Iron burden and endocrine complications in transfusion-dependent thalassemia patients In Sarawak, Malaysia: a retrospective study

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ABSTRACT

Introduction: Thalassaemia is one of the major health problems in Malaysia. With safe blood transfusion regime, the lifespan of patients with transfusion-dependent thalassaemia (TDT) has improved but at the cost of a higher risk of developing endocrine disorders. It is crucial for us to monitor the iron overload to prevent end organ damage. This study aims to evaluate the iron burden and prevalence of endocrinopathies in patients with TDT in Sarawak.

Materials and Methods: This retrospective cohort study was conducted between January 2020 to June 2020 in six government hospitals in Sarawak. A total of 89 patients with TDT, aged 10 years and above, were recruited.

Results: Out of the 89 patients, there were 54 males (60.7%) and 35 females (39.3%) with a median age of 21 years (range 10.0-65.0). Sixty-seven (75.3%) patients had beta-thalassaemia major and 15 (16.9%) patients had haemoglobin E beta-thalassaemia (HbE beta-thalassaemia), remaining seven patients had other genotypes. Thirty-one (34.8%) patients had mean serum ferritin 2500ng/ml and above, and 44 (66.6%) had liver iron concentration (LIC) ≥7mg/g. The prevalence of endocrine disorders in our cohort was 69.7%. The most common endocrinopathies were short stature (n=46, 51.7%), followed by hypogonadism (n=24, 26.9%), delayed puberty (n=23, 25.8%), hypothyroidism (n=10, 11.2%), diabetes mellitus (n=9, 10.1%), impaired glucose tolerance (n=6, 6.7%) and hypoparathyroidism (n=3, 3.3%). Endocrinopathies were significantly associated with age (p=0.01), age at initiating regular blood transfusion (p<0.01) and duration of regular blood transfusion (p<0.01).

Conclusion: Our data shows that the development of endocrinopathies in TDT can be time dependent. Early detection of endocrine-related complications and prompt treatment with iron chelation therapy are important to improve morbidity and mortality. A multidisciplinary approach with good patient-doctor collaboration is the key to improving patient care in our settings.

KEYWORDS:
Transfusion-dependent thalassaemia, iron overload, endocrine complications

INTRODUCTION

Thalassaemia is a common autosomal recessive blood disorder. It is caused by either gene deletion or point mutation that leads to the imbalance of the globin chain synthesis, ineffective erythropoiesis and chronic haemolysis. It has a wide spectrum of clinical manifestations with varying degrees of clinical severity and transfusion requirements. Regular blood transfusions have altered the outlook of the disease by improving patients' survival into the second decade while also preventing growth retardation and skeletal changes. However, with the increasing lifespan, more TDT patients suffer from chronic iron overload with iron accumulation in the liver, heart and endocrine organs.[1]

The Malaysian Thalassaemia Registry (MTR) was formally launched on May 12, 2007, to collect detailed epidemiological and clinical information on patients with thalassaemia in Malaysia. The main purpose of this registry is to enhance care through early detection, optimised treatment, and improved survival. According to the Thalassaemia Registry 2019, 4718 patients are transfusion-dependent.[2] Additionally, it is estimated that 74-140 infants are born with thalassaemia each year.[3] Bone marrow transplantation, a potentially curative treatment for thalassaemia is available in Malaysia but its accessibility is limited due to various reasons such as patient factors and socioeconomic status. Most of the patients still receive regular blood transfusions as part of treatment. Early initiation of iron chelation therapy and close monitoring are crucial to prevent complications of chronic iron overload like heart failure, liver cirrhosis and endocrinopathies.

Sarawak is the largest state in Malaysia housing a large diversity of ethnic groups. According to the Department of Statistics Malaysia, the population of Sarawak in 2019 was

This article was accepted: 07 April 2024
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2.8 million people.[4] There were 265 thalassaemia patients registered in MTR in Sarawak up to November 2019. This gave the prevalence of thalassaemia patients in Sarawak 0.01%. Among those patients that were registered, 44.5% (n=118) were transfusion-dependent, 47.5% (n=126) were patients with non-transfusion-dependent thalassaemia and 8% (n=21) of the patients had succumbed.[2] To date, there is scarce data on patients with TDT with endocrinopathies in Sarawak. Few studies that were conducted have shown a high prevalence of endocrinopathies among this population.[5,6] The risk of developing endocrine complications due to iron overload remains high despite the use of iron chelation therapy. This study aims to assess the iron burden and prevalence of endocrinopathies in patients with TDT in Sarawak.

MATERIALS AND METHODS

Study Design and Study Population

A retrospective, multicentre study was conducted at the haematology clinic or daycare at Sarawak General Hospital, Sibu Hospital, Miri Hospital, Bintulu Hospital, Limbang Hospital and Lawas Hospital. Sarawak General Hospital was the only tertiary hospital with an established haematology service. We retrieved patients with TDT who received treatment and regular follow-ups from these six government hospitals. TDT patients aged 10 years old and above, who received a regular blood transfusion every 2 to 5 weeks to keep the pretransfusion haemoglobin at least 9-9.5g/dL were included. Exclusion criteria were those aged below 10 years old, those with non-transfusion-dependent thalassaemia and those who were cured with bone marrow transplants.

A total of 95 patients with TDT were evaluated. Of these, six patients were excluded from the study as three of them had transferred to other states and we could not retrieve their medical records. A patient with beta-thalassaemia intermedia who required regular blood transfusion had become non-transfusion dependent after undergoing splenectomy. The other two patients with beta-thalassaemia major were less than 10 years old. Thus, a total of 89 patients were recruited for the study.

Data Collection

Data was collected from January 2020 to June 2020. Patients' demographic data, type of thalassaemic syndrome, blood transfusion history, iron burden (mean serum ferritin, liver iron concentration) and iron chelation therapy regime were retrieved from the patient's medical notes. Endocrinopathies were evaluated based on the Tanner staging, growth parameters and blood investigation results based on clinician assessment. The treatment of choice for the iron chelation therapy was based on the iron burden, physician judgement and patient preference.

The patient's full blood count, renal profile, liver function test, serum calcium, serum phosphate and fasting blood glucose were monitored at every clinic visit. Free T4, thyroid-stimulating hormone (TSH), luteinising hormone, follicle-stimulating hormone, oestradiol in females and testosterone in males were measured at least once a year. Iron burden was assessed using serial serum ferritin and liver iron concentration (LIC). Serum ferritin was measured at least twice to thrice a year. Individual ferritin levels were averaged to give a mean ferritin level. MRI T2* imaging was performed once a year to assess the LIC. Serum ferritin ≥2500ng/ml and LIC≥7mg/g were associated with complications related to TDT.[7] We further classified our cohort into serum ferritin<1000ng/ml, 1000-2499ng/ml, 2500-4999ng/ml, 5000-10,000ng/ml and >10,000ng/ml. LIC is classified into LIC<7mg/g, 7-15mg/g and >15 mg/g.

Short stature was defined as height below the 3rd percentile for gender and age based on national growth charts. Delayed puberty was defined as the complete lack of pubertal development in girls by the age of 13 and boys by the age of 14. Hypogonadism was defined in boys as the absence of testicular enlargement (less than 4 ml) and in girls as the absence of breast development by the age of 16. Hypothyroidism was defined as reduced free T4 levels below the lower limit of normal and elevated TSH levels above the upper limit of normal. Diabetes mellitus was defined as fasting glucose >7mmol/L or oral glucose tolerance test (OGTT) serum glucose at 2 hours >11.1mmol/L. Impaired glucose tolerance was defined as OGTT serum glucose at 2 hours >7.8mmol/L and <11.1mmol/L. Hypoparathyroidism was defined as the combination of low serum calcium concentration below the lower limit of normal together with increased serum phosphate above the upper limit of normal and low serum parathyroid hormone level.[8]

Statistical Analysis

Data were analysed using Statistical Package for the Social Sciences (SPSS) software (version 26). The data were assessed for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics were used to describe the demographic and clinical data. Continuous variables were expressed as median and range. Categorical variables were calculated as frequencies and percentages. Continuous variables between two independent groups were analysed with the independent paired T-test or Mann-Whitney U test. Categorical variables between two independent groups were analysed with the Chi-square test or Fisher's Exact test. The relationship between two quantitative variables was examined using Spearman's rank correlation coefficient. All p values presented were two-tailed, and p values <0.05 were considered statistically significant.

RESULTS

The demographic data, red cell blood transfusion, iron burden and chelation therapy of these 89 patients were summarised in Table I. There were 54 (60.7%) males and 35 (39.3%) females with a median age of 21 years (range 10.0-65.0), comprised of Malay (n=37, 41.6%) and Chinese (n=40, 44.9%) ethnicities, with only a small population from Sarawak indigenous people of Iban (n=1, 1.1%), Kedayan (n=8, 9%), and Bisaya (n=1,1.1%). 2.3% of the patients (n=2) from the area of northern Sarawak were of Kadazan ethnicities from Sabah indigenous people. 67 (75.3%) patients had beta-thalassaemia major and 15 (16.9%) patients had haemoglobin E beta-thalassaemia (HbE beta-thalassaemia). Of the remaining seven patients, one with compound heterozygous Hb Malay/beta+ mutation and beta-thalassaemia Filipino, one with compound heterozygous alpha plus thalassaemia 3.7 deletion with Hb

Table I: Demographic characteristics of patients with transfusion-dependent thalassaemia

Characteristics	Median (range)/no (%)			
	Total (n=89)	Beta-thalassemia Major (n=67)	HbE Beta-thalassemia (n=15)	Others (n=7)
Age (years)	21 (10.0-65.0)	21(10.0-36.0)	25(11.0-49.0)	16 (10.0-65.0)
Age (years)				
10-19	38(42.7)	30(44.8)	4(26.7)	4(57.1)
20-29	31(34.8)	24(35.8)	6(40.0)	1(14.3)
30-39	16(18.0)	13(19.4)	3(20.0)	0(0.0)
40-49	2(2.3)	0(0.0)	2(13.3)	0(0.0)
50-59	1(1.1)	0(0.0)	0(0.0)	1(14.3)
≥60	1(1.1)	0(0.0)	0(0.0)	1(14.3)
Gender				
Male	54(60.7)	41(61.2)	9(60.0)	4(57.1)
Female	35(39.3)	26(38.8)	6(40.0)	3(42.9)
Age of initiating regular blood transfusion (years)	1(0.3-34.0)	1(0.3-7.0)	4(0.5-9.0)	5(1.0-34.0)
Duration of regular blood transfusion (years)	20(2.0-56.0)	20(8.0-36.0)	22(2.0-46.0)	14(4.0-56.0)
Mean annual transfusion volume (ml/kg/year)	198.9(100.0-281.0)	203.5(108.0-281.0)	186.3(100.0-280.0)	181.8(109.0-242.0)
Serum ferritin(ng/ml)				
<1000	14(15.7)	11(16.4)	2(13.3)	1(14.3)
1000-2499	44(49.4)	32(47.8)	8(53.3)	4(57.1)
2500-4999	15(16.9)	10(14.9)	4(26.7)	1(14.3)
5000-10000	13(14.6)	12(17.9)	1(6.7)	0(0.0)
>10000	3(3.4)	2(3.0)	0(0.0)	1(14.3)
LIC(mg/g)[a]				
<7	22(33.3)	19(34.5)	3(33.3)	0(0.0)
7-15	18(27.3)	15(27.3)	1(11.1)	2(100.0)
>15	26(39.4)	21(38.2)	5(55.6)	0(0.0)
Chelation Therapy[b]				
Monotherapy	53(59.6)	39(58.2)	7(46.7)	7(100.0)
Dual therapy	35(39.3)	28(41.8)	7(46.7)	0(0.0)
None	1(1.1)	0(0.0)	1(6.6)	0(0.0)

[a]66 patients had undergone MRI T2* [b]88 patients were on iron chelation therapy

Table II: Association of clinical factors with development of endocrinopathies in TDT patients

Clinical factors	Endocrinopathies		
	Yes	No	p-value
Gender n(%)[a]			0.77
Male	37(59.7)	17(63.0)	
Female	25(40.3)	10(37.0)	
Age n(%)[b]			0.01
years			
10-19	19(30.6)	19(70.4)	
20-29	25(40.3)	6(22.2)	
30-39	14(22.7)	2(7.4)	
40-49	2(3.2)	0(0.0)	
50-59	1(1.6)	0(0.0)	
≥60	1(1.6)	0(0.0)	
Type n(%)[b]			0.62
Beta-thalassaemia Major	48(77.4)	19(70.4)	
HbE β-thalassaemia	9(14.5)	6(22.2)	
Others	5(8.1)	2(7.4)	
Age of initiate regular blood transfusion (mean rank)[c]	38.4	59.8	<0.01
Duration of regular blood transfusion (mean rank)[c]	52.3	28.2	<0.01
Mean annual blood transfusion volume (mean, ml/kg/year)[d]	197.6	202.1	0.65
Serum ferritin n (%)[b]			0.73
ng/ml			
<1000	11(17.7)	3(11.1)	
1000-2499	29(46.9)	15(55.6)	
2500-4999	11(17.7)	4(14.8)	
5000-10000	8(12.9)	5(18.5)	
>10000	3(4.8)	0(0.0)	
LIC n (%)[a] mg/g			
<7	15(31.9)	7(36.8)	0.40
7-15	15(31.9)	3(15.8)	
>15	17(36.2)	9(47.4)	
Chelation therapy n(%)[a]			0.87
Monotherapy	37(59.7)	16(61.5)	
Dual therapy	25(40.3)	10(38.5)	

[a]Chi-square test [b]Fisher's exact test [c]Mann-Whitney U test [d]Independent paired T-test

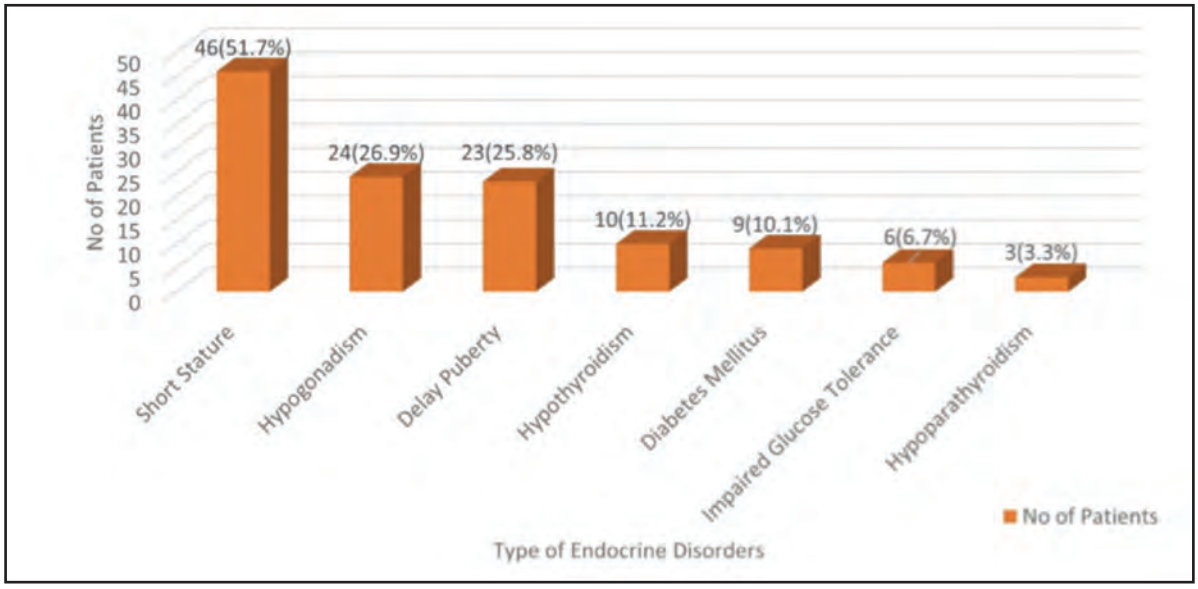

Fig. 1: Prevalence of Endocrinopaties in Transfusion-dependent Thalassaemia

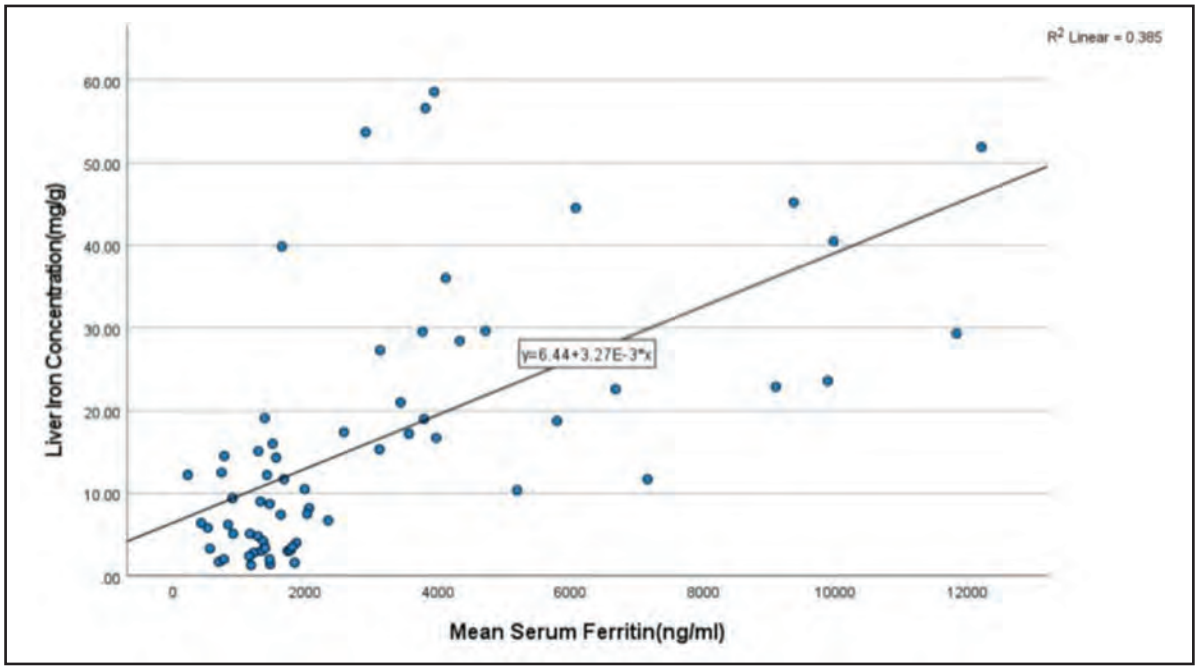

Fig. 2: Simple Scatter of Liver Iron Concentration by Mean Serum Ferritin

Adana, one with concomitant HbH and HbE beta-thalassaemia, one with heterozygous beta-thalassaemia Filipino with Hb Khon Kaen and one with Hb Constant Spring with beta thalassaemia intermedia and two had beta-thalassaemia intermedia with undetermined genotype. In our cohort, patients initiated their first regular blood transfusion at the median age of 1 year old (range 0.3-34.0) with the median years of regular blood transfusion of 20 years (range 2.0-56.0). The mean annual blood transfusion volume was 198.9ml/kg/year (range 100.0-281.0). Iron overload was assessed using the mean serum ferritin and liver iron concentration. In our cohort, 34.8% (n=31) of patients had mean serum ferritin 2500ng/ml and above and 66.6% (n=44) of the patients had LIC ≥7mg/g. 98.9% of the patients (n=88) were on iron chelation therapy, 59.6% of the patients (n=53) were on monotherapy and 39.3% (n=35) were on dual therapy (Table I). Among 53 patients who were on monotherapy, eight patients were on desferrioxamine, 15 patients were on deferiprone, and 30 patients were on deferasirox. For patients who were on dual therapy, 27 patients were on a combination of desferrioxamine and deferiprone while eight patients were on a combination of deferiprone and deferasirox.

The prevalence of endocrine disorders in our cohort was 69.7% (n=62). Among those patients with endocrine disorders, 50.0% (n=31) had one endocrinopathy, 17.7% (n=11) had two endocrinopathies, and 32.2% (n=20) had three and above endocrinopathies. The most common endocrinopathies were short stature (n=46, 51.7%), followed by hypogonadism (n=24, 26.9%), delayed puberty (n=23, 25.8%), hypothyroidism (n=10, 11.2%), diabetes mellitus (n=9, 10.1%), impaired glucose tolerance (n=6, 6.7%) and hypoparathyroidism (n=3, 3.3%) (Figure 1).

Serum ferritin was correlated significantly with liver iron concentration but with poor linearity (R2 = 0.385, p<0.01) (Figure 2). There was no clear association between serum ferritin, liver iron concentration and types of endocrine complications. However, age, age at initiating regular blood transfusion and duration of regular blood transfusion were significantly associated with the development of endocrinopathies (p<0.01) (Table II). Patients with ages 30 years and above have a higher risk of developing at least one type of endocrine disorder (p=0.02). We had done a subgroup analysis of the patient population who was younger than 30 years of age. In this cohort of patients (n = 69), they had a more severe iron burden (n=26, 83.9% had serum ferritin ≥2500ng/ml and n=32, 74.4% had LIC ≥ 7 mg/g) as compared to those who were older than 30 years old (n=5, 16.1% had serum ferritin ≥2500ng/ml and n=11, 25.6% had LIC ≥7mg/g).

DISCUSSION

The availability of safe blood transfusions and iron chelation therapy has resulted in improved disease control and patients' quality of life. For some patients who require regular blood transfusion, splenectomy has prolonged red cell survival and ultimately reduced the red cell transfusion requirement.[9] As we know, the genetic abnormality in thalassaemia syndromes leads to ineffective haematopoiesis. The defective red cells are removed by the spleen which results in splenomegaly. Thus, splenectomy lengthens the life span of red blood cells. This explains why some patients with TDT have become non-transfusion dependent after splenectomy.[9] Generally, the overall survival of patients with TDT has improved significantly and we now face major challenges worldwide with a high global prevalence of endocrine abnormalities.[10,11] In this study population, with a median age of 21 years, more than 2/3 of the patients had at least one endocrine disorder, despite almost all (98.9%) of them receiving iron chelation therapy.

Monitoring iron overload with serum ferritin or liver iron concentration via MRI T2* is crucial to establishing effective iron chelation therapy. Magnetic resonance imaging using the T2* technique to quantify liver iron concentration has become the gold standard because of its safety and reliability. However, the accessibility of MRI T2* imaging in Sarawak remains limited. In our study, there was a significant positive correlation between serum ferritin and liver iron concentrations but with poor linearity (R2=0.385; p<0.01) which is a similar result to other studies.12 This finding shows that serum ferritin can be used as an alternative option for the centres which has difficulty assessing MRI T2* imaging. Serum ferritin remains the method of choice as it is easily available and inexpensive. However, there is a limitation to the use of serum ferritin to monitor treatment response.

The relationship between serum ferritin and body iron stores is not always linear and can change from day to day. Serum ferritin is an acute-phase reactant whose levels can increase with tissue damage and inflammation.[1,13] It is also determined by the types and duration of chelation therapy. Liver iron concentration is more reliable in estimating body iron compared to serum ferritin. As we know, iron tends to accumulate in the liver and eventually in the heart and endocrine systems. LIC should be considered for patients who are on chelation therapy that is monitored with serum ferritin with uncertain responses. The study has shown that the relationship with LIC is not linear when the serum ferritin > 4000 mcg/L and patients may have a fall in LIC without a clear trend in serum ferritin in 6 to 12 months.[1,8] To assess the effectiveness of iron chelation therapy, we need to use LIC to monitor the iron burden. In general, the main goal is to identify iron overload early and optimise chelation therapy to prevent these late effects from happening. Serum ferritin is a convenient way of monitoring treatment outcomes but not without its limits. LIC is reliable but not all of the study population has access to it.

Age, age at initiating regular blood transfusion and duration of regular blood transfusion were significantly associated with the developing endocrine complications in TDT. Our study showed that patients aged 30 years and above had a higher risk of developing at least one type of endocrine disorder, which was comparable to another study in Thailand that occurred above 25 years old.[14] This demonstrates that endocrinopathies in TDT can be time-dependent. Patients with beta-thalassaemia major initiate regular blood transfusion at an earlier age than other genotypes and have a longer duration of regular blood transfusion. As a result, this group of patients is more prone to develop iron overload and endocrine complications. We need to overcome this challenge by early diagnosis of iron overload and initiating iron chelation therapy at a younger age.

Our study showed that endocrinopathy in TDT was related to growth and puberty. 46 patients (51.7%) had short stature, with 27 males (58.7%) and 19 females (41.3%). These findings were comparable to another study.[15] Arab-Zozani et al.,[15] described that male patients had a higher prevalence of short stature compared to female patients. Female patients could tolerate iron overload due to chronic oxidative stress.[15] Studies have demonstrated that Asians with TDT have a higher prevalence of developing short stature compared to Europeans.[5,15,16] The aetiology of short stature in thalassaemia can be multifactorial, which includes chronic anaemia, iron overload, desferrioxamine-induced bone dysplasia, growth hormone deficiency, hypogonadism, hypothyroidism, malnutrition and genetic short stature.[1,8] For patients who have an optimum blood transfusion and developed iron overload, we should investigate for growth hormone deficiency in these groups of patients. However, growth hormone measurement with the insulin tolerance test was not widely available in our settings.

Iron accumulation in the pituitary gonadotrophic cells leads to the development of delayed puberty and hypogonadism in TDT. We found that 26.9% of the patients had hypogonadism, which was comparable to another study in Singapore and Taiwan with similar ethnic populations, 21.9% and 23.1% respectively.[17,18] Our study cohort had a lower prevalence compared to another study done in Italy. The possible cause was that our study population was younger (median age of 21 years compared to 50 years).[10] A systemic review showed that hypogonadism was commonly seen in the older population and more prevalent in patients with TDT, especially those with beta-thalassaemia major.[19] With the advancing age of patients in TDT, we expect to have more patients with gonadal issues. It is therefore important for us to closely monitor them so that we can diagnose them early and initiate prompt treatment with iron chelation therapy and hormone replacement therapy.

This is important for Sarawak and even the whole of Malaysia to implement an effective thalassaemia screening and education programme to ensure thalassaemia is no longer a health burden to the nation. Proper genetic counselling is the key to increasing awareness of the disease, identifying carriers and reducing transmission to the offspring.[20] On the other hand, for paediatric patients with TDT, apart from regular blood transfusion and iron chelation therapy, we should change the direction of treatment. With the presence of HLA-matched related or unrelated donors and even haploidentical donors, haematopoietic stem cell transplantation (HSCT) provides a chance to cure TDT. With the advancement of the HSCT treatment, conditioning regime and control of transplant-related complications have improved over the years.[21] Adult thalassaemia patients have a more advanced disease due to chronic blood transfusion with iron overload and are not candidates for HSCT.

LIMITATIONS

There are a few limitations to this study. The sample size is small and there is a lack of prospective long-term follow-up for endocrinopathies in transfusion-dependent thalassaemia patients. Only 74.2% (n=66) of the patients in this cohort had undergone MRT T2*. Diagnostic tests to investigate endocrinopathies in TDT are not widely accessible. A possible explanation is that these facilities are only available at the tertiary subspecialty medical centre in Kuching which is far from other centres in Sarawak by road or even by air. This is a retrospective study that may not be representative of the general population and is prone to selection bias.

CONCLUSION

In this study, despite the majority of the patients receiving iron chelation therapy, 2/3 of the study cohort had moderate iron overload and a prevalence of endocrinopathies of 69.7%. These findings were higher compared to another study with a similar setting.[6] The findings of this study provide insight into the development of endocrinopathies can be time dependent. However, the limitations of this study require larger studies with more patients to provide more definitive evidence. In conclusion, early detection and close monitoring of complications with individualized therapy are crucial to address these issues, especially at an earlier age to prevent complications in adulthood. Endocrinopathies may increase the overall disease burden when the population ages. Good patient-physician collaboration with a multidisciplinary approach is important to improve the care of patients with transfusion-related endocrine dysfunction.

ACKNOWLEDGEMENTS

We would like to thank the Director General of the Ministry of Health for the permission to publish this paper. We would like to extend our appreciation to all the healthcare workers who are involved in taking care of the thalassaemia patients in Sarawak.

DECLARATION OF CONFLICTING INTEREST

The authors declared no conflicting interests in the research, authorship and publication of this article.

FUNDING

The authors received no financial support for the research and authorship. However, the authors received financial support from the Malaysian Society of Haematology for the publication of this article.

ETHICAL APPROVAL

This study obtained approval from the Malaysian Medical Research and Ethics Committee, Ministry of Health (NMRR-19-3577-51668).

INFORM CONSENT

A waiver of informed consent for this study as it only involved a retrospective review of patients' recorded data.

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