Prevalence of fractures among Thais with thalassaemia syndromes

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ABSTRACT

Introduction: The association of fractures with thalassaemia syndromes is well established. The aim of this study was to determine the prevalence and risk factors for fracture in Thai people with thalassaemia syndromes.

Methods: A retrospective study and a patient interview were conducted in 201 Thai thalassaemia patients who attended the Division of Haematology, Department of Medicine Siriraj Hospital, Thailand. The patient interview questionnaire included sections on demographics, medical, orthopaedic and surgical history, usage of tobacco and alcohol, as well as questions that pertained to fracture. The risk factors for fracture were determined by odds ratio.

Results: The prevalence of fracture in Thai people with thalassaemia syndromes was 35.3 percent. Fracture occurred more often in beta thalassaemia patients (44.1 percent) than in alpha thalassaemia patients (16.9 percent). Upper extremity was the most common site of fracture, while falls and motor vehicle accidents were the most common causes of fracture, and cast/splint was the most common choice of treatment. 28 percent of the patients sustained multiple fractures. Among alpha thalassaemia patients, adults sustained fractures more frequently than children and adolescents. In contrast, beta thalassaemia children had a greater rate of fracture than the adults and adolescents. The risk factors for fracture in thalassaemia patients included male gender, beta thalassaemia, splenectomy, transfusion and a low body mass index.

Conclusion: A high prevalence of fracture is observed among Thais with thalassaemia. The aetiology was found to be multifactorial.

Keywords: fracture, prevalence, retrospective, thalassaemia, trauma

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INTRODUCTION

Thalassaemia and haemoglobinopathies are the two most common genetic diseases in Thailand. Thalassaemic and abnormal haemoglobin genes are spread throughout the country with varied frequencies. About 30%–40% of the Thai population carry the thalassaemic and abnormal haemoglobin gene. About 1% of the Thai population, or approximately 50,000 people, have thalassaemia, with an annual incidence of more than 10,000.[1,2]

Previous reports have described the association between homozygous beta-thalassaemia and severe osseous abnormalities.[3] Both pathological fractures and premature epiphyseal fusion can result in marked long bone deformities.[4-6] The mechanism for these abnormalities in thalassaemia has been explained by the underlying massive ineffective erythropoiesis, erythroid expansion of the medullary bone with thinning of the cortical bone, as well as metabolic and endocrine dysfunction secondary to transfusional iron overload.[7,8]

From the 1960s to 1970s, a high rate of fracture in thalassaemia patients was documented when transfusion and chelation regimens were not optimised.[9] Subsequent studies in the 1980s also reported a high frequency of fracture (30%–50%).[5,6] Lower fracture rates (15%–19%) were reported in the 1990s among transfusion-dependent beta-thalassaemia patients of Mediterranean and Middle Eastern origins.[10,11] However, no study specifically addressed the prevalence of fractures among Thais with thalassaemia syndromes. In this retrospective study, we aimed to establish the prevalence of fractures as well as to ascertain the predisposing factors for fracture among Thais with thalassaemia.

METHODS

A retrospective chart review and patient interview were conducted at the Division of Haematology, Department of Medicine Siriraj Hospital, Thailand. All thalassaemia patients who attended the outpatient haematology units were included in this study. Patients who declined to participate in the study were not included. Written informed consent was obtained from all participants before the interview. The study was reviewed and approved by the Siriraj Ethics Committee (Si 493/2008 [2008-09-19]).

Table I. Demographics, growth, menarche and iron status in thalassaemia patients.

	No. of patients (%)			p-value
	All (n = 201)	Alpha-Thal (n = 65)	Beta-Thal (n = 136)	
Age (yrs)	34.7 ± 12.4	42.7 ± 11.7	30.8 ± 10.7	< 0.001[a]
Gender				
Male	61 (30.3)	13 (20.0)	48 (35.3)	< 0.05[b]
Female	140 (69.7)	52 (80.0)	88 (64.7)	
Weight (kg)*	50.4 ± 8.0	50.9 ± 7.8	50.1 ± 8.1	> 0.05[a]
Height (m)*	1.57 ± 0.09	1.55 ± 0.08	1.59 ± 0.09	< 0.05[a]
BMI (kg/m^2)*	20.2 ± 2.7	21.0 ± 2.7	19.7 ± 2.6	< 0.01[a]
Age at menarche (yrs)* (n = 132)	15.7 ± 2.1	15.6 ± 2.3 (n = 52)	15.7 ± 1.9 (n = 80)	> 0.05[a]
Serum ferritin (ng/ml)*	2,846 ± 2,817	1,366 ± 2,617	3,322 ± 2,721	< 0.001[a]

* Data expressed as mean ± standard deviation.
[a] p-value derived using unpaired student's *t*-test; [b] p-value derived using Fisher's exact test
Thal: thalassaemia; BMI: body mass index

The patient's medical history was obtained by reviewing the patient interview and medical record. Data on demographics, underlying disease, transfusion regimens as well as usage of tobacco and alcohol were recorded as general information. Information on the site of fracture, age of the patient, cause of fracture and type of treatment were collected as part of fracture history. The aetiology of fracture was classified into four categories: fall, sports or recreational injury, motor vehicle accident and heavy object trauma. The treatment of fractures was categorised as cast/splint, surgery, hospitalisation and no treatment. The sites of fractures were classified into the following categories: upper extremity (including shoulder, arm, forearm, wrist and hand), lower extremity (including leg, ankle and foot) and spine/back/pelvis.[8]

The medical record review included documentation of transfusions and the recent laboratory values (serum ferritin level). Transfused patients were defined as those who received more than one transfusion per year, whereas non-transfused patients were those who had never received blood transfusion before this study. In addition, regular transfusion was defined as > 12 transfusions per year, or at least one transfusion every four weeks. For the purpose of analysis in this study, beta thalassaemia was divided into homozygous beta thalassaemia (n = 12) and beta thalassaemia/haemoglobin (Hb) E (n = 124). Alpha thalassaemia was also divided into two groups: Hb H (n = 54) and Hb H/constant spring (n = 11).

All values were expressed as mean ± standard deviation (SD). Statistical analysis was performed using StatView for Windows version 5 (SAS Institute Inc, Cary, NC, USA). Descriptive statistics were calculated, and contingency tables were produced. Chi-square tests were performed on the categorical variables, while unpaired *t*-test was used to compare the values in beta and alpha thalassaemia patients. A p-value < 0.05 was considered to be statistically significant.

RESULTS

A total of 201 thalassaemia patients were enrolled in the present study, out of which 65 patients were categorised as alpha thalassaemia (alpha-Thal) and 136, as beta thalassaemia (beta-Thal). The demographics, growth, menarche and iron status are shown in Table I. The average age of the alpha thalassaemia patients was 42.7 ± 11.7 years and that of the beta thalassaemia patients was 30.8 ± 10.7 years. Statistical differences were observed with regard to the age ($p < 0.001$), gender distribution ($p < 0.05$), height ($p < 0.05$), body mass index (BMI) ($p < 0.01$) and serum ferritin ($p < 0.001$) between the alpha and beta thalassaemia groups. Although the beta thalassaemia patients were younger and had a lower BMI, they had a greater iron overload (up to three times) when compared with the alpha thalassaemia patients (3,322 ± 2,721 vs. 1,366 ± 2,617, respectively; $p < 0.001$). No statistical differences were observed with regard to the weight ($p > 0.05$) and age at menarche ($p > 0.05$).

In all, 71 thalassaemia patients had a history of fracture, with a prevalence rate of 35.3% (Table II). The prevalence of fracture was higher in beta thalassaemia (44.1%) than in alpha thalassaemia (16.9%) patients, yielding a statistically significant difference ($p < 0.001$). Beta thalassaemia patients also suffered their first fracture at an earlier age compared to those with alpha thalassaemia, and the difference was statistically significant (15.8 ± 11.1 vs. 29.0 ± 23.8, respectively, $p < 0.01$). However, the number of fractures

Table II. Characteristics of fracture in alpha and beta thalassaemia patients.

Characteristic	No. of patients (%)			p-value
	All (n = 201)	Alpha-Thal (n = 65)	Beta-Thal (n = 136)	
Fracture prevalence	71 (35.3)	11 (16.9)	60 (44.1)	< 0.001[a]
No. of fractures*	1.49 ± 0.89	1.27 ± 0.65	1.53 ± 0.92	> 0.05[b]
Age at first fracture*	17.8 ± 14.4	29.0 ± 23.8	15.8 ± 11.1	< 0.01[b]
Total no. of fractures	106 (52.7)	14 (21.5)	92 (67.6)	
Site of fracture				
Upper extremity	66 (62.3)	9 (64.3)	57 (61.9)	
Lower extremity	25 (23.6)	4 (28.6)	21 (22.8)	
Spine/back/pelvis	15 (14.2)	1 (7.1)	14 (15.2)	
Cause of fracture				
Fall	52 (49.1)	7 (50.0)	45 (48.9)	
Recreation/sport	6 (5.7)	0 (0.0)	6 (6.5)	
Motor vehicle	39 (36.8)	5 (35.7)	34 (36.9)	
Heavy objects	9 (8.5)	2 (14.3)	7 (7.6)	
Treatment of fracture				
Cast/splint	81(76.4)	9 (64.3)	72 (78.3)	
Surgery	9 (8.5)	3 (21.4)	6 (6.5)	
Hospitalisation	8 (7.5)	1 (7.1)	7 (7.6)	
Not treated	8 (7.5)	1 (7.1)	7 (7.6)	

* Data expressed as mean ± standard deviation.
[a] p-value derived using unpaired student's *t*-test; [b] p-value derived using Fisher's exact test
Thal: thalassaemia

did not significantly differ between these two groups (1.53 ± 0.92 vs. 1.27 ± 0.65, respectively, p > 0.05). The most common site of fracture was the upper extremity (62.3%). The majority of these fractures were caused by falls (49.1%) and motor vehicle accidents (36.8%). As would be expected, over three-quarters of all fractures (76.4%) were treated with a cast or splint, while only about 16% were treated with surgery or hospitalisation. In addition, 20 out of the 70 (28.1%) thalassaemia patients with fractures sustained multiple fractures (data not shown).

The prevalence of fracture was also compared according to age group (Table III). All fracture patients (n = 71) were classified according to their ages: children (0–10 years), adolescents (11–17 years) and adults (≥ 18 years). Among the alpha thalassaemia patients, the adults (63.6%) showed a higher prevalence of fracture compared to the children and adolescents (18.2% for both). In contrast, among the beta thalassaemia patients, a higher prevalence of fracture was observed in the children (41.7%) as compared to the adolescents and adults (28.3% and 30.0%, respectively). No statistically significant difference was observed in the fracture prevalence when the analysis was performed using both the age group and diagnosis (chi-square p-value = 0.09).

The significant risk factors for fracture were male gender (odds ratio [OR] 2.58), a diagnosis of beta thalassaemia (OR 3.87), previous splenectomy (OR 2.82), previous transfusion (OR 3.04) and a low BMI. Age, alcohol intake, a history of smoking, the type of transfusion and serum ferritin level were not significant risk factors (p > 0.05) (Table IV).

DISCUSSION

The present study found a 35.3% prevalence of fracture in Thai thalassaemia patients. This high prevalence of fracture is consistent with that reported by other authors,[8,12] but substantially lower than the rate of 50% reported in the 1970s and 1980s.[5,6,9] Our results also differ from two recent reports on transfusion-dependent beta thalassaemia patients by Basanagoudar et al[13] and Vogiatzi et al,[14] which observed an overall fracture prevalence of 12%. This may be explained by the less effective transfusion and chelation regimens in Thailand.[15] Therefore, improvement in transfusion technique and chelation regimen is recommended so as to reduce the rate of fracture among Thai thalassaemia patients. Furthermore, antiresorptive medication is also considered for treatment of low bone mass in these thalassaemia patients, although it is not routinely prescribed in Thailand due to the high cost. Ongoing efforts in securing government funding should be emphasised.

Table III. Prevalence of bone fractures according to age group.*

	No. of patients (%)			
	Total	Children (0–10 years)	Adolescents (11–17 years)	Adults (≥ 18 years)
Alpha-Thal	11	2 (18.2)	2 (18.2)	7 (63.6)
Beta-Thal	60	25 (41.7)	17 (28.3)	18 (30.0)
All patients	71	27 (38.0)	19 (26.8)	25 (35.2)

* There was no significant difference in fracture prevalence between alpha and beta thalassaemia patients by age group ($p > 0.05$).
Thal: thalassaemia

Table IV. Factors related to fracture prevalence in Thai patients with thalassaemia syndrome.

	No. of patients (%)		p-value
	Fracture (n = 71)	No fracture (n = 130)	
Male gender	31 (43.7)	30 (23.1)	< 0.01[a]
Hb typing (beta-Thal)	60 (84.5)	76 (58.5)	< 0.001[a]
Alcohol intake	19 (26.8)	26 (20.0)	> 0.05[a]
Smoking history	6 (8.5)	5 (3.8)	> 0.05[a]
Splenectomised	31 (43.7)	28 (21.5)	< 0.01[a]
Blood transfusion	55 (77.5)	69 (53.1)	< 0.001[a]
Type of transfusion	15 (21.1)	25 (19.2)	> 0.05[a]
Age (yrs)*	33.1 ± 12.7	35.5 ± 12.1	> 0.05[b]
BMI (kg/m2)*	19.4 ± 2.8	20.6 ± 2.5	< 0.01[b]
Serum ferritin (ng/ml)*	3,075 ± 2,533	2,697 ± 2,990	> 0.05[b]

* Data expressed as mean ± standard deviation.
[a] p-value derived using unpaired student's *t*-test; [b] p-value derived using Fisher's exact test
Thal: thalassaemia; Hb: haemoglobin; BMI: body mass index

In this study, patients with alpha thalassaemia were found to have lower rates of fracture compared to those with beta thalassaemia. This finding was similar to that published from the Thalassaemia Clinical Research Network of North America (TCRN), where it was reported that fractures occurred more frequently in beta thalassaemia major (16.6%) and beta thalassaemia intermediate (12.2%) patients as compared to beta thalassaemia/Hb E (7.4%) and alpha (2.3%) patients.[12,14] This lower frequency of fracture in alpha thalassaemia is likely related to the mild degree of haemolysis and low disease activity as opposed to the moderate to severe degree of haemolysis and high disease activity found in beta thalassaemia.[16,17]

The TCRN results indicated that the high fracture incidence in thalassaemia is associated with aging and low lumbar bone mass.[14] In contrast to the above, our finding suggests that the epidemiology of fracture is quite different among alpha and beta thalassaemia patients. It was observed that fractures occurred more frequently in young patients with beta thalassaemia. This may also be related to either a high disease activity in beta thalassaemia or a lack of parental protection of the chronically ill Thai child. Upper extremity was the most common site of fracture, while falls and motor vehicle accidents were the most common causes of fractures. Cast/splint was the most common method of treatment. The findings were similar between the two types of thalassaemia.

Many significant predictors of fracture prevalence in thalassaemia, such as the type of thalassaemia, male gender, hypothyroidism and age, have been reported by Fung et al.[8] In the present study, we also found similar significant predictors as those previously described. The risk factors for fracture include male gender, a diagnosis of beta thalassaemia, previous splenectomy, previous transfusion and a low BMI. Hence, it is clear that fracture incidence in thalassaemia has a multifactorial aetiology.[12,14]

The limitation of this study was its design as a retrospective, questionnaire interview study. Hence, some patients may imperfectly recall their history of fracture during childhood. Furthermore, there were only a small number of respondents compared to other

studies. This is the only study on the prevalence of fracture conducted in the Thai thalassaemic population.

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