Endocrine Complications in Transfusion Dependent Thalassaemia in Penang Hospital

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SUMMARY

Frequent blood transfusions can lead to iron overload which may result in several endocrine complications especially in the absence of adequate chelation therapy. The objectives of this study are to determine the prevalence of endocrine complications in transfusion dependent thalassaemia patients and the correlation of endocrine complications with the degree of iron chelation. This retrospective study looked at cases of adult patients with transfusion dependent thalassaemia treated in the Haematology Unit, Penang Hospital. Of the 25 transfusion dependent thalassaemia patients, there were 10 male and 15 female patients respectively with almost equal number of Malay and Chinese patients (13 and 12 patients respectively). Short stature was seen in 36.0% of our patients. In our cohort, 12 patients had delayed puberty (male 70.0% and female 33.3%). Prevalence of osteoporosis was 36.0%. Hypogonadism was noted in 40.0% of males and 46.7% of females. 53.4% of the female population had menstrual abnormalities with prevalence of primary and secondary amenorrhoea at 26.7% each. The prevalence of other endocrinopathies was much lower: 8.0% had diabetes mellitus and only one patient had hypocortisolism. Iron chelation appeared insufficient in our study population. The high frequency of endocrine complications noted in our study supports the rationale for regular follow-up of transfusion dependent thalassaemic patients to ensure early detection and timely treatment of associated complications.

INTRODUCTION

Thalassaemia represents a group of recessively inherited haemoglobin disorder which is characterized by reduced synthesis of globin chains. Frequent blood transfusions can lead to iron overload which may result in several endocrine complications especially in the absence of adequate chelation therapy. The objectives of this study were: a) to determine the prevalence of endocrine complications in transfusion dependent thalassaemia patients treated in the Haematology Unit, Penang Hospital, b) to determine the correlation of endocrine complication with the degree of iron chelation.

MATERIALS AND METHODS

This was a retrospective study. Demographic and anthropometric data, menstrual history, family history of diabetes, initiation and duration of blood transfusion and chelation therapy were collected and analyzed. Percentiles of height and weight were determined by growth diagram. Puberty staging was based on Marshall-Tanner Chart. Delayed puberty was defined by absence of breast development in girls by the age of 14 and absence of testicular enlargement in boys (less than 4 ml) as measured by Prader's orchidometer by the age of 16. Short stature was defined as final height below mean parental height. Hypogonadism was defined as low testosterone/oestradiol level or subjects who were on testosterone/oestrogen replacement. Primary amenorrhea was defined as absence of menarche by the age of 16. Secondary amenorrhea was defined as the absence of menstruation for six months or more after menarche. Hypothyroidism was defined according to TSH/FT4, or based on the history of treatment with levothyroxine for previously diagnosed hypothyroidism. Hypoparathyroidism was diagnosed when there was low serum calcium concentration, with increased serum phosphate and low serum intact parathyroid hormone (with a reference range of 13-54 pg/ml.). Patients were diagnosed with diabetes mellitus based on WHO criteria or history of insulin therapy or oral anti-diabetic therapy. Osteopenia was defined as a T score between – 1 and – 2.5 and osteoporosis below – 2.5 (World Health Organization Study Group, 1994). Z score represents the number of standard deviations above or below the age and sex matched mean reference value; a low bone mass as a Z score between – 1 and – 2.5 and severely low bone mass below – 2.5. The mean serum ferritin level during the study period in individual patient was calculated from latest readings available as well as the mean ferritin level during the prepubertal period (age 1-10 year) and the mean ferritin level during the pubertal period (age 11-16 year). All transfusion dependent thalassaemia patients who received monthly to two monthly transfusions in the Haematology Unit Daycare were included in this study. Paediatric patients < 12 year old were excluded from the study.

Data were analyzed using Statistical Package for Social Sciences (SPSS) software (version 13.0). Numerical data were presented as mean +/- standard deviation. $P < 0.05$ was considered significant. All factors were tested for their distribution model. We considered Mann-Whitney test, where distributions were not normal, to investigate different levels of associations. Statistical analysis was done with 95% confidence interval.

RESULTS

Patient characteristics (Refer Table I)

Of the 25 transfusion dependent thalassaemia patients, there were 10 male and 15 female patients respectively with almost

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equal number of Malay and Chinese patients (13 and 12 patients respectively). Mean age at the time of study was 23.1 +/- 5.9 years. Demographic characteristics of study population were shown in Table I. Mean age at diagnosis was 3.9 +/- 3.3 year (range from 2 month to 12 year). Mean age at onset of blood transfusion was 55.9 +/- 40.3 months. Forty percent (10 out of 25) of patients had undergone splenectomy at a mean age of 14.3 years.

Iron chelation therapy

Iron chelation therapy was initiated at a mean age of 11.9 year (range from 4 year to 27 year). Mean serum ferritin level over the last one year was 4337 +/- 2189.3 ng/ml. Therapeutic characteristics were as shown in Table II.

Prevalence of endocrine complications

The prevalence of endocrine complications in transfusion dependent thalassaemia patients treated in the Haematology Unit, Penang Hospital was 68.0% (17 of 25 patients had ≥ 1 endocrine complication). 88.2% of these patients had more than one endocrine complication.

Short stature was seen in nine patients (36.0%). In our cohort, 12 patients had delayed puberty (male 70.0% and female 33.3%). Prevalence of osteoporosis was 36.0%. Hypogonadism was noted in 44.0% of patients. 53.4% of the female population had menstrual abnormalities. The prevalence of primary and secondary amenorrhoea was 26.7% respectively.

The prevalence of other endocrinopathies was much lower: Two patients (8.0%) had diabetes mellitus and only one patient (4.0%) had hypocortisolism. None of our patients developed hypoparathyroidism or hypothyroidism. The summary of endocrine complications observed in our blood transfusion dependent thalassaemia patients is shown in Table III. Table IV shows the comparison of prevalence of endocrine complications among various regions.

Table I: Demographic Characteristics of Study Population

Characteristics	Value
Age (year)	23.1 +/- 5.9*
Height (cm)	156.2 +/- 8.5*
Weight (kg)	45.1 +/- 5.9*
Sex	
• Male	10 (40.0%)
• Female	15 (60.0%)
Ethnic	
• Malay	13 (52.0%)
• Chinese	12 (48.0%)
• Indian	0 (0.0%)
• Others	0 (0.0%)
Classification of Thalassaemia	
• Beta Major	16 (64.0%)
• E / Beta	8 (32.0%)
• Others (E Barts Constant Spring)	1 (4.0%)
Viral Screen	
• HIV + ve	0 (0.0%)
• HEP Bs Ag + ve	1 (4.0%)
• HEP C RNA + ve	3 (12.0%)

*MEAN +/- SD

Association of endocrine complications with serum ferritin level (Refer Table V)

Mean serum prepubertal and pubertal ferritin level were significantly higher in patients with hypogonadism than those without hypogonadism (P<0.01). Likewise mean serum prepubertal and pubertal ferritin level were significantly higher in patients with amenorrhoea than those without amenorrhoea (P<0.05). In our series, mean serum ferritin level was significantly higher in patients with osteoporosis. Both mean pre-pubertal and pubertal ferritin levels were significantly correlated with osteoporosis. There was no significant correlation found between either short stature, diabetes mellitus or delayed puberty and serum ferritin level.

DISCUSSION

Endocrine dysfunction is well recognized in patients with transfusion-dependent thalassaemia and is thought to reflect the consequence of iron overload[3,6]. They are among the most common consequences of the disease worldwide, affecting patients' quality of life and causing considerable morbidity and mortality[6]. Although data from developing countries are limited, studies elsewhere have documented complications such as osteoporosis[2,4,6-7,9], hypothalamic–pituitary dysfunction[1-6,8], hypothyroidism[1-6,9], hypoparathyroidism[1-6], adrenal insufficiency[5-6] and pancreatic dysfunction[1-6].

The W.H.O. definition of osteoporosis relates only to adult women and not to men or children. The major reason for this is that the relationship between bone mass and fracture risk is not so clearly established in men as in post-menopausal women and not at all established in children. For this reason we expressed values as Z scores.

The prevalence rate of endocrine complications observed in our study was comparable to studies from other regions. The prevalence rate of osteoporosis, hypothyroidism and hypoparathyroidism were lower than other regions.

Amenorrhoea (53.4%), delayed puberty (48.0%) and hypogonadism (44.0%) are the three most common endocrine complications noted in our thalassaemia patients. Similar findings were also noted by other researchers[1,3,5]. The prevalence of other endocrinopathies such as short stature and osteoporosis were much lower compared to other centres whilst the prevalence of diabetes mellitus appears to be comparable (Refer Table IV). None of the patients in our cohort had hypothyroidism and hypoparathyroidism

Table II: Therapeutic Characteristics of Study Population

Characteristics	Mean +/- SD
Age at Diagnosis of Thalassaemia (year)	3.9 +/- 3.3
Age at Initiation of Transfusion (month)	55.9 +/- 40.3
Age at Initiation of Chelation (year)	11.0 +/- 5.6
Age at Splenectomy (year)[1]	14.3 +/- 4.5
Pre-transfusion Hb in Last 1 Year (g/dl)	8.4 +/- 0.9
Pre-pubertal Ferritin Level (ng/ml)	4796 +/- 3118.8
Pubertal Ferritin Level (ng/ml)	5000 +/- 2385.9
Ferritin Level Last 1 year (ng/ml)	4337 +/- 2189.3

[1]Only 10 patients had undergone splenectomy

Table III: Endocrine and Metabolic Complications Observed in Blood Transfusion Dependent Thalassaemia

Complications	N	%
Osteoporosis	9	36.0
Hypogonadism	11	44.0
• Female	7	46.7
• Male	4	40.0
Menstrual Abnormalities	8	53.4
• Primary Amenorrhoea	4	26.7
• Secondary Amenorrhoea	4	26.7
Delayed Puberty	12	48.0
• Female	5	33.3
• Male	7	70.0
Short Stature	9	36.0
Diabetes Mellitus	2	8.0
Hypocortisolism	1	4.0
Hypoparathyroidism	0	0.0
Thyroid Disorder	0	0.0

Table IV: Endocrine Complications Rate Reported in Various Studies

SITE (REFERENCE) / COMPLICATIONS	Hosp. Penang	Hong Kong 1	Italy 2	Israel 3	Iran 4	Iran 5
Short Stature	36.0%	68.5%	57.0%	36.0%	39.3%	65.7%
Hypogonadism	44.0%	68.5%	25-30%	59.0%	17.6%	72.0%
Delayed Puberty	48.0%	68.5%	43.0%	48.1%	76.7%	72.0%
Amenorrhoea	53.4%	-	50.0%	53.8%	40.5%	-
Osteoporosis	36.0%	-	81.0%*	-	53.6%	-
Diabetes Mellitus	8.0%	Sometimes	5-15.0%**	5.1%	8.7%	7.3%
Hypothyroidism	0.0%	Rare	50.0%	7.7%	7.7%	6.0%
Hypoparathyroidism	0.0%	Rare	3.6%	10.2%	7.6%	7.3%
Hypocortisolism	4.0%	Rare	-	-	-	0.7%

*Including osteopenia
**Including Impaired Glucose Tolerance

Table V: Distribution of Quantitative Variables by Endocrine Complications in Blood Transfusion Dependent Thalassaemia

SERUM FERRITIN / COMPLICATIONS		PREPUBERTAL FERRITIN LEVEL (ng/ml)		PUBERTAL FERRITIN LEVEL (ng/ml)		FERRITIN LEVEL DURING STUDY PERIOD (ng/ml)	
Amenorrhoea	YES	6759+/- 2216		6148+/-2838		5635+/-2498	
	NO	2183+/-2121	*	3661+/-1818	*	3741+/-1802	NS
Delayed Puberty	YES	5732+/-3063		5913+/-2670		4750+/-2566	
	NO	3933+/-3028	NS	4158+/-1803	NS	3958+/-1795	NS
Hypogonadism	YES	7607+/-1607		6748+/-2115		4863+/-2636	
	NO	2588+/-2009	*	3627+/-1565	*	3925+/-1756	NS
Osteoporosis	YES	7052+/-2727		6655+/-2535		4873+/-2989	
	NO	3528+/-2613	*	4070+/-1765	*	4037+/-1623	NS
Short Stature	YES	4586+/-2716		4523+/-1424		4038+/-1335	
	NO	4915+/-3404	NS	5269+/-2795	NS	4507+/-2576	NS
Diabetes Mellitus	YES	8151+/-844		6026+/-909		4508+/-37	
	NO	4505+/-3077	NS	4911+/-2463	NS	4323+/-2286	NS

* Statistically significant, P < 0.05
NS = Statistically not significant

(>10%)[2-3] whereas others showed more varied prevalence of 0-7%[4-5]. It is important to note that even in the studies in which the prevalence of overt hypothyroidism is relatively low, milder forms of thyroid dysfunction may still be present[14].

Endocrine problems in thalassaemia could result from a variety of factors, with most studies suggesting that chronic iron overloading secondary to hypertransfusion therapy is the major cause of the observed abnormalities[2,6]. The use of iron-chelating drugs has been shown to delay the development of iron-induced damage of cardiac and liver tissues, resulting in improved survival[2,3,6].

The mean serum ferritin level, both pubertal as well as prepubertal, was significantly higher in our thalassaemic patients with amenorrhoea, hypogonadism and osteoporosis. These findings support the importance of iron overload in the development of endocrine disorders[4,9-12]. However, there does not appear to be a significant difference in the mean serum ferritin levels for patients with delayed puberty, short stature and diabetes mellitus as compared to their counterparts without these complications. In comparison, both the Italian Working Group[6] and Shalitin *et al*[3] found a significantly higher serum ferritin level in patients with delayed puberty and hypogonadism than individuals with normal puberty. Furthermore, in Shalitin's study the difference was significantly only for the pubertal years.

There are a few limitations to be considered in relation to the findings in our study. The sample size is small, the cohort is young and there is limited prospective follow-up. Statistical analyses therefore have limited power, and hence our simple models may not be able to optimally identify patients at high risk of endocrinopathies. Efforts will be made to follow up these patients over a longer period of time and hopefully the results will have a more accurate predictive value.

The ability of deferoxamine to prevent iron induced endocrine complications is less well defined, but with increased survival, the consequences of endocrine failure become more important. Some researchers suggested that early initiation of chelation (before the age of 10 year), with effective long-term chelation therapy, assures normal puberty in the majority of patients[3,6,15]. However, the initiation of iron chelation therapy at a young age is associated with bone toxicity and, consequently may decrease growth.

The relatively high frequency of endocrine dysfunctions noted in our study (prevalence rate of 68.0%) may reflect inadequate chelation therapy and suboptimal management of associated complications. The mean age of initiation of chelation therapy in our cohort is 11.0 +/- 5.6 years. This is not surprising as prior to 2005, iron chelation therapy was not government funded and not many thalassaemics could afford full treatment. These findings reinforce the importance of regular follow-up of patients with transfusion dependent thalassaemia for early detection and management of associated complications[5-6].

CONCLUSION

The high frequency of endocrine complications noted in our study supports the rationale for regular follow-up of transfusion dependent thalassaemia patients to ensure early detection and timely treatment of associated complications.

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