International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 29-12-2019; Accepted: 30-01-2020; Published: 23-02-2020
www.medicalsciencejournal.com
Volume 6; Issue 2; 2020; Page No. 150-154

Assessment of liver function profile in children's diagnosed with thalassemia receiving multiple blood transfusions

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Abstract
Thalassemias are inherited blood disorders characterized by decreased hemoglobin production. Symptoms depend on the type and can vary from none to severe. Often there is mild to severe anemia (low red blood cells or hemoglobin). Anemia can result in feeling tired and pale skin [1]. There may also be bone problems, an enlarged spleen, yellowish skin, and dark urine [1]. Slow growth may occur in children. Hence based on above findings the present study was planned for Assessment of Liver Function Profile in Children's Diagnosed with Thalassemia Receiving Multiple Blood Transfusions.
The present study was planned in Department of Pediatrics, Darbhanga Medical College & Hospital, Laheraisarai, Bihar, India, during the period of April 2019 to September 2019.Total 20 cases of childrens between 1-15 years of age, who are diagnosed to have Thalassemia are included in the study.
The data generated from the present study concludes that in hepatitis seronegative thalassemic patients, regular blood transfusion along with iron chelation therapy helps in maintaining liver function and decreasing iron overload in liver. It is also recommended that Liver function test should be done regularly at 3 months interval to detect any hepatic dysfunction.

Keywords: liver function profile, thalassemia, multiple blood transfusions, bihar region, etc

Introduction
Of genetic disorders worldwide, thalassemia syndromes are among the most common. Normal adult hemoglobin produced after birth (hemoglobin A [HbA]) consists of a heme molecule linked to two α-globin and two β-globin chains (α2β2), with α-globin chain production dependent on four genes on chromosome 16, and β-globin chain production arising from two genes on chromosome 11. Deletions or mutations of one or more of these genes so that the rate of production of α- or β-globin chains is reduced results in alpha thalassemia or beta thalassemia, respectively. Thalassemia is usually asymptomatic in carriers, or presents with anemia of varying degrees in patients in whom globin-chain production is more severely impaired [1].
Patients with alpha-thalassemia trait or beta-thalassemia trait are asymptomatic but have mild microcytic hypochromic anemia, which often goes undiagnosed or is confused with iron deficiency anemia. Recognizing the possibility of thalassemia trait by taking a complete family history and appropriate testing is important in making an accurate diagnosis. Individuals with thalassemia trait may be at risk of having a severely affected child and should be referred for genetic counseling when appropriate [2]. Similarly, the birth of a child with severe thalassemia is a trigger for genetic counseling and future prenatal testing.
Patients with severe beta thalassemia are dependent on red cell transfusions either regularly (thalassemia major) or intermittently (thalassemia intermedia). Regardless of their transfusion needs, such patients should be followed at a thalassemia comprehensive care center under the care of a hematologist, so that they can be monitored for short- and long-term complications of chronic transfusions, including iron overload with cardiac and liver damage, as well as for growth and endocrine issues, bone pathology, and infertility. Curative therapy such as bone marrow transplantation may be an option for some patients, and novel agents, as well as gene therapy, are in the pipeline [3, 4, 5].
Patients with severe alpha thalassemia requiring red cell transfusion (HbH disease) should be monitored closely in a similar fashion. Recognizing that nonimmune hydrops fetalis in mothers of Southeast Asian origin can be due to severe alpha thalassemia is important for genetic counseling and future prenatal testing. Rarely, patients with Hb Bart hydrops fetalis have been salvaged with intrauterine transfusions, but there is considerable morbidity, and this is not the standard of care [6].
Complete blood count (CBC) results and red cell indices, along with peripheral blood film examination outcomes, are usually sufficient to suspect a diagnosis of thalassemia. Hb electrophoresis can usually confirm the diagnosis of beta thalassemia, HbH disease, and HbE/β-thalassemia. Globin chain synthesis, which was once used in postnatal diagnosis, has also been used on fetal cells obtained by fetoscopy to screen the fetus for thalassemia.
Since polymerase chain reaction (PCR) assay techniques became available, several new methods have come into use to identify affected babies or carrier individuals accurately and quickly. Moreover, the sensitivity of next-generation sequencing (NGS) has allowed noninvasive screening to be done on fetal DNA obtained from maternal plasma.
Splenectomy is the principal surgical procedure used for some patients with thalassemia. However, with reports made of venous thromboembolic events (VTEs) after

splenectomy, one should carefully consider the benefits and risks before splenectomy is advocated. Patients typically receive PRBC transfusions (up to 20 mL/kg) every 3-4 weeks, with clinicians aiming for a 9-10 g/dL hemoglobin level prior to the next transfusion. In some patients, shorter intervals between transfusions may be beneficial [7]. Routine administration of iron chelation is essential to avoid transfusion-related iron overload and multiorgan (especially cardiac and liver) toxicity. In 2019, the European Union conditionally approved the use of Zynteglo, the first gene therapy for the treatment of transfusion-dependent beta thalassemia [5, 8, 9, 10].

Beta thalassemia was the first described in 1925, by Thomas Cooley, a Detroit pediatrician, who reported on children of Italian origin who presented with severe microcytic anemia and other red cell abnormalities, enlarged liver and spleen, and skull and bony abnormalities. Because of the patients' ethnic origin, "Cooley's anemia" was later renamed thalassemia (thalassa in Greek means "great sea" or Mediterranean) [11]. In 1959, Ingram and Stratton postulated that decrease in β-globin or α-globin production led to a transfusion-dependent anemia, and in the latter case it resulted in HbH (β4) disease, which we now recognize as severe alpha thalassemia [12]. Three years later, Lie-injo Luan Eng, an Indonesian pathologist, described a stillbirth with Hb Bart hydrops fetalis, the most severe manifestation of alpha thalassemia [13]. We now recognize a number of thalassemia syndromes and have a better understanding of the underlying pathophysiology.

HbA, or α2β2, consists of heme combined with two α-globin and two β-globin chains. On chromosome 16, each DNA strand has two α-globin genes, whereas chromosome 11 has a single pair of β-globin genes. Nevertheless, the globin-chain output of these genes is closely matched to effectively produce HbA. In the thalassemia syndromes, mutations affecting either gene affect this balanced production of α-globin and β-globin chains, resulting in decreased hemoglobin and varying degrees of anemia [8].

Beta thalassemia is usually caused by mutations affecting a single nucleotide substitution, which can impact each step of this process. Authors refer to severe mutations, with complete absence of β-globin production, as β0 mutations, and refer to less severe mutations as β+ mutations. It is important to keep in mind that the severity of the mutation may not always correlate with the clinical picture [14]. Splice-site mutations, which are especially common, change the critical GT/AG bases around the splice site (eg, IVS1-1 G>T), rendering the splice site unrecognizable by the normal splicing process. In a "nonsense" mutation, a single base change in the exon generates a stop codon in the mRNA, resulting in premature termination of the globin chain. In a "frameshift" mutation, one or more bases on the exon are lost or inserted, resulting in a change in the reading frame of the genetic code or the production of a new stop codon. Mutations in exons may also activate a cryptic splice site, as in HbE, in which a mutation at codon 26 (G>A) results in alternate splicing, reducing the amount of β-globin production (similar to β+ thalassemia) [15]. Rarely, deletions, rather than point mutations, have been described; in Hb Lepore, a deletion leads to a fused δ/β gene, under the control of the δ-globin gene promoter, which is weak (so that mild beta-thalassemia–like behavior results).

In patients with thalassemia, mortality and morbidity vary according to the severity of the disease and the quality of care provided. Severe cases of beta-thalassemia major are transfusion-dependent, and chronic iron overload or undertransfusion can lead to cardiac failure, liver disease, chronic or acute infection, and other complications. Even patients receiving well-designed treatment regimens may be at risk for a variety of complications [17].

Hb Bart hydrops fetalis is lethal, and fetuses are stillborn with severe anemia, which is traumatic to the mother and family. Intrauterine blood transfusions have salvaged some patients in specialized centers, but there is considerable morbidity, and this is not a standard of care or an option for the vast majority of patients affected worldwide [16].

Patients with HbH disease usually have mild hemolytic anemia requiring only occasional blood transfusions, but some patients who have co-inherited nondeletional mutations such as Hb Constant Spring or Hb Quong Sze have more severe, transfusion-dependent anemia. These patients may require splenectomy, and morbidity is very similar to patients with beta-thalassemia intermedia [18].

Thalassemias are encountered among all ethnic groups and in almost every country around the world, with 15 million people worldwide having clinical thalassemic disorders. There is a wide variation in the prevalence rate for alpha and beta thalassemia in different parts of the world. In areas endemic for beta thalassemia, such as the Mediterranean countries and islands, the Middle East, and the Indian subcontinent, the carrier rate is 10-15%. The lack of systematic preventive measures in lower-income countries, means that in India alone, 10,000 new beta-thalassemia patients are added to the population each year [19]. Regions impacted by severe alpha thalassemia are Southeast Asia, the Middle East, and southern China, where the carrier rate exceeds 5%, with the rate approaching 5% in Thailand. In southern China, there are 2-3 times more fetuses afflicted with the lethal Hb Bart hydrops fetalis than with severe beta thalassemia [20, 16].

In the United States, a diverse immigrant population has meant that thalassemia can occur in any part of the country. However, the number of patients with severe alpha or beta thalassemia is limited, so finding more than 2-5 patients in any pediatric hematology center is unusual (except in a few referral centers). Nonetheless, alpha thalassemia is increasingly prevalent in the United States and accounts for more than 50% of non–transfusion-dependent thalassemia (unpublished data, courtesy of Janet Kwiatkowski). The prevalence of alpha and beta thalassemia, as well as of HbE/β-thalassemia, is increasing in California, due to a high prevalence of individuals of Asian origin, and the cord-blood screening program for detection of hemoglobinopathy there annually detects 10-14 cases of beta-thalassemia major and HbE/β-thalassemia and 40 cases of HbH disease [21].

Patients with alpha- or beta-thalassemia trait have a normal lifespan, while Hb Bart hydrops fetalis (homozygous α0 thalassemia) is lethal in utero. With regular transfusions of red cells and comprehensive care, including aggressive iron chelation, life expectancy in birth cohorts with severe beta thalassemia has been found to extend into the fourth decade and beyond. Patients with HbH disease or beta-thalassemia intermedia can be expected to survive at least as long, depending on transfusion needs and availability of care [7].

Thalassemias are inherited blood disorders characterized by decreased hemoglobin production. Symptoms depend on the type and can vary from none to severe. Often there is mild to severe anemia (low red blood cells or hemoglobin).

Anemia can result in feeling tired and pale skin [1]. There may also be bone problems, an enlarged spleen, yellowish skin, and dark urine [1]. Slow growth may occur in children. Hence based on above findings the present study was planned for Assessment of Liver Function Profile in Children's Diagnosed with Thalassemia Receiving Multiple Blood Transfusions.

Methodology

The present study was planned in Department of Pediatrics, Darbhanga Medical College & Hospital, Laheraisarai, Bihar, India, during the period of April 2019 to September 2019. Total 20 cases of childrens between 1-15 years of age, who are diagnosed to have Thalassemia are included in the study.

All the patients were informed written 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

The children between 1-15 years of age, who are diagnosed to have Thalassemia are included in the study.

Exclusion Criteria

Children <1yr or >15yrs of age. The children who were not attending the Centre regularly for blood transfusion. The children with other co-morbid conditions like cardiomyopathies, HBsAg or HCV Positive or with other severe systemic illness. Children who have undergone Splenectomy. If the parents not willing to give consent.

Results and Discussion

Thalassemia are inherited disorders characterized by abnormal production of hemo globin, associated with low hemo globin production and excessive destruction of red blood cells. They are a heterogeneous group of disorders and are considered as the most common monogenic disorder in the world.

Higher hemoglobin level, serum ferritin <1000ng/ml and normal liver function tests are indicators of good prognosis as their growth, development and quality of life was observed to be better compare to patients having low hemoglobin level, abnormal liver function tests (due to either liver siderosis or hepatitis) and higher serum ferritin levels. Clinically facial deformities-thalassemic facies, height and developmental abnormalities were observed to be minimum in patients who were better chelated and having regular blood transfusion as compare to those who were poorly chelated and irregularly transfused.

Frequent blood transfusion has also led to iron overload with many complications including endocrinopathies (in the form of growth retardation, pubertal delay, gonadal dysfunction and diabetes mellitus), behavioural and neurotic problems, cardiovascular problems, liver disease. Frequent blood transfusion can also lead to increased chances of transfusion-transmitted infections TTIs such as HIV (with risk of progression to AIDS), HBsAg, and HCV (with high risk of developing chronic hepatitis, liver cirrhosis and hepatocellular carcinoma), syphilis (VDRL) and Malaria can also occur [22].

Table 1: Age Distribution

Age group (years)	Number of patients
1–5	5
6–10	5
11–15	10
Total	20

Table 2: Liver function tests in thalassemic patients

Liver function tests	Normal value	Abnormal value
Serum bilirubin (%)	4	16
Serum glutami oxaloacetic transaminase (%)	8	12
Serum glutamic pyruvic transaminase (%)	11	9
Alkaline phosphatase (%)	5	15
Total protein (%)	16	4
Serum albumin (%)	18	2

Table 3: Serum ferritin level of thalassemia patients

Serum ferritin (ng/ml)	Number
<1000	3
1000–1999	5
2000–2999	7
3000–3999	4
4000–4999	1
Total	20

The moderate transfusion regimen practiced correctly has been shown to ensure normal growth without excessive expansion of erythropoiesis, and with effective prevention of iron overload [23]. The inevitable consequence of regular life-saving transfusions in thalassemia major is the accumulation of excess iron within tissues. This causes progressive organ damage and dysfunction which, without treatment, can lead to an increase in morbidity and mortality [24]. For patients requiring regular blood transfusions, iron chelation may represent life-saving therapy. A landmark study investigating role of desferoxamine (Desferal;) in prevention of complications of transfusional iron overload showed that survival to at least 25 years of age in poorly chelated β-thalassemia major patients was just one-third that of patients whose iron levels were well managed by deferoxamine [25]. The optimal age for initiating iron chelation therapy in patients with severe thalassemia remains uncertain, although in theory it should begin as early as possible to prevent growth and developmental defects. Guidelines from the Thalassemia International Federation recommend that chelation therapy is initiated when serum ferritin levels reach approximately 1000 ng/mL, which usually occurs after the first 10 to 20 transfusions or around 2-3 years of age [26-27].

In India, mandatory screening for HCV was introduced as late as 2002. The prevalence of HCV was found to be as high as 21% in thalassemia patients and correlated with advancing age, indicative that they may have acquired it in the period when screening of blood units for HCV was not mandatory [14]. In two studies from Western India, the prevalence of HCV in multiple transfused thalasemics was 16.7% and 17.5%, respectively [28-29].

Beta thalassemia major is characterized by total suppression of synthesis of beta chain of the hemoglobin. This leads to moderate to severe degree of anemia. Regular blood.

Transfusion is the mainstay of treatment in these patients. These patients develops iron overload, probably due to - multiple blood transfusion, increased dietary iron absorption and inadequate chelating therapy [30].

Iron overload causes injury to various organ-systems including liver, heart, kidney, endocrine system etc. Liver injury can be measured by assessing liver enzymes, bilirubin and protein levels in serum. Patients with iron overload have increased levels of thiobarbituric acid reactant and increased hepatic level of aldehyde protein adduct indicating lipid peroxidation. Collagen formation and portal fibrosis starts as early as 2 years of onset of transfusion. In absence of chelation, cirrhosis may develop in first decade of life [31].

Although 100% compliance was not seen in most patients for regular blood transfusion and adequate iron chelation but individual patients who by and large could manage frequent blood transfusion and better iron chelation had higher hemoglobin levels, normal liver function tests and lower serum ferritin levels as compared to others. Overall quality of life was also observed to be better in these patients. Higher hemoglobin level, serum ferritin <1000ng/ml and normal liver function tests are indicators of good prognosis as their growth, development and quality of life was observed to be better compare to patients having low hemoglobin level, abnormal liver function tests (due to either liver siderosis or hepatitis) and higher serum ferritin levels. Clinically facial deformities-thalassemic facies, height and developmental abnormalities were observed to be minimum in patients who were better chelated and having regular blood transfusion as compare to those who were poorly chelated and irregularly transfused.

Thalassemia major is one of the most common autosomal single-gene thalassemic disorders. It is prevalent in more than 60 countries of the world with a carrier population of up to 150 million worldwide [32]. In order to reduce the complications of severe anemia in -thalassemic patients, early and regular blood transfusion therapy is mandatory. Thalassemic patients had a risk for iron overload and for TTIs, such as HBV, HCV, CMV, and HIV [33].

Furthermore, the severity of liver cirrhosis due to HCV in patients with thalassemia may be greater because of concomitant iron overload. It has been demonstrated that iron and HCV infection are independent but mutually reinforcing risk factors for the development of liver fibrosis and cirrhosis. It appears therefore that patients with thalassemia, particularly those with poor control of iron overload, face an increased risk of developing cirrhosis. [34]

Conclusion

The data generated from the present study concludes that in hepatitis sero negative thalassemic patients, regular blood transfusion along with iron chelation therapy helps in maintaining liver function and decreasing iron overload in liver. It is also recommended that Liver function test should be done regularly at 3 months interval to detect any hepatic dysfunction.

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