

Thalassemia Major in Adults: Short Stature, Hyperpigmentation, Inadequate Chelation, and Transfusion-Transmitted Infections are Key Features

Anupam Prakash, Ramesh Aggarwal¹

Department of Medicine, Adult Thalassemia Unit, Lady Hardinge Medical College and Smt. Sucheta Kriplani Hospital, New Delhi, ¹Department of Medicine, Hamdard Institute of Medical Sciences and Research, Delhi, India

Abstract

Background: Effective transfusion and chelation have prolonged the quality and longevity of life in thalasseemics, who now survive into adulthood. Hence, adult physicians need to be aware of their clinical and laboratory profile and the problems faced by them. **Aim:** The present study was aimed to evaluate the clinical profile of adult thalasseemics. **Materials and Methods:** Adult (>18 years) thalassemia major patients ($n=19$) were evaluated clinically and fasting pretransfusion blood samples were analyzed for complete blood counts, kidney and liver function tests, plasma glucose, serum ferritin, and thyroid hormone levels. **Results:** Average age was 21.65 ± 2.47 years (range 19–28 years), 42.1% had Body mass index (BMI) <18.5. Splenectomy had been performed in 47.4% before reaching adulthood, males significantly outnumbered females (72% vs. 12.5%). Hemoglobin levels <8 g/dl were observed in 31.6% and none had serum ferritin levels in the recommended range suggesting inadequacy of both transfusion and chelation. Indirect hyperbilirubinemia was observed in 21.1% patients although kidney functions, serum protein, and albumin were normal in all patients. Electrocardiographic abnormalities, diabetes mellitus or hypothyroidism were absent. Five patients (26.3%) had contracted transfusion-transmitted viral infections – 21.1% and 5.3% respectively had antibodies to hepatitis C virus and HIV, while 5.3% were positive for Australia antigen. All patients were receiving chelation therapy – deferoxamine alone (78.9%) or along with desferrioxamine (21.1%). Average dose of deferoxamine being used was 95 ± 8 mg/kg. **Conclusion:** Adult thalassemia major patients present with a distinct clinical profile having low BMI, generalized hyperpigmentation, most are splenectomized, have low hemoglobin, inadequate chelation and harbor transfusion-transmitted infections. Adult physician needs to be aware of this profile.

Keywords: Adult, Chelation, Thalassemia major, Transfusion

Address for correspondence: Dr. Anupam Prakash, 2, Small Registrar Flats, Lady Hardinge Medical College Campus, New Delhi - 110 001, India.
E-mail: prakashanupam@hotmail.com

Introduction


Thalassemia major has long remained in the domain of pediatricians but advances in medical science and improved health care have contributed to the longevity of life and its quality; to the extent that it now needs attention of the adult physicians too. As of today, most physicians do not have to encounter thalasseemics as their

patients. Moreover, knowledge and management issues relating to thalassemia are unknown to most physicians. It is surprising that a Medline Search reveals less than 10 articles on topics concerning adult thalassemia. There is a severe resource data crunch at a time when information needs to be readily available to the physicians, the emphasis being on “evidence-based medicine.”

This study aims to evaluate the clinical profile of thalassemia major patients surviving into adulthood so as to orient the physicians and the general practitioners to adult thalassemia patients.

Materials and Methods

The study included all adult patients of thalassemia (>18 years old) who are attending the Adult Thalassemia

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Care Unit (Department of Medicine) for their management. The Department of Pediatrics at our institute, which happens to be a tertiary institute, runs a Thalassemia Day Care Unit, wherein about 250 patients regularly receive transfusion and all patients who attain 18 years of age are referred to Adult Thalassemia Care Unit (Department of Medicine) for management, from where these data are being reported. This Adult Thalassemia Care Unit is the first of its kind in India. All patients were evaluated clinically and investigated for complete blood counts, serum urea, creatinine, bilirubin (total and direct), alanine and aspartate transaminases, alkaline phosphatase, total protein and albumin, fasting and postprandial plasma glucose, serum ferritin, and thyroid hormone levels. Pretransfusion blood samples were collected in a fasting state. All the patients were receiving packed cell transfusions for at least 15 years with the aim to keep the hemoglobin levels at about 10 g/dl. Unpaired Student's *t*-test was used to ascertain difference in clinical features between male and female thalassemia patients.

Results

A total of 19 thalassemia patients were above the age of 18 years and were availing regular transfusion services at fortnightly intervals. The clinical features have been outlined in Table 1. As is evident from the table, the height in both the male and female subjects was quite lower than the usual height in Indian adults. Only three males and one female had a height exceeding 150 cm, the maximum height achieved by a male subject being 168 cm and for the female 151 cm. The average height in male thalassemics was significantly higher than that in females (unpaired *t*-test, $P=0.023$). Despite the fact, the height was below average, the BMI was <18.5 in eight thalassemia patients (42.1%) and only one (5.3%) had a BMI >25 i.e. 25.44.

Nearly half of the patients (47.4%) had undergone splenectomy by the time they reached their adulthood. Interestingly, 72% males had undergone splenectomy as compared to 12.5% female thalassemics (unpaired *t*-test, $P=0.005$). All the remaining patients had hepatomegaly and splenomegaly to varying extents. Generalized hyperpigmentation was also present in all cases. Pubertal

growth spurt had occurred in all the cases although historically it was delayed.

Table 2 details the hematological and biochemical parameters in the adult thalassemia subjects. Average hemoglobin was similar in both male and female subjects but six (31.6%) had their hemoglobin levels <8 g/dl. Average leukocyte counts were higher in males (unpaired Student's *t*-test, $P=0.0058$). Moreover, two (18.2%) males and four (50%) females had total leukocyte counts $<4000/\text{mm}^3$. In fact, eight (72.7%) males had elevated total leukocyte counts. Platelet counts were low in two males and two female subjects. Serum ferritin levels were also similar in males and females. Surprisingly, no patient had achieved the recommended serum ferritin levels of <1000 ng/ml. None of the patients was suffering from diabetes mellitus or hypothyroidism. In fact, serum urea, creatinine, total proteins, and albumin levels were within the normal range for all patients. Four patients (21.1%) had serum bilirubin levels >1.5 mg/dl with a predominant indirect hyperbilirubinemia. One patient was positive for both hepatitis B and C virus infections and three others were only positive for HCV and one other harbored HIV infection. In total five (26.3%) patients were harboring at least one of the three infections. No electrocardiographic abnormalities were detected in any of the patients. All the patients were receiving iron chelation therapy. Four (21.1%) of the patients were receiving a combination of two iron-chelating drugs—deferiprone and desferrioxamine, while the remaining were receiving only deferiprone. Average dose of deferiprone being administered to each patient was 95 ± 8 mg/kg body weight daily in divided doses.

Discussion

Thalassemia is an autosomal recessive disorder and thalassemia major manifests as severe anemia in infancy or childhood and used to be incompatible with life in the absence of regular red cell transfusions. However, hematopoietic stem cell transplantation (HSCT) has offered a prospect of cure with a normal life expectancy and quality of life, relief from life-long blood transfusions and its attendant complications. Short of HSCT, thalassemia major patients need a two-pronged therapy in the form of "transfusion–chelation" to ensure a good quality of life along with a greater longevity.^[1] The diagnostic modalities and management principles centered on "transfusion–chelation" are well known to the pediatricians. It is only thalassemia minor/trait which may be diagnosed in adulthood and does not carry a great clinical significance being asymptomatic in majority of individuals. However, with increasing number of thalassemia major patients surviving through their adolescence into adulthood, adult physicians should brace themselves to face the challenge of dealing

Table 1: Clinical features of thalassemia patients

Clinical features	Thalassemia subjects (n=19)	Male subjects (n=11)	Female subjects (n=8)
Age (years)	21.65±2.47	20.89±1.36	22.5±3.21
Height (cm)	143.6±10.3	148.1±8.8	137.4±9.2
Weight (kg)	40.7±6.6	42.5±6.2	38.1±6.6
BMI	19.8±2.9	19.4±2.2	20.3±3.7
Splenectomy (%)	9 (47.4)	8 (72.7)	1 (12.5)

BMI: Body mass index

Table 2: Hematological parameters and serum biochemistry in adult thalassemia

Clinical parameters	Thalassemia subjects (n=19)	Male subjects (n=11)	Female subjects (n=8)
Hemoglobin (g/dl)	9.3±1.9	9.1±2.1	9.6±1.6
Total leukocyte count (per mm ³)	11756±9450	16250±9871	5577±3885
Platelet count (×10 ⁵ per mm ³)	2.09±1.14	2.2±1.24	1.87±0.99
Ferritin (ng/ml)	3946±2721	3786±2751	4165±2852
Total bilirubin (mg/dl)	1.53±1.03	1.82±1.29	1.12±0.26
Direct bilirubin (mg/dl)	0.49±0.19	0.49±0.19	0.49±0.18
Indirect bilirubin (mg/dl)	1.04±0.93	1.33±1.14	0.64±0.21
Fasting plasma glucose (mg/dl)	87.6±5.3	86.9±4.8	88.6±6.1
Serum calcium (mg/dl)	8.49±0.9	8.39±1.17	8.63±0.38
Serum phosphorus (mg/dl)	4.41±0.38	4.34±0.39	4.51±0.36
Serum total protein (g/dl)	7.47±0.59	7.56±0.57	7.35±0.64
Serum albumin (g/dl)	4.18±0.42	4.09±0.36	4.3±0.49
Alanine transaminase (IU/l)	104.68±61.14	120.45±67.44	83±46.77
Aspartate transaminase (IU/l)	104.32±80.73	127.91±93.42	71.88±47.07
Serum urea (mg/dl)	21.63±5.06	22±5.31	21.13±4.99
Serum creatinine (mg/dl)	0.37±0.1	0.37±0.12	0.37±0.09

with thalassemia in their adult patients. This totally new perspective – “what adult thalassemics will be like” has been presented in this article.

In spite of improvements in transfusion practices and availability of effective iron chelators, the life of thalassemia patients is punctuated by frequent complications. The complications relate to inadequate transfusions, inadequate chelation, transfusion-transmitted viral infections, allosensitization, iron overload and its consequences of endocrine, cardiac, hepatic disturbance; iron-chelator-related drug toxicities; osteoporosis and psychosocial problems.^[2-4] Lack of proper and trained medical expertise, periodic requirement of safe and adequate packed red cell concentrates high cost of in-line leukocyte-depleting filters and iron-chelator drugs; and poor compliance with blood transfusions, periodic monitoring, and regular chelation pose other major hurdles for the thalassemics.

Inadequate transfusions are a rule rather than the exception in India resulting in hypersplenism and greater rates of splenectomy.^[1] A total of 31.6% patients had hemoglobin levels <8 g/dl and 47.4% adult thalassemics had undergone splenectomy in the present study. The significantly high splenectomy rate in male adult thalassemics was intriguing. However, this finding could not be corroborated because of lack of similar published studies. The high total leukocyte counts observed in males can be explained as a consequence to splenectomy. The low average height, weight, and the BMI in both males and females are signs of growth failure commonly seen in inadequately chelated beta-thalassemics.^[4,5] Normal serum protein and albumin levels rule out protein energy malnutrition as a cause of growth failure.

Serum ferritin levels were high in all patients, a testimony to inadequate chelation in this group. This is despite the fact that all thalassemics were receiving iron chelation, either deferiprone alone or in combination with desferrioxamine. Even the average dose of deferiprone while being used as monotherapy was 95 mg/kg/day (range being 85–114 mg/kg/day) against the recommended dose of 75 mg/kg/day in divided doses. In fact, one study citing that deferiprone was not found sufficiently effective at the recommended dose of 75 mg/kg/day, tried a high dose of 100 mg/kg/day for 2 years and found it to be safe and effective.^[6] However, in the present study in adult thalassemics, deferiprone is not effectively chelating even at this high dose, so a higher dose may need to be tried or patients shifted to alternative iron chelators like deferasirox.^[7]

Repeated blood transfusions are associated with the serious risk of transmission of chronic viral infections, which were observed in 26.3% of the cases in the present series. Antibodies to hepatitis C virus were observed in 21% cases and the same figure has been reported from Indian thalassemics.^[3] Average serum transaminase values are higher than normal in the present study and can be attributable to chronic viral hepatitis. The absence of diabetes, hypothyroidism, cardiac arrhythmias in the present cohort can possibly be explained by the young age (early adulthood), since these are a consequence of iron overload and the prevalence therefore increases with the number of blood transfusions and so with the age. Indeed, one Indian study did not report diabetes or impaired glucose tolerance in chronically transfused patients of thalassemia major between 8 and 15 years of age.^[8] However, cardiac involvement cannot be entirely ruled out since it requires echocardiography and MRI to see for the functional and structural effects of iron

overload, respectively. The main cause of death in thalassemia is heart disease. Osteoporosis and osteopenia are extremely frequent in thalassemia affecting from 52% to 96% of patients and the prevalence rises with age.^[3] Echocardiography, MRI, and DEXA scan were not performed for the thalassemia patients in the preceding 1 year and could not be done as part of the study in view of cost constraints.

This study presents a profile of the adult thalassemia subjects and provides insight into the problems and complications faced by them despite several medical advances. The onus of dealing with these lies squarely with the adult physician and it is imperative for one and all to be aware of these.

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