β-Thalassemia intermedia: morbidity uncovered

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Chapter 6

Management

Age-related Complications In Treatment-naïve Patients With Thalassaemia Intermedia

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Age-related complications in treatment-naïve patients with thalassaemia intermedia

Numerous efforts have been made to understand the molecular and pathophysiological basis of the intermediate forms of thalassaemia (Taher *et al*, 2006). Although the term thalassaemia intermedia (TI) lacks specific molecular correlates, several studies highlight established differences in the underlying pathophysiology and associated clinical sequelae as compared to patients with thalassaemia major (Taher *et al*, 2006). However, much of these differences rely on the treatment approaches -splenectomy, transfusion, iron chelation, and foetal haemoglobin induction- undertaken after initial diagnosis. Moreover, the shortage of clinical trials that investigate treatment strategies for TI resulted in a wide variety of management practices (Taher *et al*, 2009a). Consequently, the natural history of the disease remains poorly understood.

We revaluated data collected for the Thalassaemia Intermedia Registry, a database of 584 TI patients currently registered at six comprehensive care centres in Lebanon, Italy, Iran, Egypt, United Arab Emirates, and Oman. Institutional review boards (IRBs) at each centre approved the study protocol. All patients were diagnosed with TI based on previously described criteria (Camaschella & Cappellini, 1995). Patients who had never received any treatment intervention (splenectomy, transfusion therapy, iron chelation therapy, foetal haemoglobin inducing agents) were identified and included in this study ($n = 120$). Retrieved data included demographics (age and gender); identified mutation; mean haemoglobin (Hb) and steady-state serum ferritin (SF) levels of three consecutive measurements within the year corresponding to patient age; viral hepatitis status; and presence of complications [extramedullary haematopoiesis (EMH), leg ulcers, thrombosis, pulmonary hypertension (PHT), heart failure (HF), cholelithiasis, abnormal liver function (ALF), diabetes mellitus (DM), hypothyroidism, osteoporosis, hypogonadism] according to criteria described elsewhere (Taher *et al*, 2009a). Patients were divided into four quartiles ($n = 30$ each) according to their age: ≤10, 11–20, 21–32, and >32 years, representing 37·5%, 21·3%, 17·3%, and 15·8% of the whole cohort's ($n = 584$) corresponding age intervals, respectively. Bivariate correlations between age and SF or Hb levels were evaluated using Spearman's (r_s) correlation coefficients. To estimate the incidence density ratios (rate ratios) in those who had *versus* those who did not have the complication, odds ratios were calculated, with 95% confidence intervals. We tested for linear trend with advancing age by examining the significance of the coefficients with a Chi-squared test (*p*-trend). All *P*-values are two sided with the level of significance set at <0·05.

The mean age of the patients was 21·4 ± 13·4 years (range: 2–56 years). The male to female ratio was 61:59. Homozygosity for IVS-I-6 (T→C) was the most common mutation (87·5%), followed by IVS-I-5 (G→C) (8·3%), IVS-II-1 (G→A) (2·5%) and Codon 39 (C→T) (1·7%). There was no statistically significant difference between age quartiles in the proportion of patients with co-inheritance of α thalassaemia [α^+ (-$\alpha^{3.7}$ and -$\alpha^{4.2}$) or α^0 ($-^{Med}$ and $-^{SEA}$)] or determinants associated with increased γ-chain production (Xmn-I +/+ genotype at position −158 of *HBG2*). Moreover, none of the patients had evidence of hepatitis B or C infection. The mean Hb and SF levels of the whole study group were 77 ± 16 g/l (range: 41–110 g/l) and 610·7 ± 515·1 μg/l (range: 16·7–2520 μg/l) respectively. There was a statistically significant negative correlation between age and Hb level ($r_s = -0{\cdot}679$, $P < 0{\cdot}001$; Fig 1A) and a statistically significant positive correlation between age and SF ($r_s = 0{\cdot}653$, $P < 0{\cdot}001$; Fig 1B). With advancing age, there was a statistically significant trend towards a higher rate of EMH ($P = 0{\cdot}001$), leg ulcers ($P = 0{\cdot}004$), thrombosis ($P = 0{\cdot}030$), PHT ($P = 0{\cdot}010$), hypothyroidism ($P = 0{\cdot}039$), and osteoporosis ($P = 0{\cdot}018$) (Fig 1C and Table I).

This study demonstrated a significant role for advancing age (even among paediatric and adult patients) in acquiring complications in TI. Three main factors are responsible for the clinical sequelae of TI: ineffective erythropoiesis, chronic haemolytic anaemia, and iron overload (Taher *et al*, 2006).

The degree of ineffective erythropoiesis is the primary determinant for the development of anaemia, while peripheral haemolysis of mature red blood cells remains secondary (Rund & Rachmilewitz, 2005). Although the first is mainly associated with skeletal complications attributed to compensatory EMH (Taher *et al*, 2006), the latter has been linked to more severe complications, such as PHT (Aessopos *et al*, 2007), with secondary HF, and thromboembolic phenomena (Taher *et al*, 2008). This study demonstrated a decreasing trend in Hb level with advancing age. Although our study did not specifically measure relevant markers, this may reflect progressive worsening of ineffective erythropoiesis, haemolysis, hypersplenism, or all of these, and explain the associated increasing rate of EMH, leg ulcers, PHT, and thrombosis**.** Age-related changes in adaptation to anaemia have been observed in patients with Hb E β-thalassaemia. O'Donnell *et al* (2007) suggested that advancing age had an independent and direct effect on the background level of erythropoietin production in response to anaemia. In another study, there appeared to be a difference in the overall pattern of erythropoietin response to anaemia between children and adults, although this did not reach

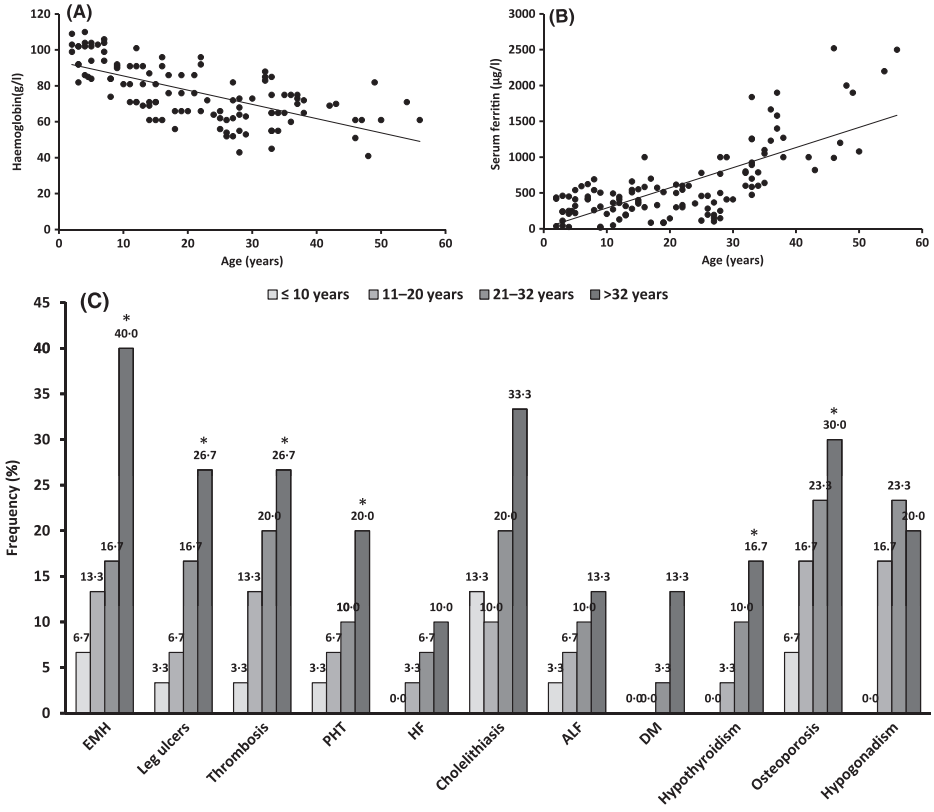

Fig 1. (A) Scatter plot of age and haemoglobin level. (B) Scatter plot of age and steady-state serum ferritin level. (C) Bar chart showing the frequency of complications across the different age quartiles. (*, statistically significant trend, EMH, extramedullary haematopoiesis; PHT, pulmonary hypertension; HF, heart failure; ALF, abnormal liver function; DM, diabetes mellitus).

statistical significance (Sukpanichnant *et al*, 1997). Moreover, in a study of erythropoietin response in patients with sickle cell anaemia, 10 adults seemed to show a lower response at approximately the same Hb level as those of children at the same level (Sherwood *et al*, 1986).

Our study also confirmed a positive correlation between advancing age and SF levels. Although no liver iron concentration measurements were done in this study, this association most probably reflects iron accumulation over time in patients with TI, which in turn explains the higher occurrence of iron-overload related endocrinopathy in older patients. The combination of ineffective erythropoiesis and chronic anaemia/hypoxia in TI results in hepcidin suppression, increased intestinal iron absorption, and increased release of recycled iron from the reticuloendothelial system. This results in depletion of macrophage iron, relatively low levels of SF, and preferential portal and hepatocyte iron loading (Taher *et al*, 2009b). Hence, transfusion-independent TI patients may still be at risk of iron-overload related morbidity, especially as older adults where iron accumulation may surpass acceptable levels.

Our study has an important clinical implication. It calls for close clinical follow up of TI patients as they get older. Despite being considered as having a milder form of the disease at initial presentation and diagnosis, TI patients are still at risk of acquiring several serious complications with the passage of time. Prospective clinical studies are thus urgently invited to assess the optimal type and timing of treatment initiation that needs to be offered to this group of patients to avoid disease-related morbidity, because an increasing percentage of patients will require treatment as they advance in age.

Authorship

ATT, KMM, MDC were responsible for conception and design, data analysis and interpretation, and manuscript writing; KMM performed statistical analysis; AE, MK, SD, KB, MSS

Table I. Incidence rate ratios for complications according to age.

	EMH		Leg ulcers		Thrombosis		PHT	
Age quartile	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Q1	1·00	Referent	1·00	Referent	1·00	Referent	1·00	Referent
Q2	2·15	(0·36–12·76)	2·07	(0·18–24·15)	4·46	(0·47–42·51)	2·07	(0·18–24·15)
Q3	2·80	(0·50–15·73)	5·80	(0·64–53·01)	7·25	(0·82–64·46)	3·22	(0·32–32·89)
Q4	9·33	(1·87–46·7)	10·55	(1·23–90·66)	10·55	(1·23–90·66)	7·25	(0·82–64·46)
p-trend	0·001		0·004		0·010		0·030	
	HF		Cholelithiasis		ALF		DM	
Age quartile	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Q1	1·00	Referent	1·00	Referent	1·00	Referent	1·00	Referent
Q2	1·00	(0·06–16·76)	1·23	(0·94–1·61)	2·07	(0·18–24·15)	1·00	(0·06–16·76)
Q3	2·07	(0·18–24·15)	1·07	(0·78–1·47)	3·22	(0·32–32·89)	1·00	(0·06–16·76)
Q4	3·22	(0·32–32·89)	1·25	(0·94–1·65)	4·46	(0·47–42·51)	4·46	(0·47–42·51)
p-trend	0·225		0·300		0·141		0·118	
	Hypothyroidism		Osteoporosis		Hypogonadism			
Age quartile	RR	95% CI	RR	95% CI	RR	95% CI		
Q1	1·00	Referent	1·00	Referent	1·00	Referent		
Q2	1·00	(0·06–16·76)	2·80	(0·50–15·73)	5·80	(0·64–24·15)		
Q3	3·22	(0·32–32·89)	4·26	(0·81–22·73)	8·85	(1·01–76·92)		
Q4	5·80	(1·23–90·66)	5·99	(1·17–30·30)	7·25	(0·82–64·46)		
p-trend	0·039		0·018		0·058			

Q1 = ≤10 years; Q2 = 11–20 years; Q3 = 21–32 years; Q4 = >32 years; EMH, extramedullary haematopoiesis; PHT, pulmonary hypertension; HF, heart failure; ALF, abnormal liver function; DM, diabetes mellitus.

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