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Original Research Article

An Observational Study Assessment of Clinico-pathological and Lab Profile of Paediatric Patients with β-thalassemia Major

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Abstract

Aim: To study the clinical profile and laboratory parameters of Thalassemia major in pediatric patients

Methodology: An observational study was conducted on 50 pediatric patients with β-thalassemia major in the Department of Paediatrics, SNMMCH, Dhanbad, Jharkhand, India for 8 months. Patients aged 1-14 year being regularly transfused were included in this study. A preformed proforma was used for data collection that included demographic details, transfusion details, and pre-transfusion haemoglobin and serum ferritin with clinical examination findings and laboratory investigation reports. The serum ferritin level was measured in all Thalassemic patients. Iron chelating agents were advised to all patients with serum ferritin level above 1000 ng/ml. Haemoglobin was measured before transfusion by Sahli's method. Blood group cross-matching was done by blood typing. Standard references were used to analyze the laboratory parameters.

Results: Out of 50 patients, 17 (34%) were male and 33 (66%) were females. 58% patients had normal stature. 12 patients belonged to 1-3 years age group, 31 belonged to 4-11years and 7 belonged to 12-14 years of age group. 19 out of 50 patients (38%) has serum ferritin level more than 2000 ng/ml out of which 15 patients (78.9%) had hepatomegaly followed by 10 out of 14 patients with serum ferritin level 1001-1500 units had hepatomegaly. In total 72% patients had hepatomegaly. Out of 50 patients, 3 (6%) had spleen size less than 2 cm, 26 (52%) had spleen size 2-7 cm, and 21 (42%) patients had spleen size more than 7 cm.

Conclusion: Iron overload is the primary and major risk factor of mortality and morbidity in thalassemia major despite advances in chelation therapy. Early application of chelation therapy can prevent complications in beta-thalassemia major patients. There is a direct adverse impact of increasing serum ferritin values with the clinical parameters and the biochemical parameters.

Keywords: Chelation therapy, Thalassemia, Hepatomegaly, Splenomegaly, Haemoglobin (Hb).

Introduction

Thalassemias are inherited blood disorders characterized by decreased hemoglobin production. Thalassemias are genetic disorders inherited from a person's parents. There are two main types, alpha thalassemia and beta thalassemia. The severity of alpha and beta thalassemia depends on how many of the four genes for alpha globin or two genes for beta globin are missing [1]. β-thalassemia major refers to the severe form of β-Thalassemia which requires early blood transfusion therapy and often is homozygous for β mutations.
Estimates suggest that approximately 1.5% of the global population (80 – 90 million people) are β-thalassemia carriers [2]. According to WHO 3.3% is the average frequency of Thalassemia carriers in India. In the state of Madhya Pradesh high prevalence of β-Thalassemia trait (20.70%) is observed [3]. As of 2015, thalassemia occurs in about 280 million people, with about 439,000 having severe disease [4]. Over the past three decades, regular blood transfusions and iron chelation have dramatically improved the quality of life and transformed Thalassemia major from a rapidly fatal disease in early childhood to a chronic disease compatible with prolonged life. It resulted in 16,800 deaths in 2015, down from 36,000 deaths in 1990 [5, 6].
Beta thalassemias are due to mutations in the HBB gene on chromosome 11, [7] also inherited in an autosomal, recessive fashion. HBB blockage over time leads to decreased beta-chain synthesis. The body's inability to construct new beta-chains leads to the underproduction of HbA (adult hemoglobin).[8] Reductions in HbA available overall to fill the red blood cells in turn leads to microcytic anemia. Due to this factor, the patient may require blood transfusions to make up for the blockage in the beta-chains.

The severity of the disease depends on the nature of the mutation and on the presence of mutations in one or both alleles. β thalassemia major (Mediterranean anemia or Cooley anemia) is caused by a βo/βo genotype. No functional β chains are produced, and thus no hemoglobin A can be assembled. This is the most severe form of β-thalassemia. Individuals with beta thalassemia major (those who are homozygous for thalassemia mutations or inheriting 2 mutations) usually present within the first two years of life with symptomatic severe anemia, poor growth, and skeletal abnormalities. Untreated thalassemia major eventually leads to death, usually by heart failure; therefore, prenatal screening is very important [9]. Untreated, it causes anemia, splenomegaly and severe bone deformities, and progresses to death before age 20. Treatment consists of periodic blood transfusion; splenectomy for splenomegaly and chelation of transfusion-related iron overload [10].

Materials and Methods

An observational study was conducted on 50 pediatric patients with β-thalassemia major in the Department of Paediatrics, SNMMCH, Dhanbad, Jharkhand, India for 8 months. Patients aged 1-14 years being regularly transfused were included in this study.

A preformed proforma was used for data collection that included demographic details, transfusion details, and pre-transfusion haemoglobin and serum ferritin with clinical examination findings and laboratory investigation reports. The serum ferritin level was measured in all Thalassemic patients. Iron chelating agents were advised to all patients with serum ferritin level above 1000 ng/ml. Haemoglobin was measured before transfusion by Sahli's method. Blood group cross-matching was done by blood typing. Standard references were used to analyze the laboratory parameters.

Inclusion criteria: All the diagnosed β-Thalassemia major patients between the age group of 1 to 14 years without co-existing cardiac or pulmonary disease.

Exclusion criteria: Children having multiple congenital anomalies along with Thalassemia major; chronic haemolytic anaemia other than β-Thalassemia major; or Beta –thalassemia with any other haemolytic anaemia

Results:

Out of 50 patients, 17 (34%) were male and 33 (66%) were females. 58% patients had normal stature. 12 patients belonged to 1-3 years age group, 31 belonged to 4-11 years of age group and 7 belonged to 12-14 years of age group.

Table 1: Demographic details

		Number	%
Gender	Male	17	34%
	Female	33	66%
BMI	Normal	41	82%
	Low	9	18%
Height	Normal stature	29	58%
	Short stature	21	42%
Age (in years)	1-3	12	24%
	4-11	31	62%
	12-14	7	14%

Table 2: Laboratory parameters

		Number	%
Serum calcium values (mg/dl)	Decreased	11	22%
	Normal	27	54%
	Increased	12	24%
Serum Phosphorus levels (mg/dl)	Decreased	21	42%
	Normal	12	24%
	Increased	17	34%
Protein values	Decreased	20	40%
	Normal	26	52%
	Increased	4	8%
Serum alkaline phosphatase levels (I/U)	Normal	22	44%
	Increased	28	56%
Creatinine levels (mg/dl)	Normal	35	70%
	Increased	15	30%
Urea levels (mg/dl)	Normal	17	34%
	Increased	33	66%
SGOT levels	Normal	20	40%
	Increased	30	60%
SGPT levels	Normal	24	48%
	Increased	26	52%
Serum bilirubin levels	Normal	22	44%
	Increased	28	56%

19 out of 50 patients (38%) has serum ferritin level more than 2000 units out of which 15 patients (78.9%) had hepatomegaly followed by 10 out of 14 patients with serum ferritin level 1001-1500 units had hepatomegaly. In total 72% patients had hepatomegaly.

Table 3: Relation of hepatomegaly with serum ferritin levels

S. Ferritin levels(ng/ml)	Number of patients	Hepatomegaly present
<500-1000	10	6 (60%)
1001-1500	14	10 (71.4%)
1501-2000	7	5 (71.4%)
>2000	19	15 (78.9%)
Total	50 (100%)	36 (72%)

Out of 50 patients, 3 (6%) had spleen size less than 2 cm, 26 (52%) had spleen size 2-7 cm, and 21 (42%) patients had spleen size more than 7 cm

Table 4: Relation of different grades of splenomegaly with age groups

Age (in years)	Spleen size		
	<2 cm	2-7 cm	>7 cm
1-3 years (n=12)	1	8	3
4-11 years (n=31)	2	16	13
12-14 years (n=7)	0	2	5

In the present study, Icterus was found to be present in 50% of cases. All the cases of this study had a normal feature which is commonly found in Thalassemic children like bony abnormalities, frontal bossing, prominent facial bones and dental malocclusion in the form of haemolytic facies were present. Oedema which can be a manifestation of both severe anaemia as well as SAM was found to be present in 6 cases.

Discussion

Inherited hemoglobin disorders are emerging as a global public health concern. An estimated 320 000 babies are born each year with a clinically significant hemoglobin disorder [11]. Nearly 80% of these births occur in developing countries. Most conservative estimates suggest that at least 5.2% of the world's population (over 360 million) carry a significant hemoglobin variant and there are in excess of 100 million β-thalassemia carriers, with a global prevalence of 1.5% [11-13]

β-Thalassemia major is the most common chronic hemolytic anemia among children and adolescents worldwide [14]. About 60 000 new patients are born annually with thalassemia worldwide [13]. Children with β-Thalassemia major usually demonstrate no symptoms until about 2-3 months of age, when beta chains are needed to pair with alpha chains to form HbA. However, in some cases, the condition may not be recognized until 3-5 years of age due to delay in the cessation of HbF production.

In this study, 17 (34%) were male and 33 (66%) were females. In the literature, other previous Indian studies have reported a further higher male preponderance of up to 68% [15] and 69.5% [16]. But a similar study carried out in Hong Kong found that the male to female ratio was equal among their studied thalassemic cases [17].

In the present study, 42% patients had short stature. The current study had a lower percentage of short stature as compared to Quaish Abdullal Salehe et al study in the year 2015, in which, 79% of the β-thalassemia patients had short stature [18, 19]. In patients with β-thalassemia, low bone marrow density and fractures occur frequently and independently of the particular syndrome. The present study found 21 cases to have hypophosphatemia which account for 42%, which may be due to renal function derangements and abnormality of bone marrow turnover [20,

21]. Iron overload is the primary and major risk factor of mortality and morbidity in thalassemia major despite advances in chelation therapy [22, 23]. The cut-off limit for serum ferritin is less than 1000 ng/ml between adequately chelated and poorly chelated patients [24, 25].

Treatments available for thalassemia patients are regular blood transfusion, iron chelation therapy in an attempt to prevent iron overload and the judicious use of splenectomy in cases complicated by hypersplenism, and hematopoietic stem cell transplantation [26]. Regular blood transfusion programs and chelation treatment have considerably improved the survival of patients with thalassemia. However, a side effect of chronic transfusion therapy is secondary iron overload, which adversely affects the functions of the heart, liver, and other organs, causing severe morbidity, and shortens the life expectancy [14]. The age of cardiac death depends primarily on access to transfusions and chelation. In transfused, but unchelated patients, the typical age at death is 10 years, primarily of cardiac causes [27].

Conclusion:

Iron overload is the primary and major risk factor of mortality and morbidity in thalassemia major despite advances in chelation therapy. Early application of chelation therapy can prevent complications in beta-thalassemia major patients. There is a direct adverse impact of increasing serum ferritin values with the clinical parameters and the biochemical parameters.

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