Original Article

Clinical and Investigative Profile of Beta Thalassemia Major Patients Visiting Tertiary Care Center in Gujarat, India

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Background : Thalassemia major is an autosomal recessive inherited blood disorder of defective synthesis of Beta Chain of Hemoglobin. With increasing medical facilities, life expectancy of Thalassemia major patients has increased. This study was carried out to study clinical and investigative profile of patients with Beta Thalassemia major patients attending Medicine OPD.

Materials and Methods : Patients of Beta Thalassemia major attending Medicine Outpatient Department were included in this retrospective and Cross-sectional Study. Detailed history and examination were done and patients' previous medical data was checked. Patients were subjected to routine hematological, biochemical investigations and S Ferritin. Data was entered in Microsoft Excel. Presentation of the Categorical variables was done in the form of number and percentage and presentation of the continuous variables was done as mean ± SD and median values.

Results : Our study population had a mean age of 22.7 years with more males than females. 40% of the patients had short stature. 80% of the patients had tanner staging ≤2 suggestive of poor development of secondary sexual characteristics. Majority of the patients belonged to the Sindhi, Lohana and the Muslim communities. Symptoms of fatigue, generalized weakness and skin pigmentation were noted in many patients. The mean PCV requirement per month was 2.08. Mean hemoglobin was 9.7 ± 1.47 gm/dl. A large part of the study population had higher ferritin levels.

Conclusion : Patients of Thalassemia major suffer from multitude of symptoms due to chronic anemia and iron overload. Safe and adequate transfusion and proper iron chelation can prevent various complications of the disease.

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Key words : Skin Hyperpigmentation, Short Stature, Tanner Staging, Blood Transfusion, Splenectomy, Iron Chelating Agents, Ferritin.

Beta Thalassemia is broadly classified in three categories, Thalassemia minor/Thalassemia trait, which is asymptomatic carrier state, Thalassemia intermediate, which is less severe form of Thalassemia and thalassemia major. Thalassemia major is an autosomal recessive inherited blood disorder of defective synthesis of Beta Chain of Hemoglobin.

India has approximately 1 lakh patients living with Beta Thalassemia major, amongst them 6000 patients are from Gujarat, where our study has been conducted[1]. It is estimated that there are approximately 10,000-15,000 babies are born with beta thalassemia major each year in India[2].

Manifestation starts at 6 months of life, when the switchover from Fetal Hemoglobin (HbF) to adult Hemoglobin (HbA) occurs physiologically in normal individuals[3]. In Thalassemia major due to the defect in beta globin gene, ineffective erythropoiesis occurs which leads to anemia, bone marrow expansion, skeletal deformities and increased GI iron absorption[4].

The diagnosis of Beta Thalassemia is based on Hb electrophoresis and genetic mutation analysis[4]. Treatment options include safe and adequate transfusion of packed red cells to maintain pre-transfusion Hemoglobin >10 gm/dl and iron chelation to remove excess iron from the body which accumulates due to hemolysis and transfusion of packed cells[4]. Transfusion of packed red cells leads to accumulation of iron in Liver, Heart, Pituitary, Thyroid, Gonads and other Organs of body, which can result in cardiomyopathy, liver dysfunction,

Editor's Comment :

- Beta thalassemia major is more common in Sindhi, Lohana and Muslim communities in Gujarat although it has now penetrated other communities also. Male patients of thalassemia major seek medical care more often than female patients.
- Patients of thalassemia major suffer from symptoms due to chronic anaemia and iron deposition in various organs and endocrine glands.
- Safe and adequate blood transfusion and adequate iron chelator therapy can reduce morbidity and mortality in patients of thalassemia major.

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Hypothyroidism, Hypopituitarism, Growth Retardation, Diabetes and delayed puberty or failure of development of secondary sexual characteristics.

Iron chelators have their own side effects like Agranulocytosis, Bone Marrow Suppression, Raised Liver Enzymes, Joint Pain, Decreased Hearing, Ophthalmic Complication, Injection Site Reaction, etc. Thus, patients of thalassemia suffer from multitude of signs and symptoms ranging from that due to chronic anemia, due to iron overload of various organs and side effects of iron chelators[5].

With increasing medical facilities life expectancy of patients with Thalassemic major has reached up to the 4^{th}-5^{th} decade of life[6]. Therefore increasing number of Thalassemia major patients are visiting physicians. This study was undertaken to study clinical and investigative profile of Thalassemia major patients attending medicine Outpatient Department (OPD) or admitted in Medicine wards.

Materials and Method

Study Design :

Descriptive, Retrospective and Cross-sectional Observational Study.

Study Population and Sample Size :

Patients of Beta Thalassemia major patients visiting Medicine Outpatient Department of Sir Sayajirao General Hospital (SSGH), Vadodara were enrolled in the study. A total of 50 patients of Beta Thalassemia major patients who fulfilled inclusion and exclusion criteria and gave written and informed consent were included in the study which was done from January, 2020 to December, 2020.

Inclusion Criteria :

(1) Beta Thalassemia major patients.

(2) Patients of more than 12 years of age and attending Medicine OPD.

Exclusion Criteria :

Thalassemia intermediate and minor patient.

Data Collection :

Permission of Institutional Ethics Committee for Human Research was taken for carrying out the study. Study was retrospective and cross sectional. After explaining the purpose and the method of the study, written and informed consent of patient about enrolment in the study was taken. After maintaining adequate privacy and confidentiality, all the patients were subjected to detailed history taking and examination by predesigned and pretested proforma. Demographic details like Name, Age, Gender, Caste, Residence etc. were noted. Patients were inquired for presence of any complaints. Detailed treatment history regarding age at first transfusion, transfusion requirement, splenectomy, use of iron chelation medicines, vaccination and previously known illness was also noted.

Family history was taken to find out whether any other family member of the patient is also suffering from thalassemia. Anthropometric examination (Height, Weight and BMI) of parents was carried out to find mid-parental height which was used to determine whether growth retardation is present in the patient.

Detailed general examination was done and presence of Pallor, Icterus, Clubbing, Lymphadenopathy, Pedal Edema, Nail Changes, Facial Appearance (presence of chipmunk facies/ frontal bossing/depressed nasal septum), bony deformities (presence of outgrowth of skull/ paravertebral masses osteoporosis/pathological fractures/spine deformities/nerve compression), pigmentation was looked for.

All patients were subjected to anthropometric examination like height, weight and BMI. Short stature was assessed by matching patient's height with target height obtained from mid-parental height. Mid-parental height for boys = (Mother's height + Father's height)/2 + 6.5cm ± 8cm and mid-parental height for girls = (mother's height + father's height)/^{2} – 6.5cm ± 8cm were obtained using above formula. Patient's height falling below mid-parental height was classified as short stature. Secondary sexual characteristics were assessed using tanner staging which includes parameters of external genitalia development (Males), breast development (Females) and growth of pubic hair (both Males and Females). Systemic examination of Respiratory system, Cardio-vascular system, Nervous system and per abdomen examination to look for organomegaly was done.

Patients' previous medical data was checked and available investigations were noted. Patients were subjected to Hemogram, Fasting and Postprandial Blood Glucose, Urine Examination, Renal Function Test, Liver Function Test, Serum Ferritin Level.

Statistical Analysis :

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the presentation of the continuous variables was done as mean ± SD and median values. The association of the variables which were qualitative in nature was analyzed using Chi-Square test/Fisher's Exact test. The association of the variables which

were quantitative in nature was analyzed using independent t test for two groups and ANOVA for more than two groups.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software version 21.0. For statistical significance, p value of less than 0.05 was considered as significant.

Results

As per Table 1, patients were divided in three age groups, ≤20 years (34%), 21-25 years (28%) and 26-30 years (38%). Mean age was 22.76 years. In 74% subjects were male and 26% subjects were female. (Fig 1)

Table 2 shows the caste wise distribution of subjects with more number of patients from Sindhi (24%), Lohana (16%) and Muslim (12%) community but it is seen in many other castes also.

We can see the distribution of clinical features faced by thalassemic patients in Table 3. Generalized Weakness (88%) and Skin Pigmentation (74%) are found to be two of the major complaints faced by patients.

Table 4 analyses the treatment history of the study subjects. In 16% of the patients were splenectomised in our study and 84% patients didn't go for Splenectomy. In 52% of study subjects were taking combination therapy comprising of more than one medicine out of available three medicines tablet deferiprone, tablet Deferasirox and injection Desferioxamine for iron chelation. The mean age at first transfusion was 5.95 months and mean PCV requirement per month was 2.08 for our study subjects.

Stature of patients was assessed by matching patient's height with target height obtained from mid-parental height. Patient's height falling below mid-parental height was classified as short stature. Analysis of stature of study subjects is shown in Fig 2. In 60% of patients had normal stature and 40% of patients

Table 1 — *Distribution of Age (years) of study subjects*

Age (years)	Frequency	Percentage
≤20	17	34.00%
21-25	14	28.00%
26-30	19	38.00%
Mean ± SD	22.76 ± 5.4	
Median (25th-75th percentile)	23 (18.25-27)	
Range	14-32	

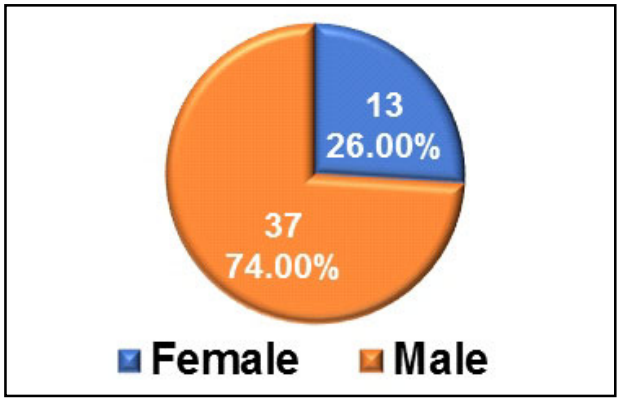

Fig 1 — Distribution of Gender of study subjects

Table 2 — *Distribution of Caste of study subjects*

Caste	Frequency	Percentage
Brahmin	2	4.00%
Goswami	1	2.00%
Jain	4	8.00%
Kurmi	1	2.00%
Lohana	8	16.00%
Marwadi	1	2.00%
Mistry	1	2.00%
Mochi	1	2.00%
Muslim	6	12.00%
Patel	1	2.00%
Prajapati	4	8.00%
Punjabi	2	4.00%
Rajput	2	4.00%
Sindhi	12	24.00%
Soni	1	2.00%
Vankar	3	6.00%
Total	50	100.00%

Table 3 — *Distribution of Clinical Features of study subjects*

Complaints	Frequency	Percentage
Fatigue	38	76.00%
Generalized weakness	44	88.00%
Skin pigmentation	37	74.00%
Growth retardation	15	30.00%
Pedal edema	13	26.00%
Icterus	23	46.00%
Abdominal distention	12	24.00%
Bony deformity	14	28.00%
Cognitive decline	11	22.00%
Hepatomegaly	34	68.00%
Splenomegaly	28	56.00%

Table 4 — *Distribution of Treatment History of study subjects*

Splenectomy	Frequency	Percentage
No	42	84.00%
Yes	8	16.00%
Iron Chelating Agents :		
Only Deferasirox (500 mg)	22	44.00%
Only Deferiprone(500mg)	2	4.00%
Combination of iron chelating agents	26	52.00%
Age at first blood transfusion(months) :		
Mean ± SD	5.95 ± 1.48	
Median (25th-75th percentile)	6(5-6.75)	
Range	4-12	
Blood transfusion requirement (per month) :		
Mean ± SD	2.08 ± 0.54	
Median (25th-75th percentile)	2(2-2)	
Range	1-3	

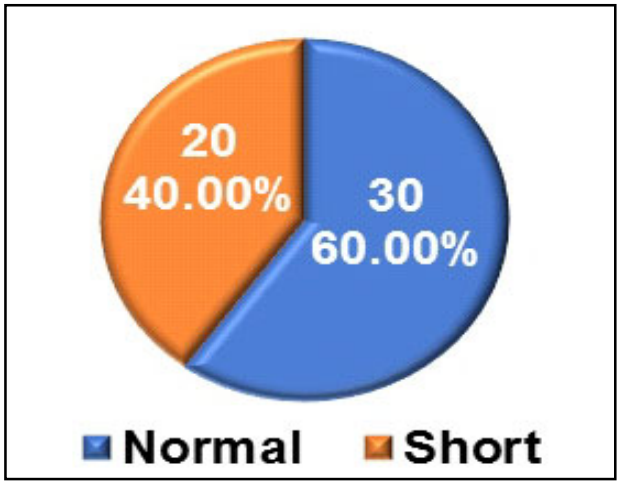

Fig 2— Distribution of stature of study subjects.

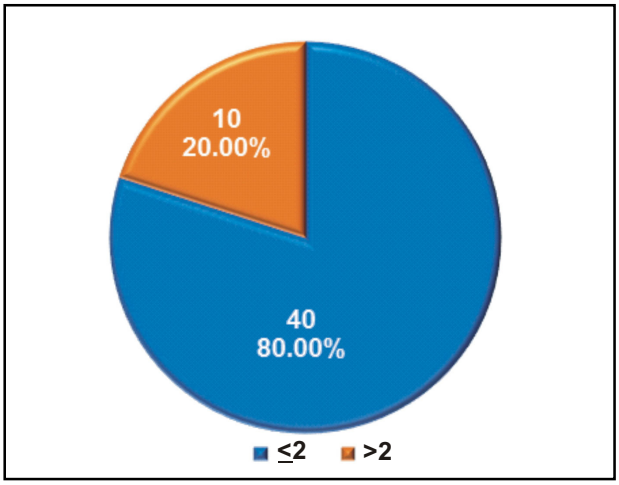

Fig 3 — Distribution of tanner stage of study subjects

had short stature.

Here, tanner staging was used as a marker of appearance of secondary sexual characteristics. 80% of patients had tanner staging of ≤2 suggestive of poor development of secondary sexual characteristics and underlying hormonal abnormalities (Fig 3).

Table 5 shows the descriptive statistical analysis of hematological and biochemical parameters of the study subjects. Mean hemoglobin was 9.7±1.47 gm/dl. Mean level of fetal hemoglobin in HPLC at the time of diagnosis of study population was 91.06% of total HB, suggesting that most of the patients belonged to severe variety of Beta Thalassemia major. The mean blood sugar in our study population was 90.92 mg/dl. Mean total bilirubin and indirect bilirubin were 1.66±0.59 and 1.29±0.5 respectively. Kidney Function Tests were normal in the study population. In this study investigative hormonal profile was not known for many patients due to financial issues. So, hormonal level of patients could not be studied. S Ferritin level of more than 1000 was seen in 74% of patients indicating that large part of study population was inadequately chelated.

Table 5 — *Descriptive statistics of Biochemical Parameters of study subjects*

Parameters	Mean ± SD	Median (25th-75th percentile)	Range
Hemoglobin (g/dL)	9.7 ± 1.47	9.7(8.45-10.8)	7.4-13.9
Total Leucocyte Count (per cubic mm)	8877.96 ± 4261.68	8120(5925-10200)	3760-26000
Platelet Count (lakhs)	3.28 ± 1.03	3.1(2.8-3.45)	1.78-8.16
HPLC Fetal Hemoglobin (%)	91.06 ± 3.53	92(90-93.75)	80-98
Random Blood Sugar/ Fasting Blood Sugar (mg/dL)	90.92 ± 29.46	84(80-93)	68-232
Total Bilirubin (mg/dL)	1.66 ± 0.59	1.6(1.2-1.875)	0.9-3.1
Direct Bilirubin (mg/dL)	0.37 ± 0.22	0.3(0.2-0.4)	0.2-1.3
Indirect Bilirubin (mg/dL)	1.29 ± 0.5	1.2(1-1.5)	0.3-2.6
SGPT (U/L)	55.88 ± 28.11	48(33.25-77.5)	14-134
SGOT (U/L)	42.7 ± 22.74	38(25.25-57.5)	10-90
ALP (U/L)	127.16 ± 35.91	120(102.5-138.75)	36-234
Ferritin (µg/L)	2725.6 ± 2160.68	1882(1015-4152.5)	386-8688

Discussion

In this study, patients of more than 12 years were taken as study subjects and the mean age was 22.7. Alireza Ansari-Moghaddam, *et al* studied 5,491 medical records of patients with thalassemia in Iran. (3936 Beta Thalassemia major, 999 Beta Thalassemia intermedia and 89 sickle Beta Thalassemia)[6]. Alireza Ansari-Moghaddam, *et al* observed the average age of thalassemia patients in their study of 23.81±11.32 years[6]. Thalassemia major once thought to be disease of pediatrics has now become major hematological disorder of medicine and hematology owing to increased life expectancy of patients due to advances in medical field and better self-care of patients. Mean survival rate of 52.42 years and 41.97 years was reported in studies done in Iran and Tehran respectively[6,7].

This hospital-based study had a greater number of male patients than females. (74% males *versus* 26% females) Alireza Ansari-Moghaddam, *et al* showed that when larger Thalassemic population (n=5491) is taken into consideration incidence of Thalassemia among male and female are almost equal[7]. Gender discrimination for reaching for long lasting treatment of Thalassemia major by few families of remote villages may be

one of the reasons for a smaller number of female patients in this study.

Patel AG, *et al* screened 32,857 students and observed prevalence of Beta Thalassemia trait as 4.7% in Muslims, 4.4% in Hindus and 4% in Jain community[8]. Amongst Hindu communities they observed higher prevalence of Beta Thalassemia trait in Gamit, Chaudhary and Vasava tribal communities followed by Lohana and Sindhi communities[8]. This study had majority of patients from Sindhi, Lohana and Muslim communities. Although it has now penetrated to other castes also and that may be due to the rise in inter-caste marriages.

Renzo Galanello, *et al* noted that major symptoms of Thalassemia major patients were fatigue, poor musculature, growth retardation, abdominal distention and skeletal changes[9]. This study also showed that various complaints faced by Thalassemia patients were Generalized Weakness, Fatigue, Skin Pigmentation, Growth Retardation and Bony Deformity. Classically, individuals with severe Beta Thalassemia have been presented with variable but often very severe degrees of anemia, expansion of the Bone Marrow spaces secondary to erythroid hyperplasia, hepato-splenomegaly and extramedullary hematopoiesis[10]. Iron overload can lead to Cardiac Dysfunction, Endocrine Abnormalities, Particularly Hypogonadism, Low Growth Hormone, Hypothyroidism and Diabetes Mellitus[10].

Dhanya R, *et al* (N=1087) noted that median age at first transfusion in their study was 8 months and 10.24% patients were splenectomised in their study[11]. In this study we observed that 16% of patients were splenectomised, mean age of first transfusion was 5.95 months. Current guidelines in management of Thalassemia do not recommend usual practice of splenectomy unless there is absolute indication, due to increased risk of infection, thrombosis, portal and pulmonary hypertension and gall stone formation post splenectomy. Indications of splenectomy are splenomegaly (size >20cm below costal margin), hypersplenism leading to pancytopenia or neutropenia or thrombocytopenia and blood transfusion requirement >220ml/kg/year leading to severe symptomatic chronic anemia and growth failure[12].

Dey P, *et al* (N=50) noted that mean BMI of 20.21kg/m^2 in their study population[13]. Mean BMI of our study population was 22.29 kg/m^2, indicating that BMI of patients was not significantly affected by Thalassemia. Ehsahn Sabani, *et al* noted prevalence of short stature to be 52.3% amongst 2,446 Iranian thalassemia major patients[14]. In this study 40% of patients had short stature. Anemic status and pituitary iron deposition lead to growth retardation in Thalassemia major patients. Adequate blood transfusion and iron chelator therapy can help these patients to have normal stature in their adult life.

Romana Chowdhury, *et al* observed prevalence of Hypogonadism as 35.11% by tanner staging in their study population of 96 patients of transfusion dependent Beta Thalassemia patients[15]. Tanner staging less than or equal to 2 was observed in 80% of patients in this study. Iron overload in pituitary gland leads to suppression of FSH, LH and GH which in turn causes reduced production of sex hormones and delayed/absence of puberty in form of Hypogonadism and non-appearance of secondary sexual characteristics.

Ayyash H, *et al* (N=65) noted severe anemia with mean Hemoglobin level of 7.4 ± 0.8 g/dL and 7.36 ± 1.57 g/dL in males and females patients with Beta Thalassemia major respectively[16]. In our study pre transfusion Hb<8gm/dl was taken as cut-off for anemia, according to that 54% of patients were found to be anemic, suggesting that most of patients were not adequately transfused.

In this study, patients had unconjugated Hyperbilirubinemia due to hemolysis consistent with Beta Thalassemia major. Ayyash H, *et al* (N=65) also noted Thalassemia major patients had significantly worsened Liver Function Tests[16].

Ayyash H, *et al* (N=65) observed that serum ferritin levels in their study subjects were 7162.4 ± 3297.3 and 7068.7 ± 3826.0 ng/ml in the males and females Beta Thalassemia major patients, respectively[16]. In this study also a large part of study population was inadequately chelated and had higher Ferritin levels. Ineffective erythropoiesis and frequent blood transfusion in patients of Beta Thalassemia major patients lead to iron accumulation in body. Serum Ferritin is a marker which can effectively predict iron accumulation in the body quantitatively. Adequate iron chelation therapy is needed to control iron overload in these patients. But owing to inadequate knowledge of patients and their relatives about the need for iron chelation therapy as well as cumbersome lifelong therapy may lead to noncompliance and nonadherence to iron chelation therapy and its subsequent consequences.

Endocrinological investigations like FSH, LH, Testosterone, Estrogen and Progesterone were not available with patients and were not analyzed due to cost constraints in this study.

Conclusion

Thalassemia major is more common in certain communities like Lohana, Sindhi, Muslim communities in Gujarat although it has penetrated other communities also. Patients of Thalassemia suffer from multiple symptoms due to chronic anemic state and iron deposition in various organs and endocrine glands.

Safe and adequate transfusion to maintain pre-transfusion Hemoglobin >10gm/dl and regular iron chelation to maintain serum Ferritin <500ug/L are main cornerstone of the treatment of Thalassemia which can prevent various complications of the disease.

Apart from Bone Marrow Transplantation, which is costly and has a low success rate with high chances of graft rejection and mortality, there is no definite cure of Beta Thalassemia major at present, so prevention of the disease by awareness and policy making is the key to reduce this disease burden in the society.

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