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Study of intellectual functions and behavioural problems in children with homozygous beta thalassemia

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ABSTRACT

In this article, the author has discussed on the intellectual functions and behavioural problems in children with homozygous beta thalassemia. Beta thalassemia major is considered one of the serious health problems and the commonest hemoglobinopathy that creates a burden not only on health system but also on the affected families and children who become vulnerable to emotional, social, psychological and behavioural problems. After a detailed study, the author has concluded that thalassemic patients had a relatively mild affection for adaptive and psychosocial functioning that can be explained by social and medical support they receive, which may increase their competence and psychological wellbeing.

Keywords: intellectual functions, behavioural, problems, children, homozygous, beta thalassemia.

INTRODUCTION

Thalassemia is an inherited blood disorder in which the body makes an abnormal form of hemoglobin. Hemoglobin is the protein molecule in red blood cells that carries oxygen. The disorder results in excessive destruction of red blood cells, which leads to anemia. Anemia is a condition in which your body doesn't have enough normal, healthy red blood cells. Thalassemia is inherited, meaning that at least one of your parents must be a carrier of the disorder. It's caused by either a genetic mutation or a deletion of certain key gene fragments. Thalassemia minor is a less serious form of the disorder. There are two main forms of thalassemia that are more serious.

In alpha thalassemia, at least one of the alpha globin genes has a mutation or abnormality. In beta thalassemia, the beta globin genes are affected. Each of these forms of thalassemia has different subtypes. The exact form you have will affect the severity of your symptoms and your outlook. Thalassemia was first noted in the Mediterranean population and this geographical association explained its naming as "thalassa" which in Greek means the sea and the "Haema" is Greek for blood. Thalassemia is the most common hereditary hemoglobinopathy worldwide and a major problem in our society and many other countries. Worldwide approximately 15 million people are estimated to suffer from thalassemic disorders and at there are about 240 million carriers of beta thalassemia worldwide i.e. 1.5% of world population. The burden of Thalassemia in India is very high with nearly 12000 infants being born every year with this disorder [1-4].

The main defect is not in the molecular structure of haemoglobin; rather, the abnormality is in the quantitative synthesis of each alpha and beta chain, resulting in an unbalanced synthesis of globin chains and in the precipitation of additional chains, which ultimately causes impairment in the maturation and survival of red blood cells and of the red blood cell lysis.[5-7]

Types of Beta-thalassemia

Beta-thalassemia is the most common type of thalassemia occurring in three forms: thalassemia minor, thalassemia intermedia and thalassemia major.

Children with beta-thalassemia major suffer from severe anemia, and if not treated with blood, the disease will lead to heart failure and death in early childhood. During the first few months of life, beta-thalassemia major which is often diagnosed in childhood shows itself with decrease in fetal hemoglobin levels on the one hand, and an increase in iron deposition in the blood on the other.[8-10]

In children with beta-thalassemia major, iron overload is the main cause of disorders in various organs. Iron accumulation damages tissues at the end of the first decade of life and that is the time when a set of symptoms appears. These symptoms include impaired growth, hypothyroidism, adrenal insufficiency, cardiac and hepatic complications, hypoxemia, cognitive disorders in the central nervous system (CNS) and long-term brain injuries. Several studies examined the brain of thalassemic patients and reported higher iron deposition in their putamen, caudate nucleus, and motor and temporal cortices. The putamen, caudate nucleus, motor and temporal cortex are important for cognitive function and for implicit and explicit memory.

In most cases, neurologic involvement in beta-thalassemia major patients does not initially present relevant signs and symptoms (i.e., subclinical); they are presented only during neurophysiological and neuropsychological evaluation.

CNS complications generally present as cognitive dysfunction, which usually results from iron deposition and neurotoxicity of desferrioxamine (DFO) which is commonly used as a chelating agent in children with beta-thalassemia major. Other risk factors for brain damage include transient ischemic attacks, asymptomatic brain infarcts and visual and auditory toxicity of DFO.

According to Piaget's theory of cognitive development, biological principles governing the individuals' physical activities and growth can also be applied to their mental activity and growth. In this theory, intelligence is thought as an adaptive process which requires a balance between organism and environment. Also, novel cognitive constructs and abilities, which require general factors emanating from social life, grow in accordance with growth and aging.

In the literature, there are few studies on the Verbal, Performance and Full intelligences of children with beta-thalassemia and healthy counterparts as a part of their cognitive perception. Such findings are generally contradictory and ambiguous. A number of studies suggest that Thalassemia causes cognitive disorders but other studies found that this disease has no impact on cognition or if there is any, it is very limited.

The therapeutic regimen in beta thalassemia major is complex, lifelong and inconvenient, requiring repeated hospitalizations and blood transfusions, which often affects the child's physical and mental health negatively.

It is expected that these children are at high risk of developing behavioral and psychosocial problems like opposition, passiveness, anxiety, phobias and depression, which affect their self-confidence and give rise to emotions and thoughts which negatively affect their quality of life and compliance to therapy. Many of the thalassemic children experience fear related to intravenous line insertion and subcutaneous infusion pumps. Children with thalassemia in the pre-school and latency age groups are usually anxious and excessively dependent on their parents. They display psychosomatic symptoms and are frequently absent from school. Thalassemic children have more of negative self-concept when compared to their normal counterparts. However, data regarding the psychosocial aspects of thalassemia major are scanty and controversial.

In India, only medical management of thalassemia is the concern even today, probably because till about two decades back, the life span of thalassemic children was limited and the medical problems of the disease were so severe that all other aspects of the illness and its management were neglected. Now, with increased life expectancy and dramatic improvement in the medical management of thalassemia, the psychosocial and behavioral problems in these children and their

recognition and management at an early stage are coming to the forefront. Hence, this study has been undertaken to assess these problems in thalassemic children and the factors affecting them, so as to emphasize on the importance of achieving not only physical well-being but also the mental and social well-being of a thalassemic child, so that strengths and weaknesses of these children are identified and appropriate educational and rehabilitation strategies can be suggested.

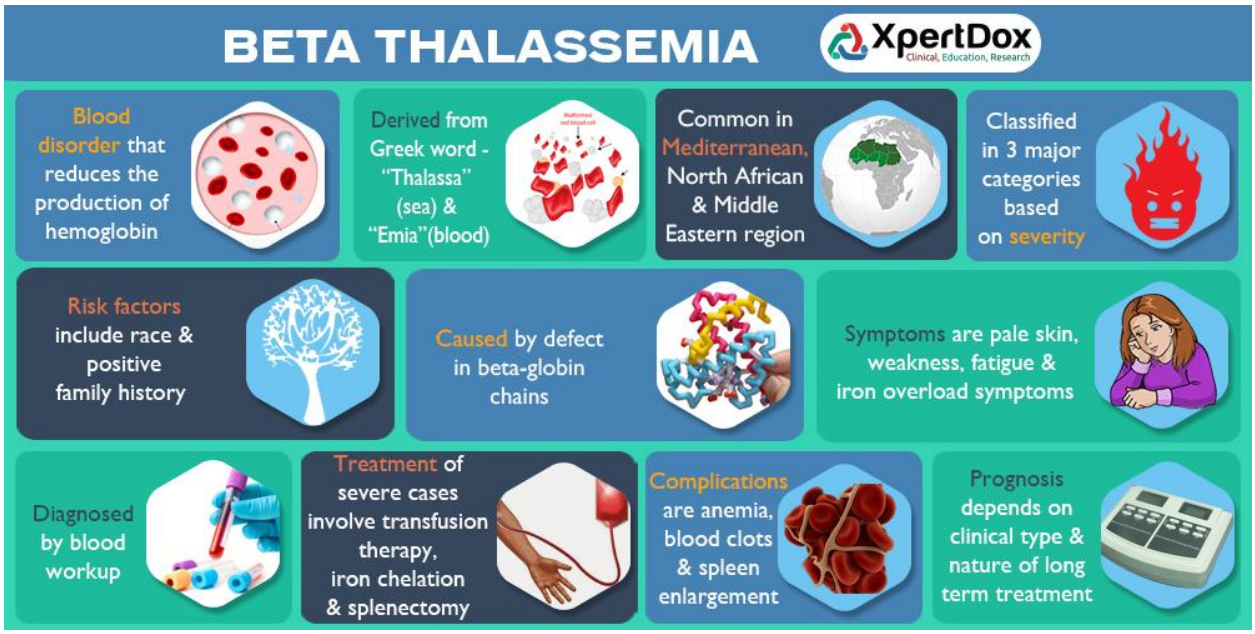


Figure 1: Basics of Beta- thalassemia

Symptoms

There are several types of thalassemia. The signs and symptoms you have depend on the type and severity of your condition. Thalassemia signs and symptoms can include:

- Fatigue
- Weakness
- Pale or yellowish skin
- Facial bone deformities
- Slow growth
- Abdominal swelling
- Dark urine

Some babies show signs and symptoms of thalassemia at birth; others develop them during the first two years of life. Some people who have only one affected hemoglobin gene don't have thalassemia symptoms.

Causes

Thalassemia is caused by mutations in the DNA of cells that make hemoglobin — the substance in red blood cells that carries oxygen throughout your body. The mutations associated with thalassemia are passed from parents to children. Hemoglobin molecules are made of chains called alpha and beta chains that can be affected by mutations. In thalassemia, the production of either the alpha or beta chains are reduced, resulting in either alpha-thalassemia or beta-thalassemia. In alpha-thalassemia, the severity of thalassemia you have depends on the number of gene mutations you inherit from your parents. The more mutated genes, the more severe your thalassemia. In beta-thalassemia, the severity of thalassemia you have depends on which part of the hemoglobin molecule is affected.

Complications

Possible complications of moderate to severe thalassemia include:

- **Iron overload.** People with thalassemia can get too much iron in their bodies, either from the disease or from frequent blood transfusions. Too much iron can result in damage to your heart, liver and endocrine system, which includes hormone-producing glands that regulate processes throughout your body.
- **Infection.** People with thalassemia have an increased risk of infection. This is especially true if you've had your spleen removed.

In cases of severe thalassemia, the following complications can occur:

- **Bone deformities.** Thalassemia can make your bone marrow expand, which causes your bones to widen. This can result in abnormal bone structure, especially in your face and skull. Bone marrow expansion also makes bones thin and brittle, increasing the chance of broken bones.
- **Enlarged spleen.** The spleen helps your body fight infection and filter unwanted material, such as old or damaged blood cells. Thalassemia is often accompanied by the destruction of a large number of red blood cells. This causes your spleen to enlarge and work harder than normal.

  An enlarged spleen can make anemia worse, and it can reduce the life of transfused red blood cells. If your spleen grows too big, your doctor might suggest surgery to remove it.
- **Slowed growth rates.** Anemia can both slow a child's growth and delay puberty.
- **Heart problems.** Congestive heart failure and abnormal heart rhythms can be associated with severe thalassemia.

REVIEW OF LITERATURE

While β-thalassemia major (β-TM)-related physiological complications have been well established, less is known about implications for neuropsychological and cognitive function.

Samaneh et al. (2015) conducted a case control study in children with beta thalassemia major. The aim of this study was to evaluate intelligence quotient in children with beta-thalassemia major and healthy counterparts using Wechsler Intelligence Scale. Within a case-control design and using convenience sampling method, the study was carried out in Zahedan and Shiraz in 2012. Participants were matched based on their age, gender and city of residence (40 children with beta-thalassemia major and 40 healthy children aging 6 to 12 years. Wechsler Intelligence Scale Revised (WISC-R) was used to find the participants' Verbal Performance and Full intelligence scores. The scores of the two groups were then compared using descriptive analysis and independent t-test. As compared with their healthy counterparts, children with beta-thalassemia major were found to have lower scores on both Verbal Scale and Full Scale IQ ($P<0.01$); however, the difference between the two groups' scores on Performance Scale fell short of significance. This study concluded that Intelligence decline does not necessarily occur in children with beta-thalassemia. They are just slightly lower than their healthy counterparts and they need to receive more attention in education in order to improve.

In order to evaluate cognitive function in β-thalassemia major patients and identify the relationship between possible cognitive dysfunction and the following: demography, transfusion and chelation characteristics, iron overload, and disease complications, a cross sectional study was conducted by Raafat N et al. (2015). 100 beta-thalassemia major children and 100 healthy controls who matched well in terms of age, sex, and socioeconomic status were studied. All participants underwent psychometric assessment using Wechsler Intelligence Scale for Children–Third Edition, Arabic version. The mean Full-Scale IQ and Performance IQ of patients were significantly lower than those of controls, whereas no significant difference was found for Verbal IQ. No significant relationship existed between IQ and any of the assessed parameters. The study concluded that Performance IQ, not Verbal IQ, was significantly affected in β-thalassemia major patients, but there was no clear association between IQ and any of the parameters.35

Hemolysis and repeated blood transfusions in children with beta-thalassemia major cause iron overload in various organs, including the brain, and may lead to neurodegeneration.

Hemolysis also causes decreased levels of nitric oxide, which serves as a volume transmitter and slow dynamic modulation, leading to cognitive impairment. Based on this principal Septiana et al. (2017) conducted a study. The objective of this study was to assess for correlations between serum ferritin as well as nitric oxide levels and cognitive function in children with thalassemia major. This was an analytical study with cross-sectional design on 40 hemosiderotic thalassemia major patients aged 6-14 years. The study was done at the Thalassemia Clinic in Dr. Hasan Sadikin Hospital, Bandung, West Java, from May to June 2015. Serum ferritin measurements were performed by an electrochemiluminescence immunoassay; serum nitric oxide was assayed by a colorimetric procedure based on Griess reaction; and cognitive function was assessed by the Wechsler Intelligence Scale for Children test. Statistical analysis was done using Spearman's Rank correlation, with a significance value of 0.05. Abnormal values in verbal, performance, and full scale IQ were found in 35%, 57.5% and 57.5%, respectively. Serum nitric oxide level was significantly correlated with performance IQ (P=0.022), but not with verbal IQ (P=0.359) or full scale IQ (P=0.164). There were also no significant correlations between serum ferritin level and full scale, verbal, or performance IQ (P=0.377, 0.460, and 0.822, respectively).

Gamayani et al. (2017) conducted an observational descriptive study, with cross-sectional study design, in the outpatient clinic of the Pediatric Thalassaemia Unit of Hasan Sadikin Hospital, Bandung, Indonesia. The aim of this study was to determine the characteristics of cognitive deficits such as attention and executive function in children with beta thalassaemia major. One hundred children with beta thalassaemia major aged 8-14 years old participated in this study. All subjects performed vigilance, verbal fluency and block design test. The mean age of subject was 10.94±1.72 years, predominantly male (52.0%). The mean frequency of transfusions per month was 1.30±0.52 times. The mean haemoglobin level was 6.36 ± 0.80 g/dL, and the mean ferritin levels was 4164.42 ± 2238.60 µg/L. Most of subject was using deferiprone for iron chelation (78.0%).Attention impairment was found in 26% of children and executive function impairment was presented in 23% of children. Both impaired attention and executive function were found in 21% of children.

The mean age of this group was 9.63 ±1.29 years, the mean haemoglobin level was 6.40±0.8 g/dL and the mean ferritin level was 3654±1526 µg/L. The frequency of transfusion per month was 1.42 ±0.74 times, and time from the first diagnosis was 9.87 ±1.3 years. This study showed that almost quarter children with beta thalassaemia major suffer from impaired cognitive function, 26%, 23% and 21% for attention, executive function, and both attention and executive function respectively. This study found that the haemoglobin level was low and ferritin level was high. Impairment of attention and executive function are important concern, because they comprise the ability of cognitive function. According to this study, monitoring of cognitive function should be applied as early as possible to detect any kind of cognitive abnormalities in children with beta thalassaemia major so that the intervention can be done as quickly and accurately to improve their quality of life.

Karimi et al. (2006) did a study for analysis of intelligence quotient in patients with homozygous beta-thalassemia. Aim of the study was to compare the intelligence quotient (IQ) of patients with thalassemia major to that of normal children. The study was conducted in April and May 2002 on 294 homozygote beta-thalassemia patients, (157 male and 137 female, mean age of 13.2 years; range, 9-18 years). These 294 patients were randomly selected from the 984 TM patients who routinely refer to Shiraz Cooley's Medical Center in Dastgheyb Hospital, Iran for blood transfusion.

Another 294 subjects age and gender matched control group were studied. Intelligence quotients were computed using the Ravin test. The mean IQ score +/- standard deviation (SD) in the thalassemia group was 109.83 +/- 15.94. This score revealed no statistically significant difference with the control group's score ($p<=0.079$). A correlation existed between the thalassemia patients' IQ and their level of education ($p<0.049$). The IQ of thalassemia major patients does not differ significantly from the normal population.

Hongally et al. (2012) studied behavioral problems in multi-transfused thalassemic children. Objective of the study was to assess the behavioral problems in multi-transfused thalassemic children and psychosocial factors affecting them. The study

was conducted in a tertiary care level hospital and research institute catering mainly to a population of low socioeconomic status. The study was a cross-sectional study involving 50 multi-transfused thalassemic children of age 5-10 years. Fifty multi-transfused thalassemic children, aged 5-10 years, not suffering from any other major medical illness, were included. Child Behavior Check List (Achenbach) (CBCL) was used to collect data from each parent regarding the child's behavior. Parental Attitude Scale was applied. Descriptive statistical analysis was used with analysis of variance (ANOVA) and Student's t test to find the significance of data. The CBCL total scores were high in 32% patients, indicating the presence of behavioral problems. Higher CBCL scores were found in children of older age group, those with poor school performance, whose mothers' education was more than eighth standard, had history of death of thalassemic relative in family, greater duration of diagnosed illness, poor pre-transfusion hemoglobin level, and who had longer periods of school absenteeism. This study concluded that behavioral problems are common in multi-transfused thalassemic children. Early diagnosis and intervention of behavioral problems in these children would make them cope with thalassemia better.

MATERIAL AND METHODS

Study design: This was a cross-sectional study

Study setting: The study was conducted in Department of Pediatrics Pt B.D. Sharma Post Graduate Institute of Medical Science, Rohtak.

Study period: One year

Ethical considerations: An institutional ethical clearance was obtained prior to commencement of study. A patient information sheet was provided to mother and father representatives.

Study participants: Children aged 6-14 years having established diagnosis of beta- thalassemia major with hemoglobin electrophoresis.

Inclusion criteria:

Children aged 6-14 years with established diagnosis of beta-thalassemia major who were registered with the thalassemia clinic in Pt. B.D. Sharma PGIMS, Rohtak

Exclusion Criteria: Children who were having:

1. Global development delay
2. Psychiatric co-morbidities
3. Neurodegenerative disorders

Sample size: 100

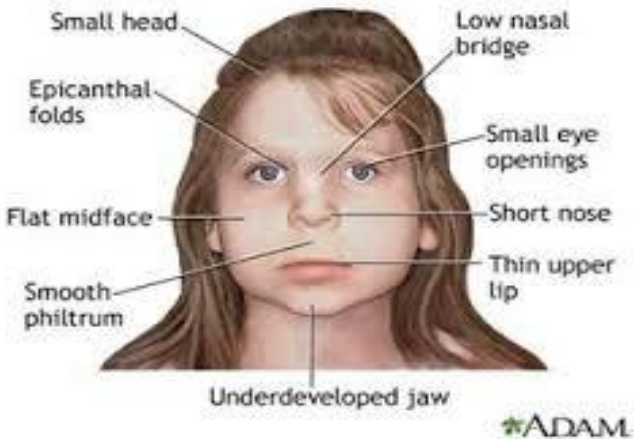


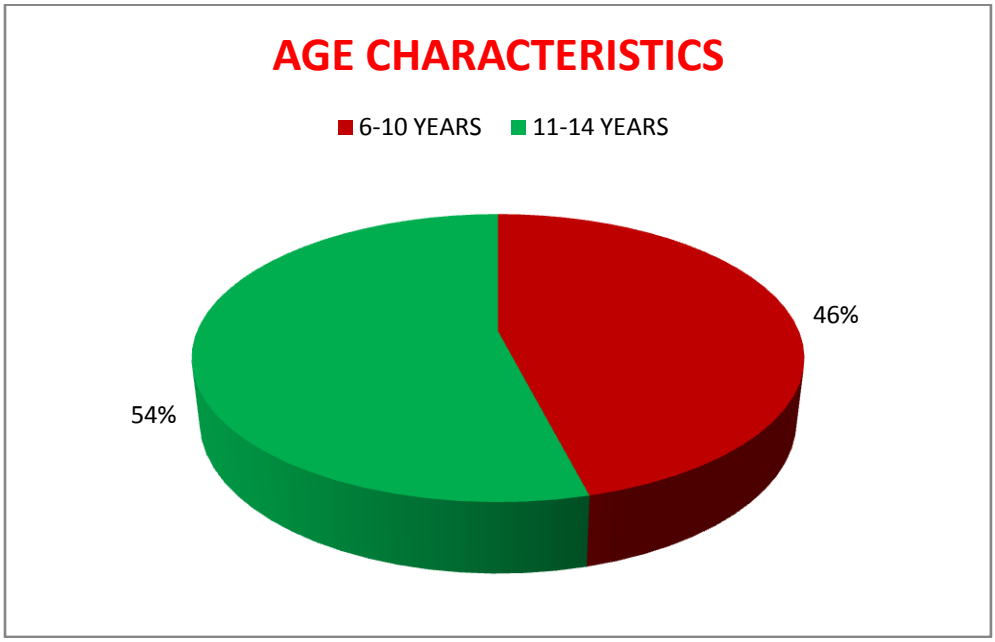
Figure 2: Children having established diagnosis of beta- thalassemia major with hemoglobin electrophoresis

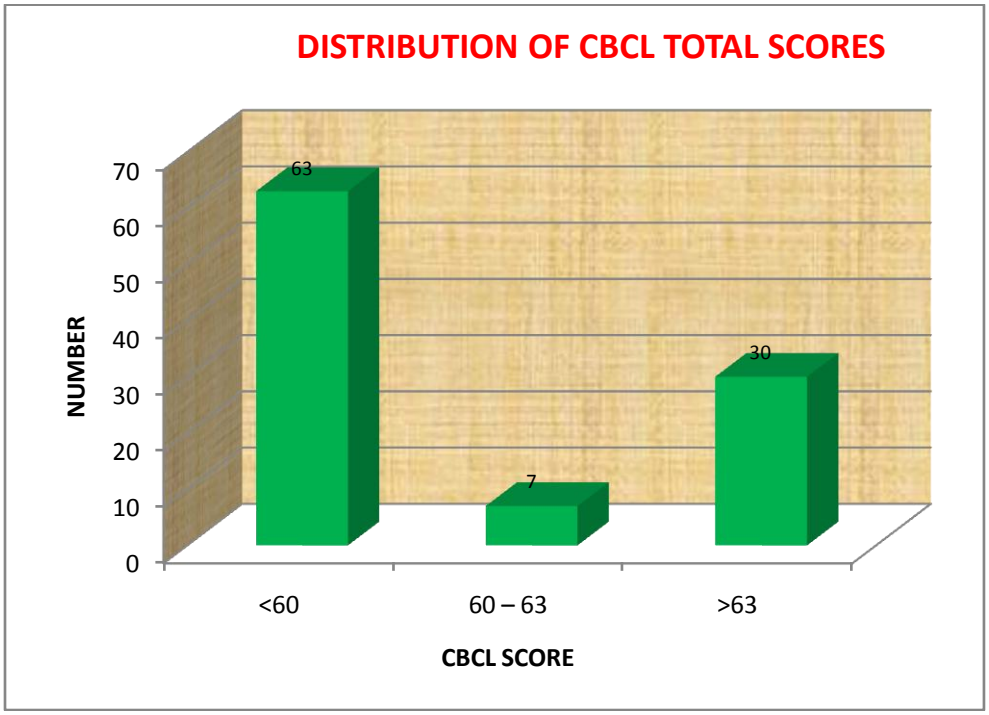
METHODOLOGY

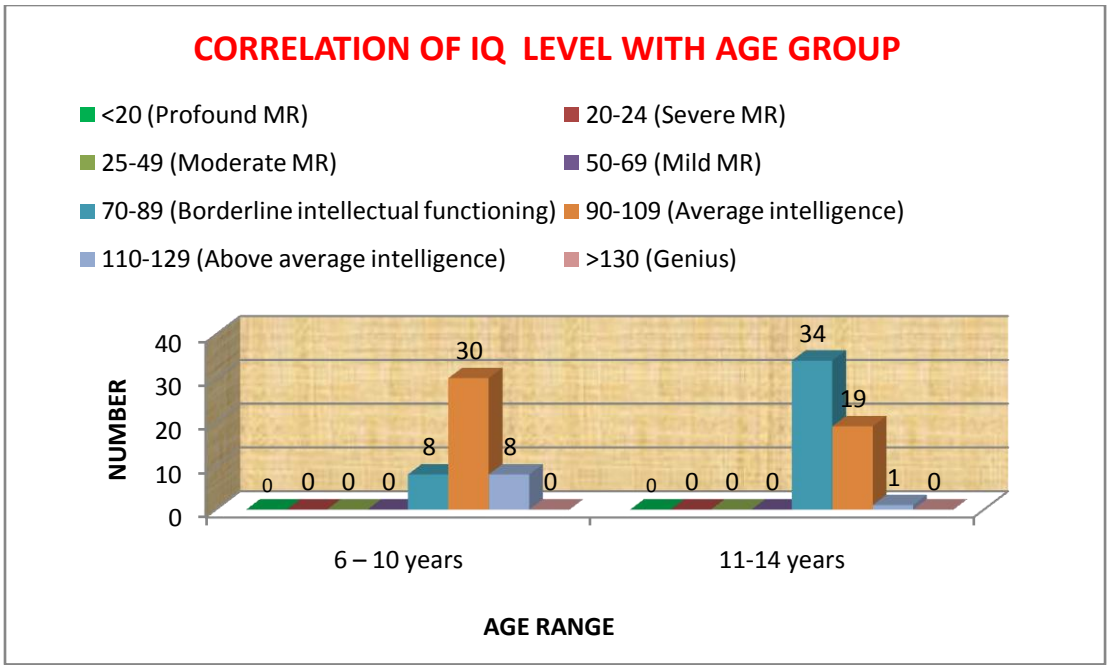
One hundred patients were randomly selected who routinely visit Pt. B.D. Sharma PGIMS, Rohtak for blood transfusion. The IQ evaluation was performed at 7±5 days after transfusion. All the selected patients were subjected to psychometric assessment using Malin's Intelligence Scale for Children by Dr Arthur J. Malin (an Indian adaptation of the Wechsler Intelligence Scale for Children) that provided the output of their verbal and Performance subtests and a combined Full Scale IQ test.[46] The assessment included 6 verbal subtests and 5 performance subtests:-

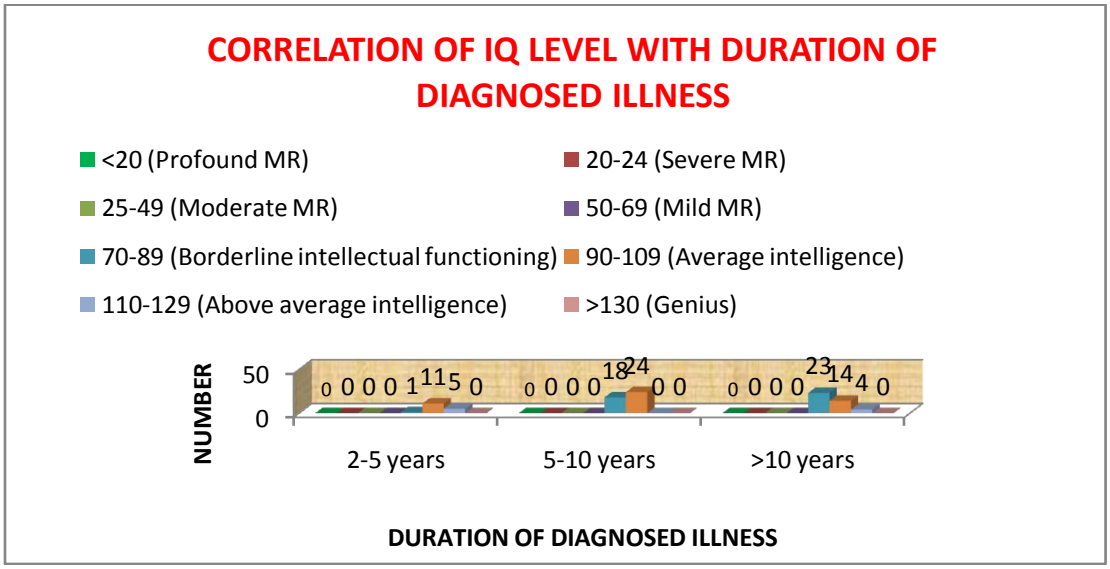
Verbal IQ subtests:

1. Information
2. Digit span
3. Vocabulary









OBSERVATIONS AND RESULTS

This cross-sectional study was conducted in the Department of Pediatrics, Pt B.D. Sharma Post Graduate Institute of Medical Science, Rohtak over a period of One year. A patient information sheet was provided to mother and father representatives. Children aged 6-14 years having established diagnosis of beta-thalassemia major were included in the study.

The following observations and results were made as under:

Table 1: Age distribution

Age Group	Frequency	%
6-10 yr	46	46%

11-14 yr	54	54%
Total	100	100%
Mean ± SD	10.17 ± 2.85	
Median	11	
Range	6–14	

Table 1 explains age distribution of the study group. One hundred children with beta-thalassemia major were enrolled out of which 46 children were between 6-10 year and 54 were between 11-14 year age group. The age range was 6 year to 14 year with median age of 11 year. Mean ± SD was 10.17±2.85 year.

Table 2: Sex distribution

Gender	Frequency	%
Male	56	56.0%
Female	44	44.0%
Total	100	100%

Table 2 shows distribution of children according to their sex. 56 children were male and 44 were female.

PREVENTION & TREATMENT OF THALASSEMIA

In most cases, you can't prevent thalassemia. If you have thalassemia, or if you carry a thalassemia gene, consider talking with a genetic counselor for guidance if you want to have children. There is a form of assisted reproductive technology diagnosis, which screens an embryo in its early stages for genetic mutations combined with in vitro fertilization. This might help parents who have thalassemia or who are carriers of a defective hemoglobin gene have healthy babies. The procedure involves retrieving mature eggs and fertilizing them with sperm in a dish in a laboratory. The embryos are tested for the defective genes, and only those without genetic defects are implanted into the uterus.

Lifestyle and home remedies

You can help manage your thalassemia by following your treatment plan and adopting healthy-living habits.

a) **Avoid excess iron.** Unless your doctor recommends it, don't take vitamins or other supplements that contain iron.
b) **Eat a healthy diet.** Healthy eating can help you feel better and boost your energy. Your doctor might also recommend a folic acid supplement to help your body make new red blood cells. To keep your bones healthy, make sure your diet contains enough calcium and vitamin D. Ask your doctor what the right amounts are for you and whether you need a supplement. Ask your doctor about taking other supplements, as well, such as folic acid. It's a B vitamin that helps build red blood cells.

c) **Avoid infections.** Wash your hands frequently and avoid sick people. This is especially important if you've had your spleen removed. You'll also need an annual flu shot, as well as vaccines to prevent meningitis, pneumonia and hepatitis B. If you develop a fever or other signs and symptoms of an infection, see your doctor for treatment.

Diet for thalassemia

A low-fat, plant-based diet is the best choice for most people, including those with thalassemia. However, you may need to limit iron-rich foods if you already have high iron levels in your blood. Fish and meats are rich in iron, so you may need to limit these in your diet. You may also consider avoiding fortified cereals, breads, and juices. They contain high iron levels, too. Thalassemia can cause folic acid (folate) deficiencies. Naturally found in foods such as dark leafy greens and legumes, this B vitamin is essential for warding off the effects of high iron levels and protecting red blood cells. If you're not getting enough folic acid in your diet, your doctor may recommend a 1 mg supplement taken daily. There's no one diet that can

cure thalassemia, but making sure you eat the right foods can help. Be sure to discuss any dietary changes with your doctor ahead of time.

Treatment options for thalassemia

The treatment for thalassemia depends on the type and severity of disease involved. Your doctor will give you a course of treatment that will work best for your particular case. Some of the treatments include:

- blood transfusions
- bone marrow transplant
- medications and supplements
- possible surgery to remove the spleen or gallbladder

Your doctor may instruct you not to take vitamins or supplements containing iron. This is especially true if you need blood transfusions because people who receive them accumulate extra iron that the body can't easily get rid of. Iron can build up in tissues, which can be potentially fatal. If you're receiving a blood transfusion, you may also need chelation therapy. This generally involves receiving an injection of a chemical that binds with iron and other heavy metals. This helps remove extra iron from your body.

CONCLUSION

The present study shows that behavioral problems prevalence is very high in multi-transfused thalassemic children. Therefore, the periodic assessment of these children for any psychosocial morbidity will help in early diagnosis and treatment. Hence it would improve the mental health and would make them cope with thalassemia and its complex and lifelong management regimen and hence have a better quality of life.

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