condition. Diagnosis of MIS-A requires evidence of current or recent COVID-19 infection with severe dysfunction involving one or more extrapulmonary organs and raised inflammatory markers.[1] The patient should not have another more likely alternative diagnosis.[1] Previously those patients with severe pulmonary disease were excluded to avoid inclusion of patients in which organ dysfunction might be the result of tissue hypoxia.[1] However this exclusion criteria was not in the latest case definition of MIS-A, published by CDC in May 2021 (Table

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Corresponding Author: Seow Chee Keong
Email: ckseow92@gmail.com

Table I: Relevant investigation during hospitalization

Blood investigation (Units)	Day 1 of admission	Day 4 of admission (24 hours after IVIG)	Prior to discharge (72 hours after IVIG)
Total white blood cells count (cells/μL)	34.8	20.3	13.1
Absolute neutrophil count (cells/μL)	32.3	16.4	9.7
Absolute lymphocyte count (cells/μL)	1.5	2.5	2.0
Platelets count (cells/μL)	85	254	245
Serum Urea (mmol/L)	23.7	16.7	9.3
Serum Creatinine (μmol/L)	219	116	79
Alanine transaminase (U/L)	128	151	139
Aspartate transaminase (U/L)	130	105	-
CRP (mg/L)	260	117	22
D-dimer (mg/L)	32.49	-	-
Procalcitonin (ng/mL)	24.35	2.9	-
Ferritin (pmol/L)	7830.2	-	-
High sensitivity Troponin I (ng/L)	5700.51	-	-
NT-proBNP (pg/mL)	10324	-	-
Peripheral blood film	Normochromic and normocytic red blood cells (RBC), no fragmented cells or nucleated RBC seen. As for white blood cells (WBC) count, it is increased predominantly neutrophils. Many neutrophils show toxic granulation. Some dysplastic neutrophils observed. Reactive lymphocytes are easily seen. Left shift seen. No blast. Platelet count was adequate with few large platelets and occasional giant platelets seen. Few small platelet clumps present. No evidence of microangiopathy hemolytic anaemia (MAHA).		
Microbiological and serological investigation			
Nasopharyngeal swab for SARS-CoV-2 PCR	Negative		
HIV Ag-Ab, HepBsAg and Anti-HCV	Negative		
Blood, urine and stool culture	No growth		
Imaging			
ECG	Sinus tachycardia with mild T inversion at precordial leads		
Transthoracic echocardiogram	Mild global hypokinesia with ejection fraction 45%, no pericardial effusion		
Chest radiography	Clear lung fields (as shown in Figure 1)		
Ultrasound abdomen	No significant abnormality detected		

Table II: Multisystem Inflammatory Syndrome in Adults (MIS-A) case definition information for healthcare providers[2]

Case definition of MIS-A by CDC
A patient aged ≥21 years hospitalized for ≥24 hours, or with an illness resulting in death, who meets the following clinical and laboratory criteria. The patient should not have a more likely alternative diagnosis for the illness (e.g., bacterial sepsis, exacerbation of a chronic medical condition).
Clinical criteria
Subjective fever or documented fever (≥38.0 C) for ≥24 hours prior to hospitalization or within the first three days of hospitalization and at least three of the following clinical criteria occurring prior to hospitalization or within the first three days of hospitalization. At least one must be a primary clinical criterion. A. Primary clinical criteria a. Severe cardiac illness Includes myocarditis, pericarditis, coronary artery dilatation/aneurysm, or new-onset right or left ventricular dysfunction (LVEF<50%), 2nd/3rd degree A-V block, or ventricular tachycardia. (Note: cardiac arrest alone does not meet this criterion) b. Rash and non-purulent conjunctivitis B. Secondary clinical criteria a. New-onset neurologic signs and symptoms Includes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barré syndrome) b. Shock or hypotension not attributable to medical therapy (e.g., sedation, renal replacement therapy) c. Abdominal pain, vomiting, or diarrhea d. Thrombocytopenia (platelet count <150,000/ microliter)
Laboratory criteria
The presence of laboratory evidence of inflammation and SARS-CoV-2 infection. A. Elevated levels of at least two of the following: C-reactive protein, ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin B. A positive SARS-CoV-2 test during the current illness by RT-PCR, serology, or antigen detection

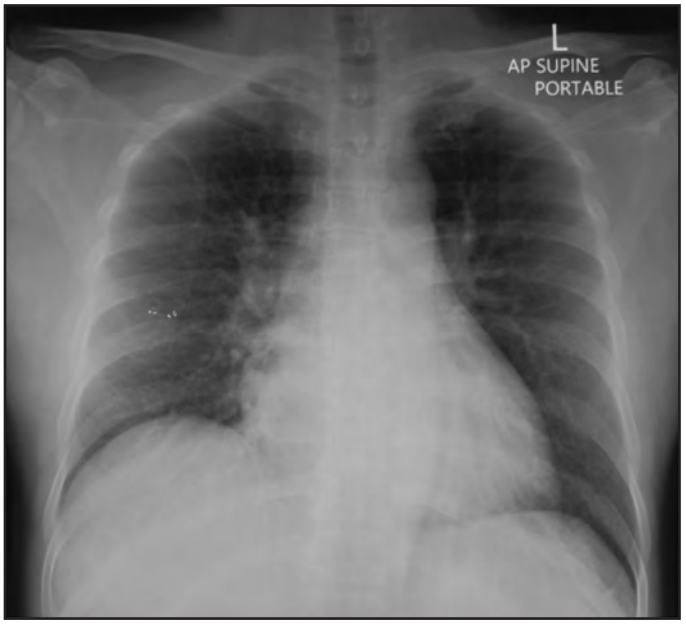

Fig. 1: This chest X-ray was taken on the day of admission.

II).[2] Our patient fulfilled both old and new case definition of MIS-A.

Pathophysiology of MIS-A is still not well understood. Postulated mechanisms of extrapulmonary manifestations in COVID-19 included endothelial damage and thromboinflammation, dysregulation of immune responses, and maladaptation of ACE2-related pathways.[3] Possible similar mechanisms responsible in the pathophysiology of MIS-A.[1] In a case report published by Boudhabhay and colleagues, the renal biopsy of the reported case with MIS-A revealed a thrombotic microangiopathy (TMA) picture with mainly neutrophil interstitial infiltrate.[4] Another unfortunate MIS-A case, autopsy findings of the heart revealed endotheliitis and vasculitis which involved the small cardiac vessels and extending into the surrounding epicardial fat and interstitial spaces.[5] The most interesting finding in this autopsy is that the coronary arteries were spared from the inflammatory cells infiltration, unlike the typical findings of coronary artery involvement in childhood Kawasaki disease.[5,6]

The interval between COVID-19 and the development of MIS-A symptoms was reported to be between 2–5 weeks.[1] In a retrospective cohort study of a single center, patients with MIS-A were in a younger age group compared to those with acute COVID-19.[7] One third of those patients with MIS-A (5 out of 15) required intensive care treatment.[7] Another case series of 51 patients with MIS-A showed that cardiovascular abnormalities were the most frequently reported findings (82.5%), followed by fever (80.4%), gastrointestinal symptoms (72.5%) and respiratory symptoms (54.9%).[8] Only 2 reported mortality out of 51 patients with MIS-A in that particular case series.[8]

As the postulated pathophysiology of MIS-A is a dysregulated immune response, various immunomodulatory medications have been tried, for examples glucocorticoid (especially intravenous methylprednisolone), intravenous immunoglobulin (IVIG), anakinra (Interleukin-1 inhibitor), tocilizumab (Interleukin-6 inhibitor) and eculizumab (monoclonal anti-C5 antibody).[1,4,5,7-9] In a case series written by Bastug and colleagues, the majority of reported cases (60.8%) were treated with glucocorticoids and 37.3% of the reported cases were treated with IVIG.[8] However, at the moment there are no widely accepted treatment guidelines available for MIS-A in contrast with MIS-C. American College of Rheumatology suggested a stepwise approach of immunomodulatory therapies in MIS-C where IVIG is the first-tier therapy and glucocorticoid is used as adjunctive therapy in patients with severe disease or those with a refractory course of disease.[10]

Clinicians are more acutely aware of MIS-C among the paediatric population, but adults are not excluded from getting this complication of COVID-19. In this difficult time with increasing cases of COVID-19 beleaguering Malaysia and the rest of the world, clinicians should be aware of such an entity and have a high index of suspicion for early diagnosis and management to improve outcome. The diagnosis of MIS-A in patients with no clear epidemiology history of SARS-CoV-2 infection can be challenging, as some patients can be asymptomatic of COVID-19 but develop MIS-A subsequently.[1] Thus for these patients, SARS-CoV-2 serology is an important investigation in reaching the diagnosis of MIS-A.

CONCLUSION

We report here a case of MIS-A who responded well to IVIG and to the best of our knowledge, is the first reported case in Malaysia. Hopefully, through this case report, this will be able to increase the awareness of MIS-A as it is likely underdiagnosed during this pandemic.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Jejunal gastrointestinal stromal tumour masquerading as an ovarian cancer: A case report

Sohail Mushtaq, FRCS[1,2], Richelle Chua Huey Bing, MD[1,2], Sim Sze Kiat, MS[1], Nik Azim Nik Abdullah, MS[2]

[1]Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, Kota Samarahan, [2]Department of surgery, Hospital Umum Sarawak, Jalan Hospital Kuching, Sarawak

SUMMARY

A 60-year-old lady presented with lower abdominal discomfort and a huge palpable intra-abdominal mass for 4 months, with significant weight loss over half a year. Transvaginal ultrasonography and computed tomography (CT) abdomen showed a large right solid cystic mass likely ovarian in origin. The CA-125 was raised. With the provisional diagnosis of ovarian cancer patient underwent laparotomy at Hospital Umum Sarawak, Malaysia. However intraoperative findings showed that uterus and both ovaries were normal. The tumour was arising from the jejunum and adherent to the dome of the urinary bladder and right broad ligament. The tumour was resected and final diagnosis was jejunal gastrointestinal stromal tumour (GIST). We described this case which was misinterpreted as an ovarian cancer.

INTRODUCTION

Gastrointestinal stromal tumour (GIST) is the most common primary mesenchymal tumours of gastrointestinal tract and the cell of origin is the interstitial cell of Cajal.1 About 75% of GISTs have mutations in tyrosine kinase, and 10% have mutations in PDGFRα. GIST is typically a disease of adults in 5th or 6th decade of life. It is relatively more common in males. GIST can arise anywhere from oesophagus to rectum but common sites are stomach (50-60%) jejunum, ileum (25-35%) and duodenum (10%).[1]

Clinical features of small bowel GISTs include, gastrointestinal bleeding, abdominal pain, abdominal mass or intestinal obstruction.[1,2] Sometimes they are discovered incidentally on endoscopy or imaging performed for some other reason. Surgical resection is the mainstay of treatment. Asymptomatic small bowel GISTs smaller than 2 cm may be observed and treated conservatively.

CASE REPORT

A 60-years-old lady presented to the Sarawak General Hospital with lower abdominal discomfort and palpable abdominal mass for 4 months, associated with anorexia and significant loss of weight. Systemic review was unrevealing. She had past history of hypertension, dyslipidaemia and gout. There was no family history of malignancy or anaemic symptoms. Abdominal examination showed large, intra-abdominal mass at right lower quadrant. The mass was non-tender, firm in consistency and mobile side to side. Its upper margin was reaching up to umbilicus but lower margin was not reachable. Rest of systemic examination was unrevealing.

Laboratory tests revealed a low haemoglobin level (8.1g/dl), otherwise no abnormality was seen in the total white cells, platelets count, liver and renal functions, and coagulation profile. Tumour markers showed elevated CA -125 =64.2U/ML (normal <35U/ML) but normal CEA

Abdominal and transvaginal ultrasonography showed a large, solid, irregular right adnexal mass. A Computerised tomography scan (CT) showed a large well-encapsulated solid-cystic pelvic mass measuring 11.5 x 16.7 x 17.4 cm arising from the right adnexa with no clear plane with dome of urinary bladder and right round ligaments suggestive of a malignant ovarian tumour (Figure 1). There was no evidence of liver or peritoneal metastasis.

With the provisional diagnosis of ovarian cancer, the patient underwent laparotomy under gynaecological team. Intraoperatively, the tumour was found to be arising from the antimesenteric border of jejunum 20 cm from the duodenojejunal junction measuring 18 x 16 cm. The tumour was adherent to the dome of urinary bladder and right broad ligament of uterus. There were no enlarged mesenteric lymph nodes or peritoneal nodules. Uterus and both ovaries were normal. Patient was then referred to on call general surgical team. With an intraoperative diagnosis of jejunal GIST, the tumour was resected with a gross clear margin. Serosal defect at the dome of urinary bladder repaired with vicryl 3/0 suture. About 15 cm segment of jejunum was resected en-block with tumour and anastomosis performed (Figure 2). The tumour was very vascular and intraoperative blood loss was about 500 ml.

Post operatively patient recovery was uneventful. She was started on clear fluids on day1, liquid diet on post-operative day 2 and progressed to soft diet on day3. She was discharged on post-operative day 6.

Histopathological examination revealed tumour with spindle cell proliferation arranged in vague fascicular, storiform and haphazard patterns with extensive areas of necrosis. The tumour cells displayed mild nuclear pleomorphism. Mitotic count was about 30/50hpf. No marked nuclear atypia or abnormal mitotic figures noted. The tumour involved the submucosa, muscularis propria and serosa of the small intestine. All resected margins were free of tumour. In

This article was accepted: 07 December 2021
Corresponding Author: Sohail Mushtaq
Email: msohail@unimas.my

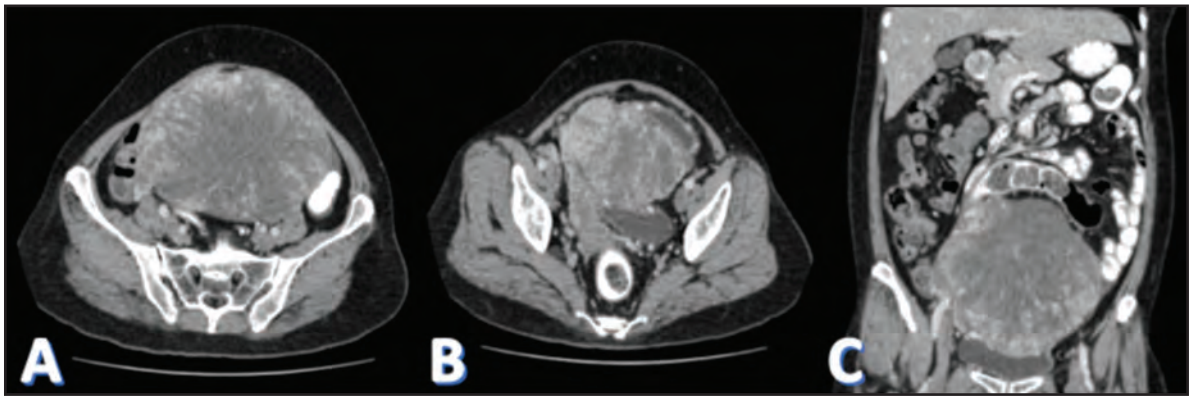

Fig. 1: CT scan of abdomen and pelvis (A, B – transverse sections; C – coronal section) showed a solid cystic mass with no clear plane with right broad ligament and dome of urinary bladder.

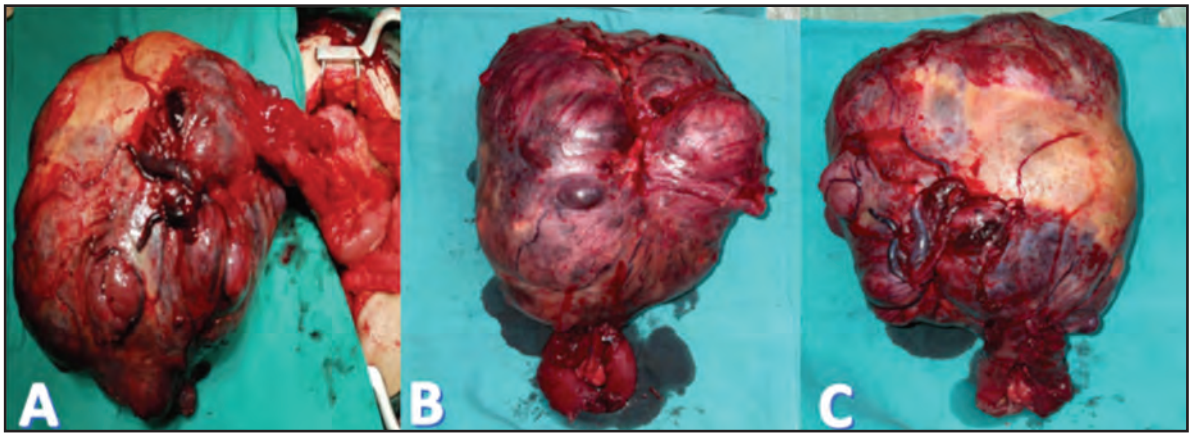

Fig. 2: Intraoperative photos. Large vascular tumour arising from antimesenteric border of jejunum (A). Resected specimen with segment of jejunum (B and C).

addition, immunohistochemical staining showed the tumour cells expressed diffuse DOG-1 and CD117 positivity whereas negative toward SMA, CD34, HMB45. The Ki67 proliferative index was about 10%. The final diagnosis was jejunal GIST with risk of progression.

During follow up patient was doing well. Abdominal wound has healed with no complications. She has been referred to our oncology department for adjuvant targeted therapy.

DISCUSSION

GISTs account for about 0.2% of gastrointestinal tumours.[1] Small bowel is the second common site of gastrointestinal stromal tumours after stomach. Jejunal GISTs are extremely rare.[1,2] Common symptoms of GISTs include occult or overt gastrointestinal bleeding, abdominal mass, intestinal obstruction or incidental finding on endoscopy or imaging. GISTs may be endophytic presenting as submucosal lesions. Mucosa overlying the GIST may ulcerate producing an umbilicated appearance on endoscopy. GISTs may be exophytic where the main bulk of tumour is on the external surface of bowel or stomach. In our case the GIST was exophytic type.

Depending on the clinical suspicion upper GI endoscopy and CT scan are the investigations of choice. In our case, CT scan did not show any relation of the mass with the bowel and patient had no history suggestive of GI bleeding or obstruction.

Histopathology and immunohistochemistry are diagnostic tests for GIST. Jejunal GIST show variable morphology.[1] Tumours may be composed of spindle cells, epithelioid cells, or mixed spindle and epithelioid cells. Immunohistochemical assays are positive for CD117 and DOG-1.[1,2]

Behaviour of GIST may vary from benign to malignant depending on the tumour site, size and mitotic rate.[2,3] Size greater than 5 cm, mitoses larger than 5/50 high-powered fields, and non-gastric site indicate poor prognosis.

GISTs may invade local organs, spread to peritoneum or distant organs like liver, lungs, and bones.[3] Spread to lymph nodes is very rare.

Surgery with clear margin is the mainstay of curative treatment.[3,4] During surgery tumour should be handled gently to avoid capsule rupture which can result in spread of tumour in the peritoneal cavity and recurrence later. In our

case the jejunal GIST was adherent to serosa of the dome of urinary bladder. The tumour was resected completely including the serosa and superficial muscle layer of urinary bladder.

Targeted therapy with tyrosine kinase inhibitors like imatinib has important role in the management of GISTs. Neoadjuvant imatinib may downstage large tumour thus allowing organ preserving resections.[4] Adjuvant imatinib may prevent recurrence in large (>1cm) tumours.[4] Tyrosine kinase inhibitors are recommended even in metastatic GIST to control the growth of tumour.[4,5]

CONCLUSIONS

Small bowel GISTs are rare. High index of suspicion is required in any patient presenting with abdominal or pelvic mass. Although modern imaging like CT scan are very helpful in reaching a definite diagnosis in majority of cases, however in some cases the final diagnosis is only revealed at operation. Surgery is the mainstay of treatment. Adjuvant treatment with tyrosine kinase inhibitors is recommended especially in large tumours to prevent recurrence.

ACKNOWLEDGEMENT

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CASE REPORT

Peptide receptor radionuclide therapy induced carcinoid crisis: A case report

Siow Ping Lee, MRCP[1], Azraai Bahari Nasruddin, MRCP[1], Subashini Rajoo, MRCP[2]

[1]Endocrine Unit, Department of Medicine, Hospital Putrajaya, Wilayah Persekutuan Putrajaya, Malaysia, [2]Endocrine Unit, Department of Medicine, Hospital Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia

SUMMARY

Peptide receptor radionuclide therapy (PRRT) is a therapeutic option in inoperable or metastatic neuroendocrine tumours (NETs). PRRT proved to be promising in prolonging survival and delaying disease progression in patients with advanced bronchopulmonary carcinoid. However, it may lead to worsening of carcinoid symptoms or even precipitate carcinoid crises. The incidence of PRRT induced carcinoid crisis would be between 1–10%. This usually takes place during the first PRRT cycle, either during the tracer infusion or 12–48 hours' post-administration. We report a 62-year-old man with underlying metastatic lung carcinoid tumour who developed carcinoid crisis at 10 hours after receiving PRRT. The carcinoid crisis was successfully treated with intravenous octreotide infusion, corticosteroid, a selective 5-HT3 receptor antagonist, parenteral ranitidine and chlorpheniramine for H1 and H2 antagonism respectively.

INTRODUCTION

Carcinoid tumours are neuroendocrine tumours (NETs) that are relatively slow-growing, but sometimes exhibit profuse metastatic behaviour, most often to the liver and lungs. Various vasoactive peptides such as bradykinin, tachykinin, histamine and serotonin secreted from these tumours are rapidly metabolized by the liver via the portal circulation. In cases of hepatic metastases where peptides escape hepatic metabolism or are directly released into the systemic circulation, patients present with carcinoid syndrome.[1] Carcinoid syndrome is the collection of symptoms and signs including diarrhoea, flushing, tachycardia, bronchoconstriction, and right-sided heart failure.[1]

Carcinoid crisis is a severe complication of carcinoid syndrome in which a massive release of biologically active substances takes place. It is a rare, life-threatening condition with hemodynamic instability i.e. tachycardia, arrhythmias, metabolic acidosis, and/or mental status disorders, along with high mortality rate.[2] Carcinoid crisis is usually precipitated by stress, invasive procedures, induction of anesthesia, tracheal intubation, tumour manipulation, hypercapnia, hypothermia, hypotension, hypertension, initiation of chemotherapy, or drugs that cause a release of histamine including peptide receptor radionuclide therapy (PRRT).[3,4] We report a patient with metastatic lung carcinoid who developed carcinoid crisis after receiving PRRT and he was successfully treated with intravenous octreotide infusion.

CASE REPORT

A 62-year-old man presented at the Hospital Putrajaya, Wilayah Persekutuan Putrajaya, Malaysia with 2 months' history of flushing and intense diarrhoea in June, 2018. He was not hypertensive and he had no history of headache, palpitation or sweating. Measurement of 24 hours urinary 5-hydroxyindoleacetic acid (5-HIAA) showed high concentration of 3677.79 mg/day (normal range: 2–8 mg/day). The imaging revealed a heterogenous enhancing irregular lung mass at left lower lobe measuring 3.7 x 3.1 x 3.6 cm (Figure 1A); multiple liver metastasis with the largest lesion at segment VII measuring 3.9 x 5.6 cm (Figure 2A); and multiple lytic and sclerotic bone lesions. Gallium (Ga)–68 DOTATATE scan showed evidence of somatostatin receptor avid disease in the lung mass, multiple liver lesions and bones. The lung mass at left lower lobe demonstrated standardized uptake value maximum (SUV max) of 11.9 (Figure 1B). On the other hand, the largest liver lesion demonstrated SUV max of 11.1 (Figure 2C). A tru-cut biopsy of the lung mass revealed no malignant cells. In view of high clinical suspicious of malignancy, an ultrasound guided liver biopsy was performed and the histopathological examination (HPE) was consistent with well-differentiated NET. His chromogranin A (Cg A) level was elevated at 59916 ng/ml (normal range: ≤ 225 ng/mL). He was then started on monthly intramuscular injection of octreotide 30 mg, a long acting-release (LAR) somatostatin analogue (SSA) and he eventually underwent left lung lobectomy in October, 2018 four months after the presentation. The HPE result showed carcinoid tumour grade 1 with clear margin and 2 lymph nodes involvement.

He developed coronary vasospasm with octreotide LAR at 4 months post-operatively and the treatment was switched to monthly subcutaneous injection of lanreotide 120 mg, another long acting SSA. A repeated Ga–68 DOTATATE scan at 6 months' post-surgery showed resolution of the lung disease (Figure 1C); but demonstrated evidence of somatostatin receptor avid disease progression in the liver and bones. The segment VII lesion had increased to 4.2 x 6.2 cm (Figure 2B). At the same time, patient had multiple episodes of carcinoid crisis with flushing, worsening diarrhoea and hypotension requiring intravenous (IV) infusion of octreotide and shorter interval of long acting SSA injection (2 weekly intervals). A surveillance Ga–DOTATATE PET/CT scan performed at 15 months after the surgery showed extensive disease in liver and bones; indicating progression of the disease. Hence, a PRRT was planned to halt the progression of the disease and for symptoms control. We

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Corresponding Author: Siow Ping Lee
Email: patricia82@hotmail.my

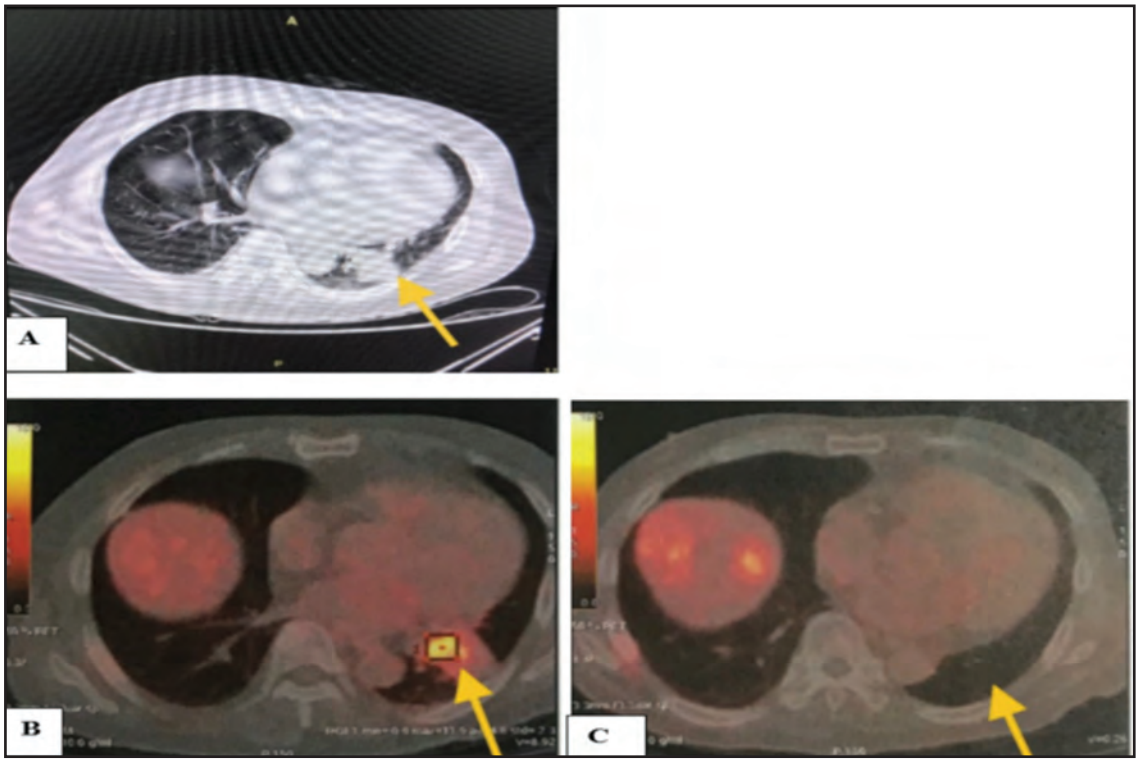

Fig. 1: Ga-68 DOATATE PET/CT scan showing (A) irregular left lower lobe lung mass before lobectomy (B) with the SUV max of 11.9 (C) has resolved after the surgery.

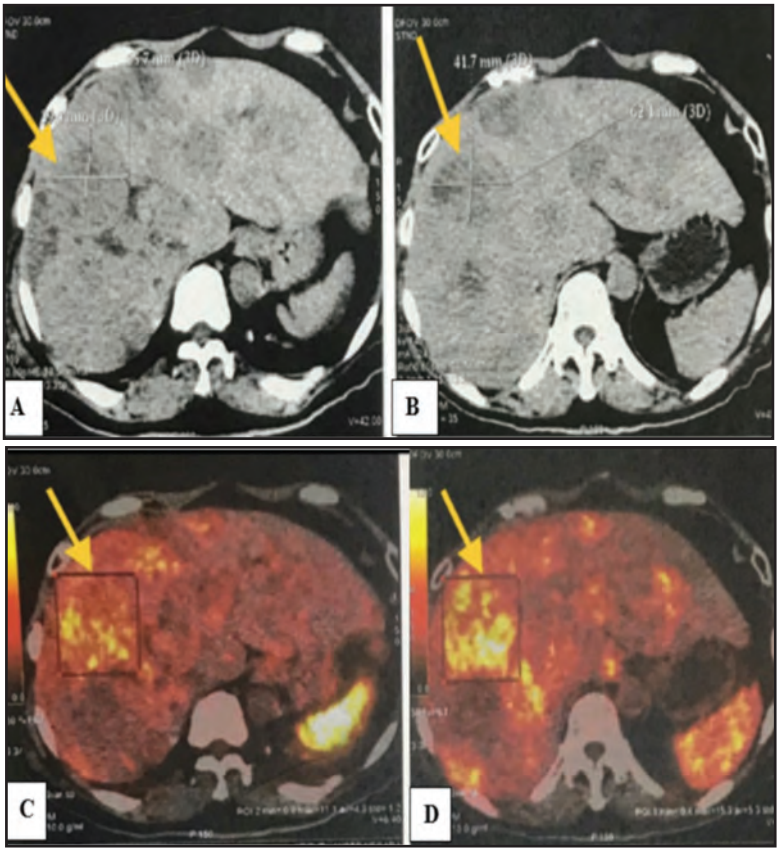

Fig. 2: Ga-68 DOTATATE PET/CT scan showing heterogenous hypodense lesions throughout both enlarged and lobulated liver lobes with the largest lesion measuring 3.9 x 5.6 cm (A) before the surgery and it has increased in size measuring 4.2 x 6.2 cm (B) at 6 months post-surgery. Ga-68 DOTATATE PET/CT scan showing the tracer uptake by the largest lesion at segment VII with the SUV max of 11.1 (C) before the surgery and the intensity has increased with the SUV max of 15.3 (D) at 6 months' post-surgery. The liver lesions also have increased in number post-surgery.

stopped the long acting SSA a month before 177Lu–labelled PRRT to prevent competitive binding of 177Lu–octreotate to the somatostatin receptors. The patient however, refused multiple daily injection of short acting octreotide at that time.

The patient received his first cycle of 200mCi of 177Lu–labelled PRRT. Pre-medications such as IV granisetron (selective 5-HT3 receptor antagonist) 2 mg, IV dexamethasone 4 mg and proton pump inhibitor were given. He had flushing and diarrhoea at 7 hours post-PRRT, hence, IV octreotide 50 mcg/hour was commenced. Unfortunately, the patient developed carcinoid crisis at 10 hours post PRRT administration. He developed severe hypotension with the blood pressure (BP) of 70–80/40–60 mmHg and tachycardia of 120–146 beats per minute (bpm). He also had multiple episodes of intense diarrhoea and flushing extending from head down to his abdomen. He was immediately resuscitated with crystalloid. The IV octreotide was increased from 50 mcg/hour to 100 mcg/hour. At the same time, subcutaneous lanreotide 120 mg was administrated at 12 hours of PRRT. Regular parenteral ranitidine (50 mg IV) and chlorpheniramine (10 mg IV) were given on top of hydrocortisone (50 mg IV). His BP eventually increased to 110–120/60–70mmHg and his heart rate reduced to 80–90 bpm. The IV octreotide was slowly tapered down by 25 mcg each hour and then stopped 24 hours after PRRT. He was discharged well with oral prednisolone 30 mg daily and oral chlorpheniramine 4 mg 3 times per day for a total duration of 3 days. He was also given symptomatic treatment for his diarrhea with oral granisetron 1 mg when necessary.

DISCUSSION

We describe here a case of carcinoid crisis following PRRT. Although infrequent, carcinoid crisis can occur during or even a few days after the administration of PRRT. The incidence of PRRT induced carcinoid crisis is between 1–10%.[2] To our knowledge, the first case of PRRT induced carcinoid crisis was reported by Davì et al.[4] in a patient with metastatic bronchial NET (atypical carcinoid). The carcinoid crisis usually happens during the first PRRT cycle, either during the infusion or 12–48 hours' post-administration.[3]

Several mechanisms have been postulated for carcinoid crisis after PRRT. Acute tumour lysis mediated by radiation cellular damage, resulting in sudden release of supra-physiological amount of hormonally active substances, leads to profound carcinoid symptoms.[3,4] Discontinuation of somatostatin analogue (SSA) prior to therapy may also contribute to the rebound increase in bioactive peptides. Other identified mechanism also includes emotional stress response to hospitalization and/or therapy. Lastly, administration of amino acids such as lysine and/or arginine as a renal protective measure may play a role in the pathophysiology of PRRT induced carcinoid crisis.[3] These amino acids might be used as substrates for the synthesis of vasoactive hormones by the carcinoid cells.[3] However, exact mechanism is yet to be elucidated, as there are only few reported cases.

De Keizer et al.[3] reported that all 6 patients suffering from carcinoid symptoms following PRRT had extensive tumour burden and liver metastases, and 3 had skeletal metastasis too. All of them suffered from severe carcinoid symptoms such as intense diarrhoea or flushing even prior to PRRT. In two of the patients, hormonal symptoms were so severe that discontinuation of SSA before PRRT was impossible. In all 6 patients, the hormonal crisis occurred during the first PRRT cycle; 3 of them during or directly after 177Lu–octreotate infusion, and in the other 3 crisis, 48 hours after PRRT. Cg A levels were elevated in all the patients and 5-HIAA elevation was reported in the 3 carcinoid patients.

Our patient was at high risk of developing carcinoid crisis. He had extensive tumour burden with liver metastasis as well as high levels of both Cg A and 5-HIAA. In addition, our patient has had multiple episodes of life-threatening carcinoid crisis even prior to commencement of PRRT. His post PRRT carcinoid crisis occurred 10 hours after PRRT which is probably due to emotional stress in combination to amino acid infusion. It is unlikely that this crisis was induced by tumour lysis secondary to beta irradiation as it is observed to occur relatively late, more than 24 hours post therapy.[3]

Treatment of a carcinoid crisis aims at preventing the release of the mediators from tumour tissue and/or blocking their effects on target organs. Gonzalo et al.[5] had proposed a protocol for carcinoid crisis prevention and management post PRRT. Identification of high-risk patients is the important first step.[5] The high-risk cases include those with previous history of carcinoid crisis, those with carcinoid symptom flare after cessation of long-acting SSA 4–6 weeks before PRRT requiring short acting SSA to control symptoms, or any patient with high tumour burden especially within the liver. Our patient had all the mentioned high-risk factors.

Correction of electrolyte disturbance, dehydration and hypoproteinemia before PRRT is also a crucial step. [5] PRRT pre-medications typically should include corticosteroid, a selective 5-HT3 receptor antagonist, parenteral ranitidine and chlorpheniramine for H1 and H2 antagonism, respectively.[5] In case of high tumour burden and therefore risk of tumour lysis, allopurinol can be included in the premedication protocol chart if renal function is satisfactory[5], but it was not given in this case.

Though long acting SSA is avoided 4 weeks prior to PPRT, to overcome competitive somatostatin receptor binding, administration of high boluses (250–500 mcg) or infusion (50 mcg/hour) of short acting octreotide is advisable. In the event of carcinoid crisis developing during or immediately after PRRT infusion, IV bolus as high as 500–1000 mcg octreotide can be administered, with treatment repetition at 5-minutes intervals until control of symptoms is achieved. Alternatively, following an IV bolus dose, continuous infusion of octreotide at a dose of 50–100 mcg/hour may be started.[5] Long-acting SSA should be then resumed 24–48 hours post-PRRT, followed by tapering off the short-acting octreotide infusion. There were some limitations pertaining to the management of this patient. The short acting octreotide infusion was commenced only after he developed carcinoid symptoms. It should be given earlier when the PRRT started, knowing that he is at very high risk of developing carcinoid crisis.

CONCLUSIONS

Although well tolerated, 177Lu–labelled PRRT may trigger carcinoid crisis, and clinicians need to be aware of this fact. In patients who develop a carcinoid crisis with their first PRRT cycle, additional precautions need to be taken before the administration of further cycles, including continuation of SSA with the doses and protocol mentioned above, corticosteroids, prolonged observation in hospital after therapy including planned intensive care monitoring in selected cases.

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CASE REPORT

The bleeding umbilicus: An uncommon presentation of endometriosis

Nurjasmine Aida Jamani, MMed[1], Zalina Nusee, MMed[2], Hamizah Ismail, MMed[2]

[1]Department of Family Medicine, Kulliyyah of Medicine, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, Kuantan Pahang, Malaysia, [2]Department of Obstetrics and Gynaecology, Kulliyyah of Medicine, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, Kuantan Pahang, Malaysia

SUMMARY

Dysmenorrhea is a common presentation in women of reproductive age in primary care. It can negatively affect the quality of life of a woman and restrict her daily activities. Endometriosis is the most common diagnosis for secondary dysmenorrhea. However, cutaneous endometriosis is an uncommon presentation of endometriosis. It requires a thorough history, physical examination and histological findings for definitive diagnosis. This paper reports an interesting case of a 47- year-old woman with primary cutaneous umbilical endometriosis and its management. Her final diagnosis was primary umbilical endometriosis with Stage 3 endometriosis based on the patient's history, clinical and surgical findings. The patient was discharged well on day three of operation and has been well since then with no signs of recurrence.

INTRODUCTION

Dysmenorrhea is a common complaint seen in primary care. The prevalence varies between 16-81% between countries.[1] It can be classified into primary and secondary dysmenorrhea. Primary dysmenorrhea is defined as painful menses in the absence of any pathology. In contrast, secondary dysmenorrhea presents with specific pelvic pathology. The latter requires further evaluation and investigation.

Endometriosis is the most common cause of secondary dysmenorrhea. It is defined as the presence of endometrial tissue gland outside the uterine cavity. It typically affects other pelvic organs such as the ovaries, fallopian tubes, uterine ligaments, and pelvic walls.[2] The prevalence of endometriosis has been reported to be 10% in the general female population, predominantly among women of reproductive age.[3] They can present with dysmenorrhea, deep pelvic pain and dyspareunia. Endometriosis can also occur elsewhere such as in the thorax, gastrointestinal tract and skin (cutaneous).

Cutaneous endometriosis is the presence of endometrial tissue in the skin. The most-reported site is the umbilicus, around 30-40% which could be primary or secondary.[2] Primary cutaneous umbilical endometriosis (UE) is rare compared to secondary umbilical endometriosis. In secondary UE, seedling happens at a surgical scar after an abdominal surgery.

Despite primary UE is rare and this is known to gynaecologists, UE is unfamiliar to others, especially the primary care physicians. Hence, we report a case of a 47 - year-old woman presenting with dysmenorrhea and cyclical bleeding from the umbilicus.

CASE REPORT

A 47- year -old woman presented with dysmenorrhea for one year. Previously, she never had any history of dysmenorrhea during her younger days. The pain usually presented before menses and sometimes she had fainting spells. On each menstrual cycle, she also noticed minimal blood-stained over her umbilicus but did not notice any nodule or mass. She attained menarche at the age of 12 years and has had regular menses since then. She has no menorrhagia or dyspareunia. She had no medical illness and has never done any surgery. She had three children, and all were delivered vaginally.

Her family physician gave her regular analgesics. She initially responded to analgesics but later, the pain became severe. She was then referred to a gynaecologist for further assessment.

On examination, she was on day 3 of menses. She was not pale with normal vital signs. Abdominal examination was soft and non-tender. A violaceous coloured nodule was noted, measuring 1.0x0.8cm in the umbilicus with blood-stained (Figure 1A and 1B). No active bleeding was seen and no pelvic mass was palpable. Other examination was unremarkable, including vaginal examination.

Transabdominal and transvaginal ultrasound scans showed a normal size anteverted uterus and no adnexal mass seen. Blood investigations were normal except for raised serum CA 125 (228 U/ml). A diagnosis of severe dysmenorrhea secondary to endometriosis with cutaneous involvement was made. Initially she was treated with oral Dienogest 1 tablet daily for five months. Her symptoms slightly improved for three months but later recurred. She was then counselled for surgical treatment and agreed to it.

Umbilical nodule excision and total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO) were performed (Figure 2A). Intraoperatively, the uterus was normal in size, with endometriosis deposits seen posteriorly.

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Corresponding Author: Nurjasmine Aida Jamani
Email: minaida@iium.edu.my

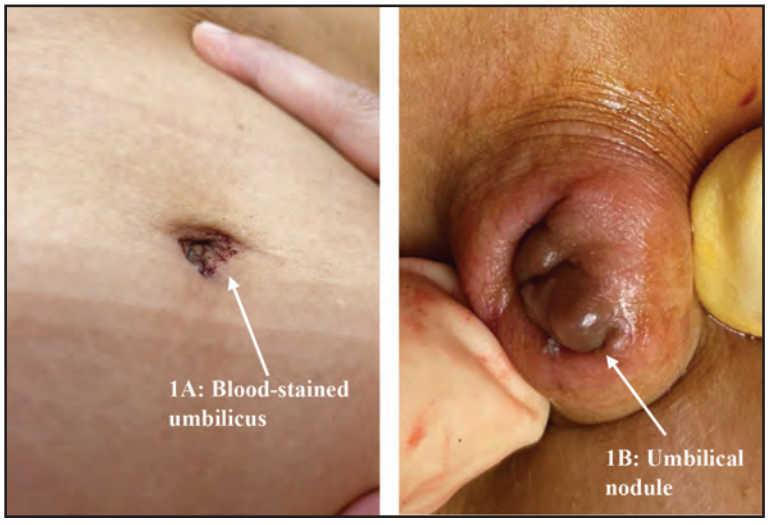

Fig. 1: (A) Bloodstain at the umbilicus during menstrual cycle and (B) closed-up image of the violaceus umbilical nodule.

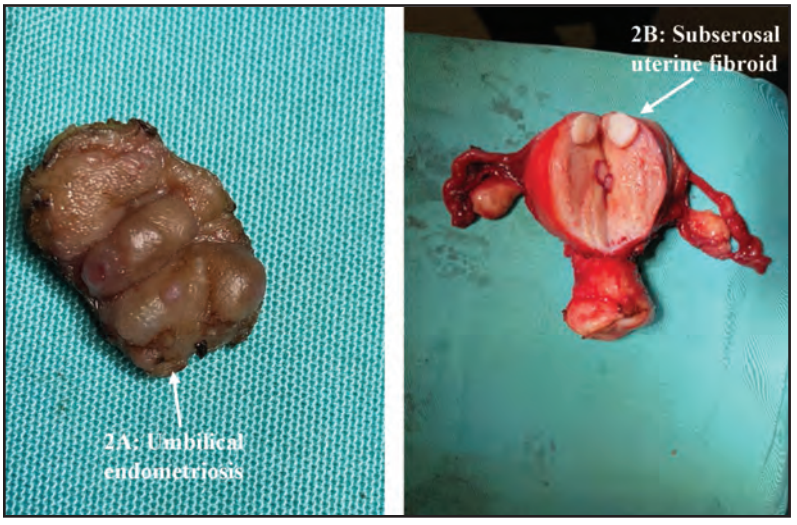

Fig. 2: (A) Excised umbilical nodule with endometriosis (white arrow). (B) Presence of subserosal uterine fibroid (white arrow).

There was a presence of 0.5x 2.0cm subserosal fibroid anteriorly (Figure 2B). The uterus was adhered to the sigmoid colon, and the Pouch of Douglas was obliterated. The tubes, ovaries and adjacent structures were normal. There were no complications during intraoperatively and postoperatively.

Histopathological examination of the uterus and ovaries confirmed leiomyomata with no signs of endometrial hyperplasia, malignancy, or extra-endometrial gland deposits. Meanwhile, the excised umbilical nodule tissue revealed fibro-adipose connective tissue with multiple foci of endometrial glandular tubes and surrounding endometrial stroma with a clear surgical margin. The findings were consistent with the diagnosis of umbilical endometriosis.

Her final diagnosis was primary umbilical endometriosis with Stage 3 endometriosis based on the patient's history, clinical and surgical findings. The patient was discharged well on day three of operation and has been well since then with no signs of recurrence.

DISCUSSION

Cutaneous endometriosis primarily affects women in their reproductive age. It accounts for 0.5-1% of all ectopic sites of endometriosis.[4] The mean age is 35.1-37.7 years of age. The commonest site is the umbilicus, even though other areas such as arm, groin and caesarean section scar has been reported.[2,5] It usually presents as a papule or nodule, which is firm, bluish in colour, and measures less than 2cm in diameter.[5]

UE can be classified as primary or secondary based on the patient's surgical history. In primary umbilical endometriosis, the deposits are spontaneous compared to the secondary, which is associated with prior abdominal surgery.[6] UE patients usually present with dysmenorrhea, cyclical pain at the umbilicus, bleeding, and swelling associated with the menstrual cycle.[6,7]

Numerous theories are proposed to understand the pathogenesis of primary and secondary cutaneous

endometriosis. These include the embryonal rest theory, retrograde menstruation theory, the coelomic metaplasia theory, and migratory pathogenesis theory cellular proliferation. It is postulated that the primary UE occurs as a result of endometriosis seeding. The seeding happens via bloodstream or lymphatics drainage where the umbilicus act as a physiologic scar.[5,8]

As in our patient, the diagnosis is usually made based on the clinical history and physical examination.[9] Abdominal nodule and dysmenorrhea were the commonest presentations reported by Victory R et al.[5]

Blood investigations and imaging modalities such as ultrasound and MRI can be helpful when the diagnosis is in doubt or to evaluate the differential diagnosis of umbilical lesions and the neighbouring structures.[3] Most reports concluded that imaging investigations were not superior to physical examination.[3] CA 125 may be raised but may not be conclusive.[9] However, histopathological examination (HPE) remains the gold standard for definitive diagnosis.[10] Fine needle cytology is not recommended as it has a low yield for diagnosis and can cause potential contamination linked to the puncture site.[3]

Many publications do not recommend a laparoscopy investigation to look for concurrent pelvic endometriosis. The reason is that only 0-25% of patients with UE have concurrent pelvic endometriosis.[5] Our patient's case has demonstrated that there was also pelvic endometriosis despite having primary umbilical endometriosis.

Currently, there is no standard guideline in managing UE. Nevertheless, reported cases of UE have suggested surgical excision as the definitive treatment.[3,7] Some reports have recommended medical treatment consisting of oral contraception pills and gonadotropin-releasing hormone to prevent recurrence after surgery.[3] Though medical treatment is ineffective as primary treatment, for women who are near to menopause, it could be a reasonable option.

In our patient, medical treatment with oral Dienogest was chosen because of the patient's age and choice of treatment after an informed decision discussion. However, she continued to have severe dysmenorrhea despite the therapy; hence TAHBSO and excision of the umbilical nodule were offered. Surgical excision of the nodule requires a wide surgical margin of at least 1cm to avoid recurrence and malignant transformation.[10]

Countless differential diagnoses can mimic UE. It can be rather challenging for untrained eyes to distinguish between these lesions. The challenge is especially true when patients present in an atypical presentation not related to menses. Differential diagnosis of UE includes keloid, pyogenic granuloma, basal cell carcinoma, hemangioma and Sister's Mary Joseph Nodule (cutaneous metastatic carcinoma).[3] Hence, a high index of suspicion consisting of thorough history taking, physical examination and sometimes imaging modalities are needed.

CONCLUSIONS

In conclusion, our case highlights the possibility of cutaneous endometriosis, which needs to be considered when evaluating an umbilical mass with bleeding and cyclical pain during menses. Despite being uncommon, it can affect the quality of life of patients. Primary care physicians should have a high clinical suspicion for timely referral and management.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest regarding the publication of this case report.

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