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Neurocognitive Function and Its Related Potentials in Children with Beta Thalassemia Major: An Egyptian Study

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Keywords: β-Thalassemia; Neurocognitive; Children; Egyptian; Potentials

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Abstract

BACKGROUND: Repeated blood transfusions and hemolysis in β-Thalassemia major children lead to iron overload in various organs, including the brain which may cause neurodegeneration.

AIM: To evaluate intelligence quotient in children with β-thalassemia major and healthy counterparts and to assess risk factors that cause cognitive problems.

SUBJECTS AND METHODS: This case-control study was performed on 50 children aged 6-16 years old with β-thalassemia major as patients group and compared with 50 healthy children as a control group of matched age, sex, and social class. Cognitive functions were evaluated by using the Wechsler Intelligence Scale for Children. Serum ferritin and iron were measured by ELISA.

RESULTS: There were significantly lower mean performance and full-scale IQ scores of patients group in comparison with controls, whereas no significant differences between both groups as regards to a verbal IQ score. In thalassemic children, block design, comprehension and arithmetic were negatively correlated with age of disease onset, duration of illness and onset of chelation therapy. Serum iron and ferritin were negatively correlated with similarities and digit span. Serum iron levels were negatively correlated with performance IQ score.

CONCLUSION: Children with β-thalassemia major need to receive more academic attention and cognitive assessment to improve their IQ.

Introduction

β-Thalassemia major is a chronic hematologic disease of a genetic basis that is characterised by ineffective erythropoiesis, peripheral hemolysis, and severe anaemia [1]. It is the commonest chronic hemolytic anaemia in Egypt (85.1%), with a carrier rate about 9% to 10.2% from an examination of 1000 normal random subjects from different geographic areas of the country [2].

The affection of the nervous system in those patients can be attributed to many factors acting as several cumulative small injuries to the central nervous system over many years such as hemolysis and repeated blood transfusions which lead to a decrease in nitric oxide levels and iron overload in several organs, including the brain. Also, increased iron in the brain leads to oxidative stress and possible irreparable brain tissue damage, causing cognitive impairment [3], [4]. Thalassemic patients are dependent on regular blood transfusion to decrease complications of anaemia and expand bone marrow [5]. This repeated blood transfusion is associated with excessive iron absorption [6], iron overload, chronic hypoxic state; in addition to neurotoxicity due to lifelong chelating therapy (deferoxamine). All of these factors lead to brain dysfunction [7], [8]. Metafratzi et al., [9] stated that there was high iron deposition in the putamen, caudate nucleus, motor and temporal cortex of patients with β-Thalassemia major. These areas are extremely important for cognitive function as for implicit and explicit memory. Other risk factors for brain damage include transient ischemic attacks, asymptomatic brain infarcts and visual and auditory toxicity of deferoxamine [10]. In another study, Economou et al., [11] demonstrated subclinical involvement of central and peripheral neural pathways in β-Thalassemia major patients and recommended regular intellectual monitoring using the Wechsler

Intelligence Scale, for early detection of any intellectual dysfunction in young β-Thalassemia major patients [12].

Therefore, this study aimed to evaluate the neurocognitive function in β-thalassemia major patients and recognising the correlation between possible neurocognitive dysfunction and various clinical parameters as the age of disease onset, the frequency of blood transfusion, iron chelating drugs, and serum ferritin, iron, and haemoglobin concentration of the patients.

Subjects and Methods

Subjects

A descriptive case-control study was conducted in the outpatient Child Health Clinic in Centre of Medical Excellence, National Research Center, Egypt, throughout 8 months. One hundred children; 50 children with b-thalassemia major (25 boys, and 25 girls; mean age, 9.57 ± 1.33 years; range, 6-16 years), were enrolled into this study and referred from the Pediatric Clinical Hematology Outpatient Clinic at Ain Shams University Hospital in Egypt. They were compared with a group of 50 healthy children with matched age, sex, educational level, parental education, and years of schooling, and socioeconomic level, which were cognitively and neurologically normal, acting as healthy volunteers. Their past medical history and clinical examination were revised for confirmation of being and their first-degree relatives completely free of any chronic disorders, including thalassemia.

The inclusion criteria comprised of children diagnosed with β-thalassemia major aged between 6-16 years with regular blood transfusions and iron chelation treatment, formal education, and no fever. The exclusion criteria were as follows: (a) had history of major mental disorders with delayed milestone development; (b) had physical disabilities that could interfere with performance, such as deafness or blindness; (c) had received prior treatment with drugs known to be neurotoxic; or (d) had history of chronic medical illness other than thalassemia that could affect cognition. Children in β-thalassemia major group were receiving blood once a month regularly to maintain their haemoglobin concentration at more than 9 gm/dl level, and they were taking deferoxamine as medication.

Written informed consent was taken from all patients' guardians before participation in the study and after complete explanation of their task in the research. The consent was approved by The Ethical Committee of The National Research Center and Ain Shams University under the registration number 16358.

Methods

Clinical assessment and anthropometric measurements

Full medical history, complete data on transfusion and chelation regimens were taken from all patients. Clinical examination was performed with special emphasis on disease-related complications and chelation therapy-related side effects. Anthropometric measurements including weight, height, and head circumferences were assessed for all the studied subjects at the National Research Centre. 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. Recalibration of all scales took place after each measurement following the recommendations of the International Biological Program [13]. Calculation of the subjects' body mass index (BMI) was done by using the formula of weight/height^2 (kg/m^2).

Laboratory investigation

After an overnight fast, venous blood samples were withdrawn from all participants and the separated sera were stored at −20°C. Routine laboratory investigations were done for thalassemic patients according to international standards, including complete blood picture, serum ferritin, and iron using enzyme-linked immunosorbent assay ELISA kit obtained from Glory Bioscience, (USA), according to manufacturer's manual.

Neuropsychological testing

All the patients and controls were subjected to IQ evaluation by using the Arabic version of the Wechsler Intelligence Scale for Children-Third Edition, (WISC-R) [14]. This test assesses the intelligence of children in three scales of full IQ, verbal IQ and performance IQ. Full-scale IQ is based on 10 tests incorporated in the verbal and performance (non-verbal) IQ scales. The administration time for the test was approximately 60 to 90 minutes. The child was allowed to complete the test in 2 separate sessions.

Verbal IQ is based on information, similarities, arithmetic, comprehension and digit span. The Comprehension subtest is a scale of the student's social knowledge and the depth of development of morals. Similarities subtest is a measure of logic, abstract thinking and verbal reasoning, while information is a scale of general knowledge, education, and long-term memory of his experience. Arithmetic and digit span subtests are measures of working, short, and long-term memory.

Performance (non-verbal) IQ is based on picture completion, coding, picture arrangement, block

design and object assembly. Block Design measures the ability to analyse and synthesise an abstract design, and production of the design from coloured plastic. The Picture Completion subtest is a measure of a student's capability of recognising closely related items. The Object Assembly subtest is a measure of the ability of visualisation of item parts of Mazes. The mazes subtest measures perceptual organisation, visual-motor coordination, and self-control.

Interpretation of IQ Score

The IQ 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;
- 69 and lower: extremely low.

Statistical Analysis

SPSS version 22 (SPSS Inc, Chicago) was used to enter, check and analyse data. Results were expressed as mean ± standard deviation (SD) for quantitative variables and as number and percentage for qualitative ones. Based on the calculated required sample size, our study included 50 subjects with β-thalassemia major. The marked differences in means for IQ between patients and controls and between males and females were analysed by unpaired Student t-test. Association between qualitative variables was done using a Chi-Squared test. Correlation between IQ and other parameters were investigated using Pearson coefficient of correlation. A p-value < 0.05 was considered significant and p < 0.01 was considered highly significant.

Results

The education level, school performance and disease complications of the two groups are shown in Table 1. In the present study, all candidates were between 6 and 16 years old. Both patients and control groups were matched as regards their age, sex, educational level, parental education, and socioeconomic status. Lower school performance, growth retardation, and positive family history of thalassemia were significantly more common in the patient's group compared to the control group. 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%.

Table 1: Education level, school performance and disease complications of the two groups

Variables		Patients group N (%)	Control group N (%)
Education level	Uneducated	4 (8%)	4 (8%)
	Read and write only	8 (16%)	13 (26%)
	Educated	38 (76%)	33 (66%)
School performance	Poor	18 (36%)	15 (30%)
	Average	22 (44%)	17 (34%)
	Above average	10 (20%)	18 (36%)
Disease complications	Positive family history	30 (60%)	0 (0%)
	Positive consanguinity	29 (58%)	0 (0%)
	Bone fracture	24 (48%)	8 (16%)
	Splenectomy	16 (32%)	0 (0%)
	Mongoloid facies	15 (30%)	0 (0%)
	Hemosidrosis	23 (46%)	0 (0%)
	Growth retardation	21 (42%)	6 (12%)
	Hypogonadism	14 (28%)	0 (0%)
	Hypoparathyroidism	8 (16%)	0 (0%)
	Hypothyroidism	25 (50%)	0 (0%)

In thalassemic patients group, the mean age at onset of symptoms was 7 ± 1.4 months, and the mean duration of illness was 9.89 ± 4.4 years. The mean frequency of blood transfusion per year is 4.08 ± 1.31times and range from 2 to 8 years. The mean duration of chelation therapy is 9.16 ± 4.43 years. Eighty-four per cent of the patients were on chelation therapy, in the form of deferoxamine as shown in Table 2.

Table 2: Clinical characteristics of the studied patients

Variables	Range	Patients group Mean ± SD
Age (years)	6-16	11.05 ± 3.83
Age at onset (months)	6-8	7 ± 1.4
Duration of illness (years)	2-15	9.89 ± 4.30
Duration of chelation therapy (years)	6-16	9.16 ± 4.43
The frequency of blood transfusion per year	2-8	4.08 ± 1.31

The mean and standard deviation of the age of children with β-thalassemia major was 9.57 ± 1.33, and that of the healthy children was 9.5 ± 1.31. In thalassemic patients group, the mean weight, and BMI (P < 0.01) were significantly lower compared to the control group. The mean serum levels of iron, and ferritin (P < 0.01) were significantly higher, while haemoglobin concentration (P < 0.01) was significantly lower compared to the control group as shown in Table 3.

Table 3: Comparison of anthropometric measures and laboratory investigations of patients group and control group

Variables	Control group Mean ± SD	Patients group Mean ± SD	t-test	P-value
Age (years)	9.5 ± 1.31	9.57 ± 1.33	0.36	0.24
Weight (kg)	44.18 ± 15.54	30.64 ± 11.15	-5.006	0.000**
Height (cm)	139.46 ± 15.07	134.62 ± 17.12	-1.5	0.137
BMI	22.18 ± 5.39	16.52 ± 2.69	-6.638	0.000**
Head circumference (cm)	52.62 ± 1.7	52. 28 ± 2.78	0.346	0.73
Hb concentration (gm/dl)	12.96 ± 1.12	11.024 ± 2.16	-3.334	0.001**
Serum ferritin (ng/ml)	142.44 ± 69.66	2453.36 ± 1297.12	12.580	0.000**
Serum iron (mcg/dl)	94.20 ± 32.16	233.09 ± 67.47	13.138	0.000**

*Significant difference at p < 0.05; **highly significant difference at p ≤ 0.01.

The mean performance IQ score (86.10 ± 20.13) of cases (P < 0.01) are significantly less than those of controls (100.98 ± 7.06), and the mean total IQ score (92.86 ± 17.72 and 101.42 ± 6.47, respectively; P < .05; whereas there is no significant difference among patients group and control group as regards to verbal IQ score (100.10 ± 16.49, and

102.30 ± 6.98, respectively; P > 0.05). The mean scores of comprehensions, similarities, digit span tests (verbal IQ subsets) of patients group are significantly lower than those of controls. The object assembly, coding, and mazes (performance IQ subsets) of patients group are significantly lower than those of controls. Comparison of verbal, performance, and full IQ scores and its subsets between patients group and control group are presented in Table 4.

Table 4: Comparison of IQ scores and its subsets between patients group and control group

Variables	Control group (N = 50) Mean ± SD	Patients group (N = 50) Mean ± SD	t-test	P value
Verbal IQ scores	102.30 ± 6.98	100.10 ± 16.49	-0.869	0.387
Information	9.72 ± 3.57	9.96 ± 1.71	-0.429	0.669
Comprehension	12.50 ± 4.86	10.70 ± 1.94	2.433	0.017*
Arithmetic	7.60 ± 3.37	7.54 ± 2.27	0.104	0.917
Similarities	11.60 ± 3.61	10.16 ± 1.83	2.513	0.014*
Digit span	5.84 ± 2.98	4.76 ± 1.66	2.239	0.027*
Performance IQ scores	100.98 ± 7.06	86.10 ± 20.13	-4.932	0.000**
Picture completion	8.02 ± 2.06	7.70 ± 3.01	-0.622	0.536
Block design	6.88 ± 3.27	6.28 ± 1.45	-1.186	0.239
Object assembly	6.82 ± 0.87	5.70 ± 3.41	-2.252	0.027*
Coding	10.20 ± 2.88	7.68 ± 4.78	-3.194	0.002**
Mazes	10.32 ± 1.88	8.98 ± 4.22	-2.053	0.043*
Full IQ scores	101.42 ± 6.47	92.86 ± 17.72	-3.209	0.002**

*Significant difference at p < 0.05; **highly significant difference at p ≤ 0.01.

A significant difference exists between males and females groups as regards digit span and mazes (P < 0.01). No significant difference present among male and female patients in other verbal performance, full IQ scores, and other IQ subtests (P > 0.05) as demonstrated in Table 5.

Table 5: Comparison between males and females as regard to IQ scores in patients group

Variables	Males Mean ± SD	Females Mean ± SD	t-test	P value
Verbal IQ scores	101.08 ± 17.71	99.12 ± 15.48	0.417	0.679
Information	10.00 ± 4.12	9.44 ± 2.97	0.551	0.584
Comprehension	13.32 ± 5.09	11.68 ± 4.57	1.199	0.236
Arithmetic	8.12 ± 3.32	7.08 ± 3.04	1.094	0.280
Similarities	11.76 ± 3.88	11.44 ± 3.4	0.310	0.758
Digit span	6.68 ± 3.08	5.00 ± 2.68	2.059	0.045*
Performance IQ scores	87.04 ± 20.42	85.16 ± 20.21	0.327	0.745
Picture completion	8.12 ± 3.47	7.28 ± 2.46	0.988	0.328
Block design	6.72 ± 3.62	5.84 ± 2.88	0.950	0.347
Object assembly	5.80 ± 3.77	5.60 ± 3.07	0.206	0.838
Coding	7.52 ± 4.16	7.84 ± 5.41	0.234	0.816
Mazes	10.16 ± 4.54	7.80 ± 3.57	2.042	0.047*
Full IQ scores	93.76 ± 18.82	91.96 ± 16.89	0.356	0.723

*Significant difference at p < 0.05.

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 as shown in Table 6.

Table 6: Distribution of IQ grades among the patient's groups

Variable	Very superior	Superior	High average	Average	Low average	Borderline	Extremely low
Full IQ scores	0 (%)	3 (6%)	4 (8%)	17 (34%)	11 (22%)	8 (16%)	7 (14%)

In thalassemic children, block design (one of performance IQ subsets), and comprehension and arithmetic (some verbal IQ subsets) were negatively correlated with age of disease onset, duration of illness and chelation therapy. No significant correlation is found between IQ scores (Verbal, performance, and full-Scale) and frequency of transfusion as shown in Table 7.

Table 7: Correlation between cognitive variables with some clinical variables

Variables		Age of disease onset	Duration of illness	Duration of chelation therapy	The frequency of blood transfusion/ year
Verbal IQ score	Pearson correlation	0.052	0.037	0.053	-0.089
	P- value	0.719	0.799	0.717	0.537
Information	Pearson correlation	0.007	-0.021	-0.011	0.014
	P- value	0.962	0.887	0.938	0.925
Comprehension	Pearson correlation	-0.406**	-0.379**	-0.382**	-0.023
	P- value	0.003	0.007	0.006	0.877
Arithmetic	Pearson correlation	-0.374**	-0.387**	-0.366**	-0.099
	P- value	0.007	0.006	0.009	0.493
Similarities	Pearson correlation	0.114	0.090	0.102	-0.127
	P- value	0.431	0.533	0.480	0.379
Digit span	Pearson correlation	-0.161	-0.214	-0.205	0.182
	P- value	0.265	0.136	0.153	0.207
Performance IQ score	Pearson correlation	-0.159	-0.196	-0.180	-0.017
	P- value	0.271	0.174	0.212	0.909
Picture completion	Pearson correlation	0.000	-0.095	-0.087	0.162
	P- value	0.998	0.512	0.549	0.261
Block design	Pearson correlation	-0.411**	-0.475**	-0.459**	-0.034
	P- value	0.003	0.000	0.001	0.815
Object assembly	Pearson correlation	-0.077	-0.137	-0.128	-0.132
	P- value	0.596	0.344	0.376	0.361
Coding	Pearson correlation	-0.133	-0.210	-0.196	-0.205
	P- value	0.357	0.144	0.172	0.153
Mazes	Pearson correlation	0.027	0.006	0.005	0.108
	P- value	0.851	0.967	0.975	0.457
Full IQ score	Pearson correlation	-0.092	-0.117	-0.099	-0.045
	P- value	0.525	0.418	0.493	0.755

**Highly significant difference at p ≤ 0.01.

Anthropometric measures as weight, and height were positively correlated with some verbal IQ subsets as comprehension and arithmetic as well as block design (one of performance IQ subsets). BMI is positively correlated with performance IQ and some of its subsets as block design and coding as well as some verbal IQ subsets as comprehension and arithmetic. Head circumference was positively correlated with arithmetic (verbal IQ subset), and coding (performance IQ subset). There were significant negative correlations between serum ferritin levels and comprehension, similarities, and digit span (some of the verbal IQ subsets). Serum total iron was negatively correlated with a performance IQ score, similarities, and digit span (some of the verbal IQ subsets). Haemoglobin concentration was positively correlated with digit span (verbal IQ subset), and object assembly (performance IQ subset) as shown in Table 8.

Discussion

Multiple risk factors contribute to cognitive impairment in β-thalassemia major patients [15]. Duman et al., [12], Vichinsky et al., [16] denoted the involvement of the nervous system in b-thalassemia major patients. They attributed the neurological problems to several causes as iron overload, bone marrow expansion, chronic hypoxia and desferrioxamine neurotoxicity in thalassemia patients.

In our study, a positive family history of β-thalassemia major was present in 60%, and positive consanguinity in 58%. Disease complications in thalassemic patients were found in the form of splenectomy that was present in 32%, growth retardation in 26%, hemosiderosis secondary to long term blood transfusion in 46%, hypogonadism 28%, and hypoparathyroidism in 16%. These findings were in agreement with Egyptian study done by Raafat et al., [17] who reported growth retardation in 42%, hemosiderosis in 46%, hypogonadism in 22%, and hypoparathyroidism in 6%, hypothyroidism in 4%, cardiac complication in 6%.

Ferritin is a protein that stores iron and exists in all tissues including the brain. Serum ferritin level is a good marker for assessing body iron stores [18]. In our study, the mean levels of serum iron, and ferritin were markedly higher, while haemoglobin concentration was significantly lower in thalassemic patients group in comparison to control group. These results come in agreement with the previous study by Fadlyana et al., [19] who assessed patients with beta-thalassemia major, registered at 2 different centres of Rawalpindi and Islamabad. They stated that the majority of patients demonstrated very high ferritin levels, in which 76% of patients had values above 250 mg/L. The high level of ferritin in beta-thalassemia can be attributed to repeated blood transfusions, ineffective erythropoiesis, and increased gastrointestinal iron absorption which causes iron overload in the body.

Thalassemia can affect growths in the fetal, infancy, pre-puberty and puberty periods [20]. The principal cause of growth disorders in β-thalassemia major patients are influenced by many factors and still debated [21]. High serum ferritin levels and iron overload in puberty were reported to cause short stature and delayed body growths in thalassemia major patients [22]. Iron overload can prohibit bone metabolisms leading to growth disorders [23], [24]. In our present study, as thalassemia is a chronic form of anaemia, the weight difference is expected compared to control. The anthropometric measures as weight and BMI were affected and significantly lower in thalassemic patients compared to controls ($P < 0.01$).

Our study analyzed the intelligence quotient of β-thalassemia major patients and healthy peers in terms of full, verbal and performance scales of IQ using 10 subscales of Wechsler IQ test for children and demonstrated that β-thalassemia major patients had marked lower performances and full-Scale IQ scores compared to controls; while, there was no difference in Verbal IQ between patients and controls. These results were compatible with Egyptian study done by Raafat et al., [17] who 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., [11] 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. These results about higher verbal scale scores are also similar to our results.

Our results partly came in agreement with those of other studies that reported impairment of full-scale IQ (including both verbal and performance components) in children with β-thalassemia major. Duman et al., [12] 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. In another study, Monastero et al., [25] assessed cognitive function in 46 β-thalassemia major patients and 46 controls of matching age, sex, and education and found that the β-thalassemia major patients, particularly those having signs of hemosiderosis, were profoundly affected on all neuropsychological tests. However, our results were not in agreement with Vichinsky et al., [16] as regards the verbal scale. Conversely, Karimi et al., [26] stated that there is no significant difference in IQ between patients of β-thalassemia major and controls. Again, Khairkar et al., [27] reported normal IQ in β-thalassemia major patients.

In our present study, the mean scores of comprehensions, similarities, digit span tests (verbal IQ subsets) of patients group are markedly lower than those of controls. The object assembly, coding, and mazes (performance IQ subsets) of patients group are significantly lower in comparison to those of controls. These findings agreed with Homayouni et al., [28], who 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, three patients (6%) were superior, (8%) of patients had high average full IQ scores, (34%) average, (22%) patients with low average, and (14%) patients with extremely low full IQ scores. Canatan et al., [29] reported that academic problems were found in 60% of a sample population of thalassemic children. These findings suggest that there is a little caring about the quality of education of those children.

Economou et al., [11] who demonstrated no association between gender of the patients and abnormal IQ in β-thalassemia major. In our study, there was a marked difference between male and female groups as regards digit span and mazes ($P < 0.01$); but, there was no marked difference between gender of the patients and other verbal IQ, performance IQ, and full-scale IQ subtests.

This study discovered a positive correlation

between weight and height with some verbal IQ subsets as comprehension and arithmetic as well as block design (one of performance IQ subsets). Body mass index (BMI) is positively correlated with performance IQ and some of its subsets as block design and coding as well as some verbal IQ subsets as comprehension and arithmetic. Head circumference was positively correlated with arithmetic (one of the verbal IQ subsets), and coding (one of performance IQ subsets). To our knowledge, the association between anthropometric measures as weight, height, BMI, head circumferences and abnormal IQ scores in the patients of β-thalassemia major has not yet been investigated.

In our study, the influence of age of onset of symptoms, frequency of blood transfusion/ year, duration of illness, and chelation therapy and the effect of concentration of haemoglobin, serum iron, and ferritin levels on IQ scores of the patients were also examined. The reasonable clarification for lower mean performance IQ in our study, in comparison to that of verbal IQ, comes from the study of Ai et al., [18] on 171 Chinese children who found that children with low haemoglobin concentration had marked lower scores in performance IQ but not in verbal IQ. They explained this by that the low Hb concentration could have affected the brain areas that are responsible for performance IQ components during the critical stage of development in early childhood. This explanation can be applied to patients of β-thalassemia major who suffered from severe anaemia in their early childhood.

In our study, there were significant negative correlations between serum ferritin levels and comprehension, similarities, and digit span (some of the verbal IQ subsets). Serum total iron was negatively correlated with a performance IQ score, similarities, and digit span (some of the verbal IQ subsets). Haemoglobin concentration was positively correlated with digit span (verbal IQ subset), and object assembly (performance IQ subset). These findings agreed with Duman et al., [12] and Vichinsky et al., [16] who found a marked negative correlation between serum ferritin concentrations with some cognitive function. These findings can be attributed to marked erythropoiesis and hemolysis. On the contrary with our study, Shehata et al., [30] stated that there is no important correlation between IQ (verbal, performance, and full-scale) and age of onset of transfusion, onset of chelation therapy, chelation compliance, and serum ferritin levels. Besides, there was no marked correlation between IQ and chelation therapy type.

In our study, abnormal block design (one of performance IQ subsets), and comprehension and arithmetic (some verbal IQ subsets) were negatively correlated with age of disease onset, duration of illness and onset of chelation therapy in thalassemic children. No significant correlation is found between IQ scores (verbal, performance, and full-Scale) and frequency of transfusion. Our results were not compatible with Economou et al., [11] who claimed no significant relation between abnormal IQ in β-thalassemia major patients and serum ferritin levels, the age of onset of symptoms, the onset of transfusion, the onset of chelation therapy, chelation compliance, type of chelation therapy, and disease complications.

In conclusion, this study concluded that performance IQ, not verbal IQ is significantly affected in the studied children with β-thalassemia major being affected by long duration of illness, and the onset of chelation therapy, and high serum ferritin and iron levels. Cognitive assessment is easy to be done, and β-thalassemia major children with learning problems need to receive more academic attention in order to improve their performance IQs.

Recommendation: Intelligence quotient tests should be a part of routine comprehensive care of β-thalassemia major patients especially cases of learning difficulties to detect cases that suffering from verbal or performance dysfunction and to be subject to the learning skills development program.

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