ISSN: 2515-8260 Volume 08, Issue 03, 2021

THE INTELLIGENCE QUOTIENT IN PEDIATRIC TRANSFUSION DEPENDENT AND NON-TRANSFUSION DEPENDENT THALASSEMIA

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ABSTRACT

Background: β-Thalassemia is a hereditary disease. The traditional method of treatment is blood transfusion and iron chelation therapy that may associated with many psychological complications. The aim of our study is to assess the intelligence quotient in patients with transfusion dependent and non-transfusion dependent β-thalassemia. Patients and methods: This study included 36 patients with transfusion-dependent thalassemia, 19 patients with non-transfusion-dependent thalassemia and 37 healthy subjects as a control group. Routine laboratory investigations were done for thalassemic patients according to international standards. Neuropsychologically tests were performed. Results: There is statistically significant difference between the studied groups regarding IQ score. On LSD comparison, the difference is significant between TDT and each of non-TDT and control groups where the lowest IQ prevailed in TDT group. There is statistically significant difference between the studied groups regarding IQ score. Low score presented only in TDT group (47.2%). High average occurred in 11.1% of non-TDT group and 13.9% of control group. Average score was present in 44.4%, 75% and 63.9% of those within TDT, non-TDT and control groups respectively. There is statistically significant difference between the studied groups regarding duration of transfusion (higher in non-TDT group).Conclusion: There is a difference in intelligence quotient and the degree cognitive affection between transfusion-dependent and non-transfusion-dependent β-thalassemia patients. Thus, IQ should be routinely assessed in B-thalassemia major patients for early detection of intellectual impairment and allow for appropriate management, in order to achieve a better life quality for this patients group.

Keywords: Intelligence Quotient; β-Thalassemia, Red Blood Cells

INTRODUCTION

β-Thalassemia is a hereditary disorder characterized by defective production of hemoglobin (Hb) and excessive destruction of red blood cells. The traditional method of treatment is blood transfusion and iron chelation therapy. Patients can suffer many psychological complications, emotional burden, and difficulty in social integration; they can have impaired abstract reasoning and deficits of language, attention, memory, constructional/visual spatial skills, and executive functions, all of which can affect quality of life **(1).**

Thalassemic patients require regular red cell transfusion to eliminate anemia complications and compensatory bone marrow expansion. However, transfusions, combined with excessive iron absorption, lead to iron deposition over various organs, principally the heart, liver, and endocrine glands. Such deposition may ultimately lead to the death of the affected patient if left untreated **(2)**. This repeated blood transfusion is associated with excessive iron absorption, iron overload, chronic

hypoxic state; in addition to neurotoxicity due to lifelong chelating therapy (deferoxamine). All of these factors lead to brain dysfunction **(3)**.

The evidence that silent infarcts occur often in adults and children with thalassemia intermedia and S-thalassemia is surprising. Vaso-occlusive events related to the sickling process in sickle cell anemia. This is not a primary mechanism of thalassemia, suggesting that other mechanisms should be considered as the basis for risk of brain injury in children with thalassemia. The most likely mechanisms would be chronic hypoxia or severe anemia resulting in poor oxygen perfusion, disruption in brain metabolism, or brain atrophy **(4)**.

Neuropsychological tests are safe and reliable for diagnosis of cognitive impairment in b-thalassemia patients, and they may even facilitate early diagnosis. Wechsler Intelligence Scale for Children–Third Edition is the most widely used test for intelligence for school-age children and adolescents **(5)**.

The aim of our study is to The aim of our study is to demonstrate and compare the intelligence quotient in transfusion dependent and non-transfusion dependent β-thalassemia patients and whether they differ in the degree of cognitive affection.

PATIENTS AND METHODS

This was a case-control study included 72 patients with β-thalassemia major who presented to Pediatric Hematology Unit, Faculty of Medicine, Zagazig University in addition to 36 healthy children. Oral consents were obtained from the patients before enrollment in the study and after complete explanation of their task in the research. The study protocol was approved by our ethical committee.

Our study patients were enrolled into Group (A) included thirty six transfusion-dependent β-thalassemia (TDT) patients and Group (B) included thirty six non-transfusion-dependent β-thalassemia (non-TDT) patients.

Inclusion criteria:

Age of patients up to 18 years with Regular blood transfusions (in transfusion-dependent thalassemia group) and iron chelation treatment with no fever. Formal education.

Exclusion criteria:

Patients had history of major mental disorders with delayed milestone development. Patients had physical disabilities that could interfere with performance, such as deafness or blindness. Patients had history of chronic medical illness other than thalassemia that could affect cognition.

Thorough history taking was obtained including: history of any cardiac or chest symptoms e.g. dyspnea, palpitation, chest pain and clinical assessment of cardiac function**,** history of disease related complications, history of concomitant medical conditions e.g. viral hepatitis and splenectomy. Frequency of blood transfusion and pretransfusion hemoglobin level, transfusion iron input in the last 3 months prior to study.

A complete physical examination was performed for all patients by assessing anthropometric measurements (including weight, height, and head circumferences). Calculation of the body weight was done to the nearest 0.1 kg by a standard clinical balance. Measuring standing body height was done to the nearest 0.1 cm by using Holtain Stadiometer. Vital signs, presence of pallor, jaundice, mongoloid facies, spleen and liver status were recorded. Cardiac examination was also performed to detect cardiomegaly, intensity of heart sounds and evidence of murmurs.

Laboratory examinations:

Routine laboratory investigations were done for thalassemic patients according to international standards including Complete blood picture monthly, Serum iron and

ferritin, Total iron binding capacity. Liver function tests (SGOT, SGPT, serum albumin and virology markers for HBV and HCV);Kidney function tests, Blood glucose level; T3, T4 and TSH; Serum calcium and phosphorus all test performed every 3 months.

Neuropsychological evaulation:

The Stanford-Binet intelligence scales (or more commonly the Stanford- Binet) is an individually administered intelligence test that was revised for the original Binet-Simon Scale by Lewis Terman, a psychologist at Stanford University. The Stanford-Binet intelligence Scale is now in its fifth edition (SB5).

Verbal IQ is based on information, similarities, arithmetic, comprehension and digit span. Arithmetic and digit span subtests are measures of working, short, and long-term memory. Performance (non-verbal) IQ is derived from scores on the remaining seven subtests: picture completion, coding, picture arrangement, blockdesign and object assembly. The Object Assembly subtest is a measure of the ability of visualization of item parts of Mazes. The mazes subtest measures perceptual organization, visual-motor coordination, and self-control. The IQ Score was graded based on the following guidelines: 130 and higher: very superior; 120-129: superior 110-119: high average ;90-109: average ;80-89: low average ;70-79: borderline and 69 and lower: extremely low.

Ethical approval:

The study was approved by the Ethical Committee of Zagazig Faculty of Medicine. An informed consent was obtained from all patients in this research. Every patient received an explanation for the purpose of the study. All given data were used for the current medical research only. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

Data analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance; difference and association of qualitative variable by Chi square test (X^2). Differences between quantitative independent groups by t test. Paired by paired t, P value was set at <0.05 for significant results &<0.001 for high significant result.

RESULTS

There is statistically significant difference between the studied groups regarding hepatitis, hepatosplenomegaly, and splenectomy. Hepatitis occurred in 16.7% of TDT group, large HSM occurred in 66.7% within TDT group versus 13.9% within non-TDT group. Eight patients with TDT group were splenectomiozed (22.2%) while no one within non-TDT group had splenectomy. There is statistically non-significant difference between the studied groups regarding diabetes, cardiac complications or BMT **(Table 1)**.

There is statistically significant difference between the studied groups regarding numbness. One third of TDT group had numbness which is significantly higher than those within non-TDT group (16.7% had numbness) while no one in control group had numbness All the studied groups had no neurologic deficits **(Table 2)**.

There is statistically significant difference between the studied groups regarding IQ score. On LSD comparison, the difference is significant between TDT and each of non-TDT and control groups where the lowest IQ prevailed in TDT

group. There is statistically significant difference between the studied groups regarding IQ score. Low score presented only in TDT group (47.2%). High average occurred in 11.1% of non-TDT group and 13.9% of control group. Average score was present in 44.4%, 75% and 63.9% of those within TDT, non-TDT and control groups respectively **(Table 3)**.

There is statistically non-significant difference between the studied groups regarding visual acuity **(Table 4)**. There is statistically non-significant difference between the studied groups regarding formal education **(Table 5)**.

There is statistically significant difference between the studied groups regarding duration of transfusion (higher in non-TDT group). There is statistically significant difference between the studied groups regarding frequency of transfusion. Within TDT group, 27.8%, 22.2% and 50% of them had transfusion once per 2, 3 weeks and once a month respectively. In non-TDT group, 2.8%, 55.6%, 11.1%, 16.7% and 13.9% of them had transfusion once per 2,3,4,5 and 6 months respectively **(Table 6)**.

Table (1): Comparison between the studied groups regarding clinical presentation and BMT:

Transfusion	TDT group N=36(%)	Non-TDT group N=36(%)	Test χ^2	Test p
Hepatitis	6 (16.7)	0 (0)	Fisher	0.025*
Hepatosplenomegaly: Absent Moderate Large	8 (0) 12 (33.3) 16 (66.7)	12 (33.3) 19 (52.8) 5 (13.9)	5.413	0.02*
Splenectomy	8 (22.2)	0 (0)	Fisher	0.005*
Diabetes	2 (5.6)	0 (0)	Fisher	0.493
Cardiac complication	3 (8.3)	0 (0)	Fisher	0.239
BMT	3 (8.3)	0 (0)	Fisher	0.239

χ^2Chi square test, *p<0.05 is statistically significant. TDT group: transfusion dependent thalassemia group, non-TDT group: non-transfusion dependent thalassemia group

Table (2): Comparison between the studied groups regarding numbness and neurologic deficits:

Numbness	Groups TDT group N=(%)	Non-TDT group N=36(%)	Control group N=36(%)	Test χ^2	Test p
Absent **Present**	24 (66.7) 12 (33.3)	30 (83.3) 6 (16.7)	36 (100) 0 (0)	14.4	<0.001**
p	P_1 0.102	P_2 0.024*	P_3 0.001**		
Neurologic deficits Absent	36 (100)	36 (100)	36 (100)		

χ^2Chi square test, *p<0.05 is statistically significant, TDT group: transfusion dependent thalassemia group, non-TDT group: non-transfusion dependent thalassemia group.

Table (3): Comparison between the studied groups regarding IQ and score

IQ	Groups			Test	
	TDT group	Non-TDT group	Control group	χ^2/F	p
	N=(%)	N=(%)	N=(%)		
Mean ± SD **Range**	87.75±5.88 76 – 100	96.39±7.1 79 – 110	96.56 ±8.22 79 – 110	17.975	<0.001**
LSD	P_1<0.001**	P_2 0.921	P_3<0.001**		
Score: **High average** **Average** **Low average** **Borderline** **Low**	 0 (0) 16 (44.4) 0 (0) 3 (8.3) 17 (47.2)	 4 (11.1) 27 (75) 4 (11.1) 1 (2.8) 0 (0)	 5 (13.9) 23 (63.9) 7 (19.4) 1 (2.8) 0 (0)	49.812	<0.001**

F One way ANOVA χ^2Chi square test *p<0.05 is statistically significant **p≤0.00 is statistically highly significant LSD Fisher least significant difference TDT group: transfusion dependent thalassemia group non-TDT group: non-transfusion dependent thalassemia group P_1 the difference between TDT and non-TDT groups P_2 the difference between non-TDT and control groups P_3 the difference between TDT and control groups.

Table (4): Comparison between the studied groups regarding visual acuity:

Visual acuity	Groups			Test	
	TDT group	Non-TDT group	Control group	χ^2	p
	N=36(%)	N=36(%)	N=(%)		
Low **Normal**	2 (5.6) 34 (97.2)	0 (0) 36 (100)	1 (2.8) 35 (97.2)	MC	0.774

χ^2Chi square test MC Monte Carlo test TDT group: transfusion dependent thalassemia group non-TDT group: non-transfusion dependent thalassemia group

Table (5): Comparison between the studied groups regarding formal education

Formal education	Groups			Test	
	TDT group	Non-TDT group	Control group	χ^2	p
	N=36(%)	N=36(%)	N=36(%)		
Low **Normal**	6 (16.7) 30 (83.3)	6 (16.7) 30 (83.3)	5 (13.9) 31 (76.1)	0.14	0.933

χ^2Chi square test, MC Monte Carlo test, TDT group: transfusion dependent thalassemia group, non-TDT group: non-transfusion dependent thalassemia group.

Table (6):Comparison between the studied groups regarding need for blood transfusion:

Transfusion	Groups		Test	
	TDT group	Non-TDT group	Z/χ^2	p
	N=(%)	N=(%)		
Duration (month): Median (range)	6 (2 – 24)	42 (24 – 156)	-7.286	<0.001**
Frequency (once/):				
/2 weeks	10 (27.8)	0 (0)		
/3 weeks	8 (22.2)	0 (0)		
/1 month	18 (50)	0 (0)		
/2 months	0 (0)	1 (2.8)		
/3 months	0 (0)	20 (55.6)		
/4 months	0 (0)	4 (11.1)	53.769	<0.001**
/5 months	0 (0)	6 (16.7)		
/ 6 months	0 (0)	5 (13.9)		
Amount (unit) Median (range)	1 (0.5 – 1)	1 (0.5 – 1)	-1.694	0.09

Z Mann Whitney test,χ^2 Chi square for trend test, **p≤0.001 is statistically highly significant, TDT group: transfusion dependent thalassemia group, non-TDT group: non-transfusion dependent thalassemia group.

DISCUSSION

Intelligence is an umbrella term describing a property of the mind including related abilities, such as the capacities for abstract thought, understanding, reasoning, planning, problem solving, communication, learning, and learning from the experience. An intelligence quotient, or IQ, is a score derived from one of several different standardized tests designed to assess intelligence **(6)**.

Seventy two patients with β-thalassemia major were included in this study. The patients were divided into two groups: Group A consisted of thirty six transfusion-dependent β-thalassemia patients and group B consisted of thirty six non-transfusion-dependent β-thalassemia patients. Thirty six age- and sex-matched healthy children served as a control group. The aim of this study was to assess the intelligence quotient in patients with transfusion dependent and non-transfusion dependent β-thalassemia.

Regarding clinical presentation and BMT, there is statistically significant difference between the studied groups regarding hepatitis, hepatosplenomegaly, and splenectomy. Hepatitis occurred in 16.7% of TDT group, large HSM occurred in 66.7% within TDT group versus 13.9% within non-TDT group. Eight patients with TDT group were splenectomiozed (22.2%) while no one within non-TDT group had splenectomy. But, there is statistically non-significant difference between the studied groups regarding diabetes, cardiac complications or BMT.

In an Egyptian study, **Raafat et al. (7)** reported growth retardation in 42%, hemosiderosis in 46%, hypogonadism in 22%, and hypoparathyroidism in 6%, hypothyroidism in 4%, cardiac complication in 6%. These findings were in agreement with **El-Alameey et al. (8)** who found that thalassemic patients had disease complications in the form of splenectomy that was present in 32%, hemosiderosis in 46%, hypogonadism in 28%, and hypoparathyroidism in 16%.

Cardiac complications were observed only in 3 transfusion-dependent thalassemic patients (8.3%). Our result in consistence with that observed by **Cunningham et al. (9)** found that 5% of patients had heart disease. On the other

hand, higher prevalence of cardiac complications was reported by **Borgna-Pignatti et al. (10) and Monastero et al. (11)** were 12% and 19.6% respectively.

Thalassemia can affect growths in the fetal, infancy, pre-puberty and puberty periods. The principal cause of growth disorders in β-thalassemia major patients are influenced by many factors and still debated. High serum ferritin levels and iron overload in puberty were reported to cause short stature and delayed body growths in thalassemia major patients. Iron overload can prohibit bone metabolisms leading to growth disorders **(12)**.

Raafat et al. (7) found marked lower performances and full-scale IQ scores and no apparent variations in verbal IQ scores in thalassemic patients' group in comparison to control group. In another study, **Economou et al. (13)** studied the IQs of children with β-thalassemia major using WISC III and said that those children had higher scores on the verbal scale than Full and performance scales, and claimed that β-thalassemia probably had increased impairments in cognitive performance.

Other studies reported impairment of full-scale IQ (including both verbal and performance components) in children with β-thalassemia major. **Duman et al. (14)** had evaluated cognitive function in 20 children with β-thalassemia major and 21 healthy controls and found that Full-Scale IQ, verbal IQ, and performance IQ ($P < 0.05$) were markedly lower in the patients.

Homayouni et al. (15) reported that the verbal IQ subsets of β-thalassemic children were significantly lower than that of healthy group in terms of information, arithmetic, comprehension, digit span, and the performance IQ subsets as picture completion, symbol search and mazes subscales of β-thalassemic children were significantly lower than that of healthy controls.

In our study, low score presented only in TDT group (47.2%). High average occurred in 11.1% of non-TDT group and 13.9% of control group. Average score was present in 44.4%, 75% and 63.9% of those within TDT, non-TDT and control groups respectively. **Canatan et al. (16)** reported that academic problems were found in 60% of a sample population of thalassemic children. Therefore, there is a little caring about the quality of education of those children. **El-Alameey et al. (8)** found that three patients (6%) were superior, (8%) of patients with high average full IQ scores, (34%) average, (22%) patients with low average, and (14%) patients with extremely low full IQ scores.

CONCLUSION

There is a difference in intelligence quotient and the degree cognitive affection between transfusion-dependent and non-transfusion-dependent β-thalassemia patients. Thus, IQ should be routinely assessed in B-thalassemia major patients for early detection of intellectual impairment and allow for appropriate management, in order to achieve a better life quality for this patients group.

No conflict of interest.

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