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Neurocognitive Function and Its Related Potentials in Children with Beta Thalassemia Major on Regular Blood Transfusion

: Research Presented By

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:Abbreviation

βTM	Beta-thalassemia major
DFO	Deferoxamine
WISC-IV	Wechsler Intelligence Scale for Children
IQ	Intelligence Quotient
Hb	Hemoglobin
VIQ	Verbal Intelligence Quotient
CNS	Central Nervous System
VCI	Verbal Comprehension Index
PRI	Perceptual Reasoning Index
WMI	Working Memory Index
PSI	Processing Speed Index
TIQ	Total Intelligence Quotient

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ABSTRACT

Background: Multiple risk factors in Beta-thalassemia major (βTM) children contribute to the impairment of their neurocognitive function. Multiple studies used different intelligence quotient (IQ) scores to assess the neurocognitive function in thalassemic children ,however, results were variable.

Objective: This study aimed to assess the cognitive functions of thalassemic children and to compare them to a well matched group of healthy controls using the Fourth Edition of the Wechsler Intelligence Scale for Children(WISC-IV(.

Subjects and Methods: A cross-sectional study recruited two groups: Group I included 50 children diagnosed with βTM on regular blood transfusions.Group II included 50 healthy control children with no underlying chronic illness, matching the patient's age, sex, education, school performance. A detailed history was taken, and clinical examination was performed; also, laboratory investigations including full blood picture and serum ferritin were done. Neurocognitive functions were assessed using WISC- IV.

Results: βTM children had no significantly lower IQ scores on cognitive function assessment than healthy children, including the mean of the Full-Scale Intelligence Quotient, as well as the mean scores of the Verbal Comprehension Index, the Processing Speed Index, the Perceptual Reasoning Index, and the Working Memory Index . There was no correlation between IQ scores and the age at the onset of disease, transfusion frequency per year, serum ferritin, onset and duration of chelation, type of chelation, parent's education, and socioeconomic status. However, IQ scores were positively correlated with pre-transfusion Hb, school performance, education, and anthropometric measurements.

Conclusion: We concluded that βTM children have no significantly lower IQ scores than healthy children, and this requires further research.

INTRODUCTION

Beta-thalassemia major (βTM) is a genetic disorder, that is known to cause chronic hemolysis exaggerated by ineffective erythropoiesis causing severe anemia)1) , Patients usually present with severe anemia, jaundice, organomegaly, growth retardation, and skeletal abnormalities. Therefore, they require chronic blood transfusion, which comes with the cost of iron overload and chronic iron deposition in different body organs(3). Neurological complications and cognitive dysfunction have been previously described in βTM patients, either due to the disease or its treatment.

Chronic blood transfusions inevitably lead to iron overload and serious clinical sequelae and patients receiving such transfusions, therefore, require lifelong chelation therapy(1) .There are substantial data demonstrating the efficacy and safety of iron chelation therapy in the treatment of iron overload in regularly transfused patients with β-thalassemia(2,3). Patients with β-thalassemia major (β-TM) have multiple risk factors for developing central nervous system (CNS) complications . 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 βTM(4). Other risk factors forebrain damage include transient ischemic attacks(TIA) ,asymptomatic brain infarcts and visual and auditory toxicity of DFO(5).

The conducted study aims to assess the magnitude of neurocognitive dysfunctions in patients with β-TM and its relation to iron chelating drugs and serum ferritin, using psychometric, neurophysiologic assessment . We aimed to assess cognitive functions in thalassemic children using the Fourth Edition of the Wechsler Intelligence Scale for Children (WISC-IV)

and to compare them to healthy children, and to correlate the results with different clinical variables.

This neurological involvement in βTM patients is primarily silent, with subclinical manifestations that can only be detected by cognitive assessment tests, For this reason, we perform this study to evaluate children with subclinical Manifestations because early recognition may help us to treat them before it's too late.

METHOD

Data Collection:

This cross-sectional study was conducted at Baqubah teaching hospital-hematology center from 1-9-2022 to 1-2-2023. One hundred children were enrolled; at an age range 6 to 16 years, with no sex predilection, divided into two groups; Group I included 50 children diagnosed with βTM receiving regular blood transfusions every 2-8 weeks. Group II included 50 healthy control children with no underlying chronic illness.

Children were excluded from the study if they had :

1-History of exposure to any factor that could affect cognitive function other than thalassemia and its treatment or any physical disability that could impair their performance, such as blindness or deafness.

2-If they hand no education.

All children were subjected to detailed history including: age of diagnosis of β-TM, duration of regular blood transfusion, duration of regular chelation therapy, number of blood transfusions per year. Also if there is any disease complications and school performance. Other investigations were documented from the patient's files including: hemoglobin level in every admission and serum ferritin level for the last 3 months.

-Neuropsychological testing

Wechsler Intelligence Scale for Children third edition Verbal IQ (VIQ) is based on information, similarities, arithmetic, vocabulary and comprehension .Performance (non-verbal) IQ is based on picture completion, coding, picture arrangement, block design and object assembly. Full-scale IQ is based on 10 tests included in the verbal and performance (non-verbal) IQ scales[11].

statistical Analysis:

All the parameters were calculated and All numeric variables were expressed as mean and blotted in the 3 tables below :

variables	Mean(range)
Age of onset (month)	(1-24)8.18
Number of patients with chelating use(n/%)	(60%)30
Number of patients without chelating use(n/%)	(40%)20
Duration of chelating use(year)	(4-11)7.3
Frequency of transfusion per year(n/year)	(6-26)13.54
Regularity of transfusion (week)	(2-8)4.52
Hb level (mg/dl)	(3.7-10)7.3
Serum ferritin (ng/dl)	(202-14.688)2441
Age(year)	(6-16)10

Table 1:show the mean for the different variables in the study

Include 50 samples : Male = 32 , Female = 18

scale	Group I(patients) GI (N=50)		Group II (controls) GII (N=50)	
	Affected	Unaffected	Affected	Unaffected
Verbal Comprehensive Index				
Similarities	_	50	_	50
Vocabulary	_	50	_	50
Comprehension	1	49	_	50
Information	1	49	_	50
Word Reasoning	1	49	_	50
Perceptual Reasoning Index				
Block Design	1	49	_	50
Picture Concepts	_	50	_	50
Matrix Reasoning	1	49	_	50
Picture Completion	_	50	_	50
Working Memory Index				
Digit Span	_	50	_	50
Letter Number Sequencing	1	49	_	50
Arithmetic	_	50		50
Processing Speed Index				
Coding	1	49	_	50
Symbol Search	1	49	_	50
Cancellation	_	50	_	50

Table2 : Wechsler Intelligence Scale (WIS-IV)

Disease Complication	% Number/percentage
Splenomegaly	(10%)5
Splenectomy	(10%)5
Bone Marrow Failure	(4%)2

Table3 : Disease Complications

RESULTS

In this study, 100 children were divided into two groups: group I (50) thalassemic children and group II (50) normal children, in group I mean for the age of onset of affected children, was 8.18 ranging from (1-24) months, and percent of male to female was 64% and mean of age for child included in this study was 10-year .percentage for Patient taken chelating therapy was 60% compared to patients not taking the chelating therapy, and mean for the duration of chelating therapy was 7.3 years ranging (4-11) year, and for frequency of transfusion per year was 13 with transfusion performed every 4 weeks. The mean for Hemoglobin Concentration was 7:3 mg/dl ranging (from 3.7-10) and serum ferritin was 2441 ng/dI ranging (from 202- 14688 number of patients with splenomegaly was 5(10%) and splenectomy was 5 (10%) and those with bone marrow failure was 2(4%)

-For the Wechsler Intelligence Scale assessment Most patients were normal with only 8 patients having Minor abnormalities in one of the parameters of the scale note all the scales as shown in table 2.

DISCUSSION

Multiple risk factors contribute to cognitive impairment in children with β-TM major. For a more refined understanding of this issue, attempts to evaluate cognitive function in β-TM major patients and identify the relationship between possible cognitive dysfunction and transfusion, iron overload, chelating use, and disease complications were done [9].

In this study, using the WISC-IV to compare cognitive functions between thalassemic children and healthy controls, we find that only a minority of patients (only 8) have some defect in single parameters other in one scale of verbal comprehension index (VCI) such as comprehension or defect in one scale of perceptual reasoning index (PRI) or the others and this in

contrast to the study performed in 2022 in Egypt on 50 patients with Beta thalassemia major which fined that there is significant impairment of cognitive function among these patients compared to the healthy control group of 50 children.[16]

Another study performed in 2017 on eighty children diagnosed with Beta thalassemia major showed impaired abstract reasoning, constructional spatial skills, and executive functions, which are more prominent in subjects with hemosiderosis. [17] Forty percent of the cases were borderline mental function for TIQ, while 41% were average TIQ. [18]

another study performed on 100 patients in 2018 Show Similar results to the above two studies [19].

another study in 2022 in India performed on 100 patients showed similar results to this study [20] , this study is recently performed same as this study, for this reason, the result is similar because management protocols for thalassemia have changed over the last few decades and hence no cognitive decline was seen in many previous studies, where newer guidelines have strictly adhered to[10-11].

In regularly transfused and supervised β-thalassemia major, intelligence status is well preserved. IQ correlates with age at diagnosis of β-thalassemia and average annual pre-transfusion hemoglobin. This highlights the importance of early diagnosis and maintenance of satisfactory hemoglobin levels. We did not find any correlation between IQ with age, gender, annual blood requirement, serum ferritin levels, and the type or combination of chelation therapy used. And this may be due to a different lifestyles between the patients in the studies and how they deal with the disease.

In this study, thalassemic children had significantly lower pretransfusion Hb and high mean serum ferritin and were found to have significantly

lower growth parameters (weight, BMI, and height) than healthy children, consistent with former studies[12-13].

The high serum ferritin in thalassemic children was attributed to iron overload associated with repeated blood transfusion, increased gut absorption of iron, and ineffective erythropoiesis [14,15].

Limitations

one of the most important limitations in this study is the limited number of children in our hospital, and the difficulty in handling the children.

Conclusion

Thalassemic children in this study show no significant Cognitive impairment compared to the Control group and this in contrast to other studies performed in Egypt which Show significantly lower Cognitive impairment. so, we need further research on a much larger group of patients so we can cover as many as possible of patients to obtain more accurate results.

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اوصي بأستلام و قبول بحث التخرج للطالبة كوثر احمد محمود بعد اكمالها متطلبات البحث كاملة و دون اي نقص و اكمالها جميع الاحصائيات و التعديلات المطلوبة منها.

ا.د زهراء نجاح خلف