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Assessment of clinical profile of children with beta-thalassemia from Bihar region

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Abstract

Thalassemia syndromes are a heterogeneous group of single gene disorders, inherited in an autosomal recessive manner, prevalent in certain parts of the world, including India. The β thalassemias and sickle cell disorders pose a significant health burden in India. The only forms of treatment 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. Marrow transplantation also has an important role in selected cases. Hence based on above findings the present study was planned for Assessment of Clinical Profile of Children with Beta-Thalassemia from Bihar Region.

The present study was planned in Department of Pediatrics, Mata Gujri Memorial Medical College and Lions Seva Kendra Hospital, Kishanganj, Bihar, India. In the present study 50 cases of childrens suffered with Beta-Thalassemia were enrolled in the present study.

The data generated from the present study concludes that all children were short statured and malnourished indicating the underlying poor nutrition acting along with the disease pathology. Serum ferritin levels were invariably elevated in all patients demanding optimal chelation therapy. All children were short statured and malnourished indicating the underlying poor nutrition acting along with the disease pathology. Serum ferritin levels were invariably elevated in all patients demanding optimal chelation therapy.

Keywords: clinical profile, children, beta-thalassemia, Bihar, etc

1. Introduction

Beta thalassemia syndromes are a group of hereditary disorders characterized by a genetic deficiency in the synthesis of beta-globin chains. In the homozygous state, beta thalassemia (ie, thalassemia major) causes severe, transfusion-dependent anemia. In the heterozygous state, the beta thalassemia trait (ie, thalassemia minor) causes mild to moderate microcytic anemia. Patients in whom the clinical severity of the disease lies between that of thalassemia major and thalassemia minor are categorized as having thalassemia intermedia. Several different genotypes are associated with thalassemia intermedia. Hemoglobin (Hb) E, a common Hb variant found in Southeast Asia, is associated with a beta thalassemia phenotype, and this variant is included in the beta thalassemia category of diseases. Patients with thalassemia minor usually do not require any specific treatment. Treatment for patients with thalassemia major includes long-term transfusion therapy, iron chelation, splenectomy, allogeneic hematopoietic transplantation, and supportive measures. Medical complications from long-term transfusional therapy - Iron overload and transfusion-associated infections (eg, hepatitis); iron overload cardiomyopathy accounts for the majority of deaths in thalassemia patients [1]. Mutations in globin genes cause thalassemias. Beta thalassemia affects one or both of the beta-globin genes. More than 200 beta-globin gene mutations have been identified in these patients; this underlies the wide genotypic and phenotypic variability of the disease. [2]. (Alpha thalassemia affects the alpha-globin gene[s].) These mutations, by causing impaired synthesis of the beta-globin protein component of Hb, result in anemia. [3, 4].

Beta thalassemia is inherited as an autosomal recessive disorder. The defect can be a complete absence of the beta-globin protein (ie, beta-zero thalassemia) or a severely reduced synthesis of the beta-globin protein (ie, beta-plus thalassemia). Peripheral smear in beta-zero thalassemia minor showing microcytes (M), target cells (T), and poikilocytes. The genetic defect usually is a missense or nonsense mutation in the beta-globin gene, although occasional defects due to gene deletions of the beta-globin gene and surrounding regions also have been reported.

In beta thalassemia minor (ie, beta thalassemia trait or heterozygous carrier-type), one of the beta-globin genes is defective, resulting in an approximately 50% decrease in the synthesis of the beta-globin protein.

In beta thalassemia major (ie, homozygous beta thalassemia), the production of the beta-globin chains is severely impaired because both beta-globin genes are mutated. The severe imbalance of globin chain synthesis (alpha >> beta) results in ineffective erythropoiesis and severe microcytic hypochromic anemia.

Peripheral smear from a patient with beta-zero thalassemia major showing more marked microcytosis (M) and anisopoikilocytosis (P) than in thalassemia minor. Target cells (T) and hypochromia are prominent. The excess

unpaired alpha-globin chains aggregate to form precipitates that damage red cell membranes, resulting in intravascular hemolysis. Premature destruction of erythroid precursors results in intramedullary death and ineffective erythropoiesis. The profound anemia typically is associated with erythroid hyperplasia and extramedullary hematopoiesis.

Although beta thalassemia is caused by a genetic mutation in the beta-globin gene (which is located on chromosome 11), many additional factors influence the clinical manifestations of the disease. That is, the same mutations may have different clinical manifestations in different patients. The factors below are known to influence the clinical phenotype.

Individuals with thalassemia minor (thalassemia trait) usually have mild, asymptomatic microcytic anemia. This state does not result in mortality or significant morbidity. The prognosis of patients with thalassemia major is highly dependent on the patient's adherence to long-term treatment programs, namely the hypertransfusion program and lifelong iron chelation. Allogeneic bone marrow transplantation may be curative.

The major causes of morbidity and mortality in beta thalassemia are anemia and iron overload. The severe anemia resulting from this disease, if untreated, can result in high-output cardiac failure; the intramedullary erythroid expansion may result in associated skeletal changes such as cortical bone thinning. The long-term increase in red-cell turnover causes hyperbilirubinemia and bilirubin-containing gallstones.

Increased iron deposition resulting from lifelong transfusions and enhanced iron absorption results in secondary iron overload. This overload causes clinical problems similar to those observed with primary hemochromatosis (eg, endocrine dysfunction, liver dysfunction, cardiac dysfunction).

A broad spectrum of neurological complications has also been reported in beta thalassemia complications, although most were subclinical. These have included the following [5]: Cognitive impairment; Abnormal findings on evoked potentials; Cerebrovascular disease; & Peripheral neuropathy. Educate patients with thalassemia minor about the genetic (hereditary) nature of their disease, and inform them that their immediate family members (ie, parents, siblings, children) may be affected. The presence of beta-thalassemia minor in both parents implies that there is about a one fourth chance that a child will have thalassemia major. Careful genetic counselling is also appropriate for patients in whom one parent has beta-thalassemia minor and the other parent has some form of beta-globin–related disease, such as sickle cell carriage. Inform patients with thalassemia minor that they do not have iron deficiency and that iron supplementation will not improve their anemia. Patients with the beta thalassemia trait generally have no unusual physical findings. In patients with beta thalassemia major, the physical findings are related to severe anemia, ineffective erythropoiesis, extramedullary hematopoiesis, and iron overload resulting from transfusion and increased iron absorption. The skin may show pallor from anemia and jaundice from hyperbilirubinemia, and the skull and other bones may be deformed secondary to erythroid hyperplasia with intramedullary expansion and cortical bone thinning. Skin ulceration may be present on the extremities. Thalassemia can result in maxillary enlargement, leading to an appearance known as chipmunk face, along with increased spaces between teeth, overbite, and malocclusion. Painful swelling of salivary glands and a dry mouth may occur, which leads to reduced salivary protection and an increased rate of tooth decay [6].

Cardiac examination may reveal heart failure and arrhythmia (eg, atrial fibrillation) [7], related to either severe anemia or iron overload. Abdominal examination may reveal changes in the liver, gallbladder, and spleen. Hepatomegaly related to significant extramedullary hematopoiesis is typically found. Patients who have received blood transfusions may have hepatomegaly or chronic hepatitis due to iron overload. The gallbladder may contain bilirubin stones formed as a result of the patient's lifelong hemolytic state. Splenomegaly typically is observed as part of the extramedullary hematopoiesis or as a hypertrophic response related to the extravascular hemolysis. In addition to cardiac dysfunction, hepatomegaly, and hepatitis, iron overload can also cause endocrine dysfunction, especially affecting the pancreas, testes, and thyroid. Transfusion-associated viral hepatitis resulting in cirrhosis or portal hypertension also may occur.

Thalassemia syndromes are a heterogeneous group of single gene disorders, inherited in an autosomal recessive manner, prevalent in certain parts of the world, including India. The β thalassemias and sickle cell disorders pose a significant health burden in India. The only forms of treatment 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. Marrow transplantation also has an important role in selected cases. Hence based on above findings the present study was planned for Assessment of Clinical Profile of Children with Beta-Thalassemia from Bihar Region.

Methodology

The present study was planned in Department of Pediatrics, Mata Gujri Memorial Medical College and Lions Seva Kendra Hospital, Kishanganj, Bihar, India. In the present study 50 cases of childrens suffered with Beta-Thalassemia were enrolled in the present study. An information sheet was explained to parents. Assent was taken from parents of both patients and control group who were enrolled in the study. Patient’s demographic data and clinical data were noted down in a specially designed thalassemia patient profile form. Patients and their parents were interviewed about the patient’s quality of life and if they experience any adverse reactions post blood transfusions when they visit for subsequent blood transfusion. All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria

Known beta thalassemic children aged between 6 months to 12 years on repeated blood transfusion were recruited for study.

Exclusion criteria

Children with other hemoglobinopathies such as hemoglobin J variant etc were excluded from the study.

Results and Discussion

Beta thalassemia represents group of recessively inherited hemoglobin disorders characterized by reduced synthesis of β globin chains resulting in severe anemia which needs repeated blood transfusion. The combination of transfusion and chelation therapy has dramatically improved the life expectancy of thalassemic children. On the other hand, frequent transfusion can led on to iron overload and may result in short stature, hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism, and other endocrine problems, cardiomyopathy, hepatic fibrosis and cirrhosis. In recent years, several authors have reported high incidence of these complications among patients suffering from thalassemia major.

In India over 20 million people have thalassemia gene. The prevalence of the gene varies between 3 to18% in north and 1 to 3% in south with certain communities like sindhis, kutchis, lohanas, bhanushalis, Punjabis, mahars, agris, gouds, etc. showing a high prevalence. [8]. It has been estimated that over 6000-8000 children, who are homozygotes of ß-thalassemia are born in India every year and unfortunately most of these children die either undiagnosed because of inadequate facilities, poor management and/or financial constraints. There are only a few thalassemia units where these children are regularly given blood transfusion and monitored for various parameters. There are hardly any long-term studies of benefits of regular therapy and endocrine or cardiac complications from our country. Data is available only from few centres and as such no statistics are available regarding total number of thalassemics, their life expectancy, actual birth rates, causes of death. Majority of people still consider thalassemia as a curse rather than an inherited disorder. [9].

Individuals with thalassemia major usually come into attention in initial two years of life where they present with severe anemia requiring regular blood transfusions for their survival. On the other hand, Thalassemia trait is characterized by mild hypochromic, microcytic anemia with elevated HbA2 levels. Except in the rare dominant forms, heterozygous beta thalassemia results in the clinically silent carrier state. HbE/ beta-thalassemia and HbC/beta-thalassemia exhibit a great range in terms of diversity of phenotypes and spectrum of severity. Estimated cost for treatment is more than 1 Lac per child per year, which is difficult to afford in developing countries. Management of thalassemics is not only traumatic to the family but also poses a tremendous socio-economic burden on the country making its control and prevention a cause of prime concern.

Table 1: Basic Details

Parameters	No. of Cases
Age	
1 – 5 years	24
5 – 8 years	10
8 – 14 years	16
Sex	
Males	27
Females	23
Family History	
Yes	6
No	44
Haemoglobin g%	5 – 7%
Transfusion Interval	3 – 4 weeks
Splenectomy	3 Cases

Table 2: Clinical Parameters

Parameters	No. of Cases
Blood Sugar	98.2 ± 21.5 mg %
Urea	23.1 ± 7.6 mg %
Creatinine	0.91 ± 0.4 mg %
S. bilirubin	1.52 ± 0.95 mg %
SGOT	54.1 ± 35.3 IU/L
SGPT	89.3 ± 42.1IU/L
Serum Total Proteins	6.72 ± 0.69 mg %
Serum Albumin	3.85 ± 0.39 mg%
Serum Globulin	3.1 ± 0.76 mg%
Thyroid Hormone:	
T3	1.31 ± 0.31
T4	8.9 ± 1.32
TSH	2.85 ± 1.9
Ferritin Levels	3014 – 3205 ng/dl
Hypothyroid Childrens	16

In general the body iron stores have been found to correlate with serum ferritin levels. However being an acute phase reactant single values of serum ferritin are not always not reliable. Despite serial measurements remains the simple and reliable method to evaluate the iron deposition and efficiency of chelation therapy. In order to evaluate clinical relevance, need for treatment, and timing and monitoring of chelation therapy, iron status should be assessed accurately.

Splenectomy should be considered if annual red cell requirement exceeds 180-200ml/ kg, provided other causes if increased consumption such as infections, hemolytic reactions have been ruled out. Symptoms of splenic enlargement, leucopenia, and/or thrombocytopenia increasing iron overload inspite of good chelation may necessitate splenectomy.

An Indian study by Jyoti Suvarna *et al* [10]. concluded that diabetes mellitus or impaired glucose tolerance was not seen in chronically transfused patients and insulin resistance with compensatory hyperinsulinemia sets earlier well before the onset of frank diabetes mellitus and correlates with the age, chelation therapy and indicators of iron overload.

Treatment of subclinical hypothyroidism is debatable. Close monitoring of the patients is necessary when treatment is considered as unnecessary. In overt hypothyroidism characterized by low T4 levels with signs and symptoms such as mental and physical letharginess, cold intolerance, weight gain, constipation etc, treatment with L- thyroxine is considered. Abnormal thyroid function may be reversible t the early stage through intensive chelation therapy.

It appears from the study that clinical spectrum of thalassemia is widely variable in all of its subtypes. Clinical features of beta thalassemia are usually manifested in younger age group starting below 5 years of age and become more severe with advancing age. Conditions like hepatic dysfunction, portal hypertension and other organ involvement causing functional impairment are found in the advanced age group HbE Beta Thalassemia appears to be less severe clinically. But the patients in this variety may show clinical features resembling those of thalassemia major even in infantile age. In most cases of HbE Beta Thalassemia, clinical severity increases with age and complications like those of Beta Thalassemia eventually develops. Sometimes these patients manifest clinical feature during adolescence with delayed puberty and undeveloped secondary sex characters. All this findings are corroborative to the findings of previous workers [11-12].

Growth of thalassemic children during the first decade largely depends upon the maintenance of fairly normal haemoglobin. Every attempt should be made to maintain the haemoglobin levels at 9.5-10gm% with frequent blood transfusions. Parents should be counselled about the importance of maintaining the adequate Haemoglobin levels. Determination of serum ferritin and routine growth monitoring at regular intervals is necessary with increasing age, to detect any disturbance in growth and to establish appropriate management protocols.

The negative impact of the disease and its treatment can affect the quality of life in patients. In this study when the quality of life of thalassemic children was compared to control group it was found that the result was significantly lower. Age at onset of anemia, age at first transfusion, irregular iron chelation therapy and low pre-transfusion hemoglobin levels were factors significantly affecting health-related quality of life. Various studies have reported that thalassemia pediatric had significantly lower health-related quality of life in all dimensions compared to their healthy counterparts. [13-14]. Also, it was observed that among all four domains of quality of life, school function was a most affected domain. This may be because thalassemia children are frequently absent from school since they routinely go to the hospital for blood transfusion. Also one of the reasons for academic performance could be that thalassemia patients may face deprecatory remarks from their peers or teachers. A school environment that includes verbal abuse and less peer support for ill children may be a problem. Insufficient knowledge of teachers about the illness and the inability to spend adequate time with chronically ill children present barriers to the integration of the chronically ill child in a classroom situation.

Conclusion

The data generated from the present study concludes that all children were short statured and malnourished indicating the underlying poor nutrition acting along with the disease pathology. Serum ferritin levels were invariably elevated in all patients demanding optimal chelation therapy. All children were short statured and malnourished indicating the underlying poor nutrition acting along with the disease pathology. Serum ferritin levels were invariably elevated in all patients demanding optimal chelation therapy.

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