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# Cognitive Function Assessment in Paediatric Patients with Beta-Thalassemia Major

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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 thalassaemic 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 patients' age, sex, education, parent's education, school performance, and socioeconomic level. 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 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 ($P<0.01$). 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, parents' education, and socioeconomic status. However, IQ scores were positively correlated with pretransfusion Hb, school performance, education, and anthropometric measurements.

**Conclusion:** We concluded that βTM children have significantly lower IQ scores than healthy children, and this requires attention for neuropsychological assessment of thalassemic children early in life to provide adequate support.

**Keywords:** β-Thalassemia; Cognitive function; Intelligence Quotient; Fourth Edition of the Wechsler Intelligence Scale for Children; WISC- IV.

## INTRODUCTION

Beta-thalassemia major (βTM) is a genetic disorder, that is known to cause chronic hemolysis exaggerated by ineffective erythropoiesis causing severe anemia [1]**.** It is the most prevalent chronic hemolytic anemia in Egypt (85.1%), a previous epidemiological study estimated the carrier rate of thalassemia in 1000 normal subjects was found to be 9-10.2%[2]**.**

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. Many risk factors were reported, including chronic hypoxia, iron deposition in the nervous system due to frequent blood transfusions, silent thromboembolism, and the neurotoxicity of Deferoxamine [4]. Furthermore, frequent school absences, frequent hospitalizations, and physical and social restrictions also lead to cognitive dysfunction [5]**.**

This neurological involvement in βTM patients is primarily silent, with subclinical manifestations that can only be detected by cognitive assessment tests, as demonstrated by *Economou et al.,* who recommended regular neurophysiological assessment by using the Third Edition of the Wechsler Intelligence Scale for Children (WISC-III) for early recognition of intellectual dysfunction in thalassemic children [6]**.**

Multiple studies have been performed to assess cognitive functions in thalassemic children using WISC-III. These studies showed significantly different results between patients and controls regarding the subsets of intelligence quotient (IQ) [7–12].

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.

## SUBJECTS AND METHODS

### *Subjects*

This cross-sectional study was conducted at the outpatient Paediatric Haematology Clinic at Benha University Hospitals from February 2022 to August 2022. 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.



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Children were excluded from the study if they had any chronic medical illness or 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.

**Ethical consideration**

**The parents/guardians of all study participants gave informed consent. This study was conducted following the ethical standards of the Helsinki Declaration of 1964, and was approved by the Research Ethics Committee at the Faculty of Medicine, Benha University, under the registration number (MS 14-1-2022).**

**Clinical assessment**

Detailed history was taken, and general and systemic examinations were done to assess the disease and its treatment-related complications and to exclude children with any condition or disability that could preclude them from this study.

**Laboratory investigations**

Laboratory data were obtained from patients' records, including full blood picture and serum ferritin levels performed within the last month. Thalassemic children were classified into severity groups according to the scoring system by *Orapan Sripichai et al.* [13]**.**

**Psychometric assessment**

The Arabic version of WISC-IV was applied to the patients and controls. The scale is a standardized measure comprised of fifteen subtests grouped into four main domains (verbal comprehension, working memory, perceptual reasoning, and processing speed), yielding to the Full-Scale Intelligence Quotient (FSIQ), a consequent score that describes the general intelligence **(Table 1)** [14]**.**

The same clinician performed this psychometric assessment to avoid subjective bias. The administration time was around one to two hours, and the child was allowed to finish the test in two separate appointments.

**Table (1): WISC-IV Domains** [14]

| **WISC-IV Domains** | **Main subsets** | **Optional subsets** |
|---|---|---|
| The Verbal Comprehension Index (VCI) Composite Score | • Similarities<br>• Vocabulary<br>• Comprehension | • Information<br>• Word reasoning |
| The Perceptual Reasoning Index (PRI) Composite Score | • Block design<br>• Picture concepts<br>• Matrix reasoning | • Picture completion |
| The Working Memory Index (WMI) Composite Score | • Digit span<br>• Letter-number sequencing | • Arithmetic |
| The Processing Speed Index (PSI) Composite Score | • Coding<br>• Symbol search | • Cancellation |
| **The Full-Scale IQ Score (FSIQ)** | • VCI<br>• PRI<br>• WMI<br>• PSI | |
| **Interpretation of IQ Score:** | FSIQ classes were defined according to WAIS-IV guidelines as follows:<br>• 130 and higher: very superior<br>• 120-129: superior<br>• 110-119: high average<br>• 90-109: average<br>• 80-89: low average<br>• 70-79: borderline<br>• 69 and lower: extremely low | |

**Statistical Analysis**

The data were recorded on an Excel sheet. The SPSS (Statistical package for social science) version 26 was used to analyse the data after ccoding. Descriptive statistics were presented in the form of mean, Standard deviation (±SD), and number and percent.

For numerical (parametric) data, the student's *t*-test was used to compare the mean of two groups, ANOVA (analysis of variance) was used to compare more than two groups data. For continuous non-parametric data, Mann-Whitney U- test was used for the inter-group analysis. Inter-group comparison of categorical data was performed using the chi-square test ($X^2$-value). The Pearson correlation coefficient (r) test correlated different parameters. *P* value <0.05 was considered statistically significant (S).

**RESULTS**

In this study, 100 children were divided into two groups: group I (50 thalassemic children) and group II (50 normal children). Patients' transfusion and chelation data are detailed in **(Table 2).** Both groups were well matched regarding age, sex, education level, parent's education, school performance, socioeconomic status, and consanguinity. However, results show that the two groups had statistically significant differences regarding weight, BMI, height, and pretransfusion hemoglobin (Hb) (P<.001) **(Table 3).**

**Table (2): Transfusion and chelation data of patients**

| Variables | Mean ± SD (range) |
|---|---|
| **Onset of transfusion (y)** | 1.24 ±1.19 (0.16-7.00) |
| **Disease duration (y)** | 8.78 ±3.03 (3-15) |
| **Transfusion frequency (n/y)** | 13.1 ±4.08 (6-27) |
| **Onset of chelation (y)** | 2.58 ±1.79 (0.83-9) |
| **Duration of chelation (y)** | 6.98 ±3.36 (1-14) |
| **Chelation type (n (%))** | |
| **No chelation** | 4 (8%) |
| **Deferoxamine** | 15 (30%) |
| **Deferasirox** | 31 (62%) |
| **Serum ferritin (ng/dl)** | 904.22 ±1055.13 (300-7000) |
| **Splenectomy (n (%))** | 24 (48%) |

Abbreviation: SD, Standard deviation; BMI, body mass index; HC, head circumference. Mean and standard deviation for parametic parameters.

**Table (3): Demographics, laboratory parameters and education level of patients and controls**

| | Group I (Patients) (n=50) | Group II (Controls) (n=50) | Test | P value |
|---|---|---|---|---|
| **Age (y) (mean ±SD)** | 10.16 ±3.07 | 10.35 ±2.36 | t=0.3 | 0.7 |
| **Sex (n (%))** | | | | |
| **Male** | 22 (44.0%) | 21 (42.0%) | $X^2$=0.04 | 0.8 |
| **Female** | 28 (56.0%) | 29 (58.0%) | | |
| **Anthropometric measurements** | | | | |
| **Weight (kg) (mean ±SD)** | 26.62 ±7.68 | 33.40 ±7.89 | t=4.4 | <0.001* |
| **Weight percentile (median, range)** | 5 (5-75) | 50 (25-75) | z=7.3 | <0.001* |
| **Height (cm) (mean ±SD)** | 130.26 ±16.14 | 135.98 ±13.97 | t=1.9 | 0.07 |
| **Height percentile (median, range)** | 10 (5-75) | 50 (25-75) | z=6.6 | <0.001* |
| **BMI (kg/m$^2$) (mean ±SD)** | 15.36 ±1.56 | 17.80 ±1.47 | t=8.1 | <0.001* |
| **HC (cm) (mean ±SD)** | 51.44 ±0.99 | 51.54 ±0.91 | t=0.5 | 0.6 |
| **Laboratory parameters (mean ±SD)** | | | | |
| **Hb (g/dl)** | 7.75 ±0.64 | 12.05 ±0.44 | t=39.2 | <0.001* |
| **WBCs (per µl)** | 9974 ±10179.95 | 8318 ±702.09 | z=1.1 | 0.3 |
| **Platelets (per µl)** | 309,180 ±65,318.28 | 311,560 ±33,626.50 | t=2.2 | 0.03* |
| **Education and Socioeconomic Status** | | | | |
| **Education** | | | | |
| **Uneducated** | 6 (12.0%) | 4 (8.0%) | $X^2$=0.4 | 0.8 |
| **Read and Write Only** | 18 (36.0%) | 19 (38.0%) | | |
| **Educated** | 26 (52.0%) | 27 (54.0%) | | |
| **Father Education** | | | | |
| **Uneducated** | 11 (22.0%) | 9 (18.0%) | $X^2$=1.5 | 0.5 |
| **Read and Write Only** | 21 (42.0%) | 17 (34.0%) | | |
| **Educated** | 18 (36.0%) | 24 (48.0%) | | |
| **Mother Education** | | | | |
| **Uneducated** | 4 (8.0%) | 4 (8.0%) | $X^2$=0 | 1 |
| **Read and Write Only** | 23 (46.0%) | 23 (46.0%) | | |
| **Educated** | 23 (46.0%) | 23 (46.0%) | | |
| **School Performance** | | | | |
| **Poor** | 13 (26.0%) | 8 (16.0%) | $X^2$=1.7 | 0.4 |
| **Average** | 24 (48.0%) | 29 (58.0%) | | |
| **Above Average** | 13 (26.0%) | 13 (26.0%) | | |
| **Socioeconomic Status** | | | | |
| **Low Class** | 30 (60.0%) | 27 (54.0%) | $X^2$=0.5 | 0.8 |
| **Lower Middle Class** | 18 (36.0%) | 20 (40.0%) | | |
| **High Middle Class** | 2 (4.0%) | 3 (6.0%) | | |
| **Consanguinity** | | | | |
| **Negative** | 23 (46.0%) | 26 (52.0%) | $X^2$=0.4 | 0.5 |
| **Positive** | 27 (54.0%) | 24 (48.0%) | | |

Abbreviations, t, t-test; X2, chi square test; Z, Mann-whitney test; BMI, body mass index; HC, head circumference; Hb, hemoglobin; WBCs, white blood cells. Mean and standard deviation for parametic parameters. Median and range for non-parametric parameters.

The mean FSIQ was (97 ± 12.58) in patients; this was significantly lower than that (122.06 ±16.68) of controls (P<.001). IQ subsets distribution among patient and control groups was statistically variable (P<.001) **(Table 4) (Figure 1)**. Most patients (60%) fell in the average subset, while the most considerable portion of the healthy controls (36%) fell in the very superior subset **(Figure 2).**

**Table (4): IQ score subsets of patients and controls**

| | Group I (Patients) (N=50) (mean ±SD) | Group II (Controls) (N=50) (mean ±SD) | *t* | P value |
|---|---|---|---|---|
| **Verbal Comprehension Index** | 31.34 ±4.23 | 40.50 ±8.18 | 7.03 | <0.001* |
| **Similarities** | 15.86 ±9.42 | 22.04 ±7.05 | 3.7 | <0.001* |
| **Vocabulary** | 18.90 ±9.78 | 26.68 ±8.25 | 4.3 | <0.001* |
| **Comprehension** | 16.80 ±7.44 | 21.42 ±5.30 | 3.6 | 0.001* |
| **Information** | 12.94 ±4.59 | 16.38 ±5.11 | 3.5 | 0.001* |
| **Word Reasoning** | 12.26 ±4.16 | 13.76 ±2.53 | 2.2 | 0.03* |
| | | | | |
| **Perceptual Reasoning Index** | 29.14 ±4.93 | 34.06 ±7.36 | 3.9 | <0.001* |
| **Block Design** | 16.76 ±7.65 | 23.76 ±8.68 | 4.3 | <0.001* |
| **Picture Concepts** | 12.22 ±4.55 | 16.06 ±3.48 | 4.7 | <0.001* |
| **Matrix Reasoning** | 14.78 ±6.53 | 15.78 ±5.39 | 0.8 | 0.4 |
| **Picture Completion** | 16.02 ±8.38 | 19.40 ±4.72 | 2.5 | 0.02* |
| | | | | |
| **Working Memory Index** | 17.82 ±4.45 | 25.44 ±4.69 | 8.3 | <0.001* |
| **Digit Span** | 11.54 ±4.09 | 18.52 ±5.35 | 7.3 | <0.001* |
| **Letter Number Sequencing** | 12.22 ±5.51 | 15.12 ±4.10 | 2.9 | 0.004* |
| **Arithmetic** | 16.10 ±6.34 | 22.28 ±4.56 | 5.6 | <0.001* |
| | | | | |
| **Processing Speed Index** | 18.70 ±4.84 | 22.66 ±4.52 | 4.2 | <0.001* |
| **Coding** | 26.64 ±12.91 | 38.38 ±12.91 | 4.5 | <0.001* |
| **Symbol Search** | 25.52 ±11.03 | 28.34 ±8.40 | 1.4 | 0.2 |
| **Cancellation** | 37.40 ±14.85 | 49.74 ±12.18 | 4.5 | <0.001* |
| | | | | |
| **Full-Scale IQ** | 97.00 ±12.58 | 122.06 ±18.68 | 7.9 | <0.001* |

Abbreviation, *t*, *t* test. Mean and standard deviation for parametic parameters.

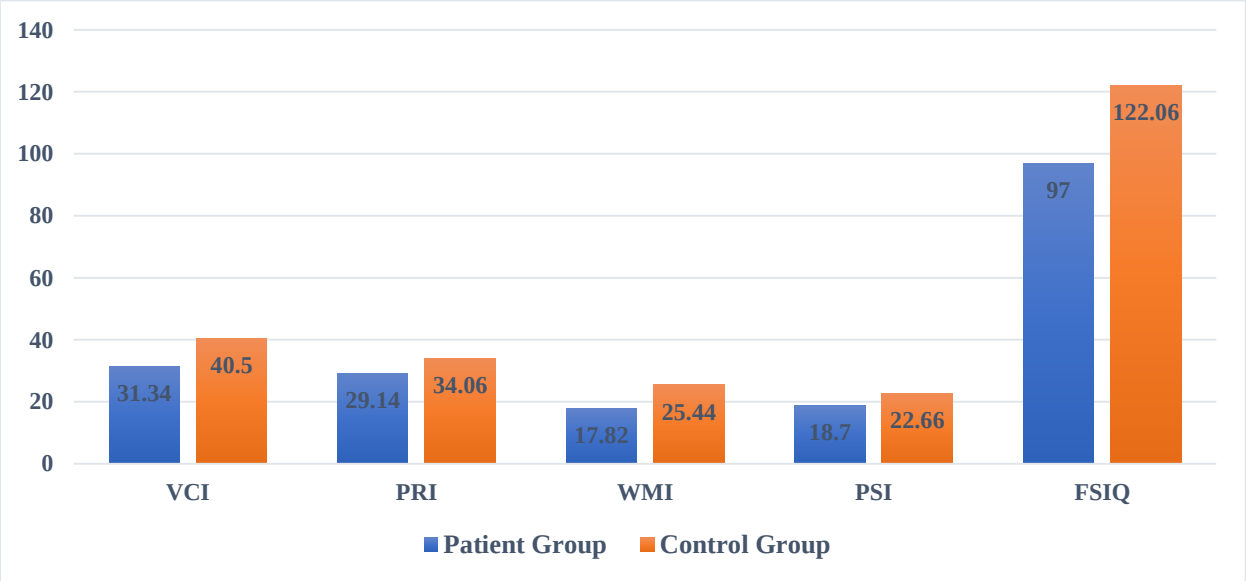


**Figure (1) IQ score subsets of patients and controls**

Abbreviation, VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; WMI, Working Memory Index; PSI, Processing Speed Index; FSIQ, Full-Scale Intelligence Quotient.

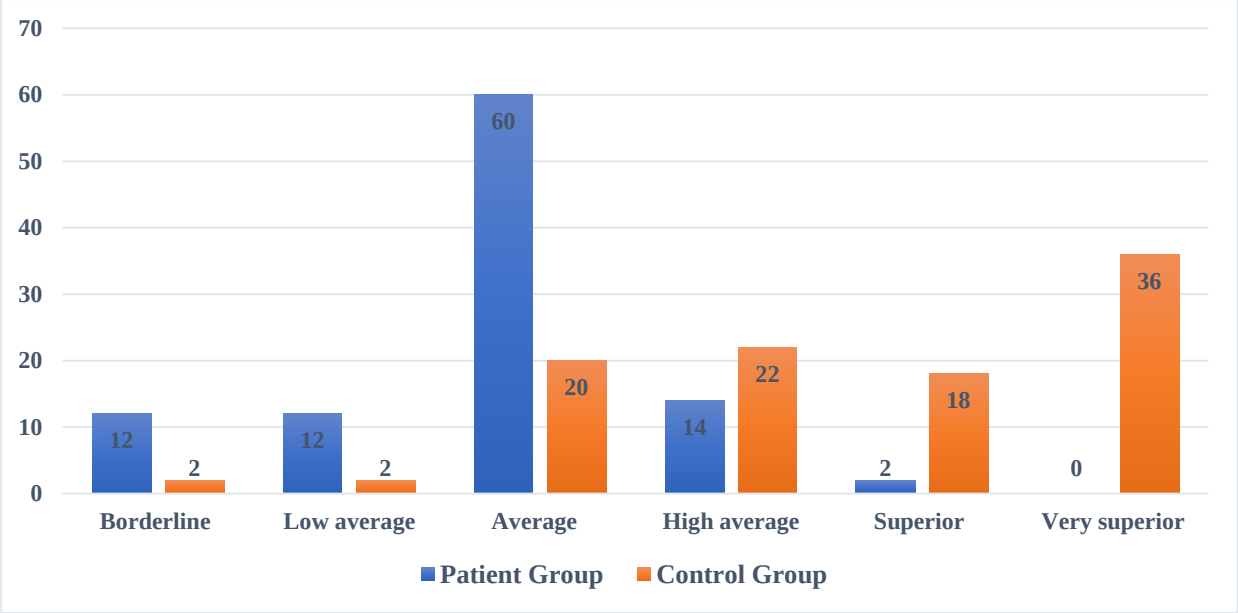


**Figure (2) IQ distribution among patients and controls.**

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No statistically significant difference was found in IQ scores and subsets regarding sex, consanguinity, and splenectomy. In the thalassemic group, there were 25 patients with moderate and 25 with severe diseases. Thalassemic patients with moderate disease had statistically lower Verbal Comprehension Index (VCI) than those with severe disease (P.04), with a mean of 30.16 ± 3.88 compared to a mean of 32.52 ± 4.31, respectively. However, the other IQ scores did not show statistically significant difference between the two subgroups.

In thalassemic children, The IQ mean scores had no correlation with the age of onset of disease, transfusion frequency, parent's education, or socioeconomic status. The VCI, Processing Speed Index (PSI), working memory index (WMI), and FSIQ were positively correlated with education (P<.005), while all IQ subsets were positively correlated with school performance (P<.05) and pretransfusion Hb (P<.001). There was no correlation with the serum ferritin, chelation type, onset and duration of chelation. Regarding the anthropometric measurements, there was a positive correlation between the VCI, WMI, PSI, and FSIQ and weight (P<.005) and height of patients (P<.001), also between FSIQ and BMI (P .046), and between the WMI, PSI, and FSIQ and HC (P<.05).

## DISCUSSION

In this study, using the WISC-IV to compare cognitive functions between thalassemic children and healthy controls, the mean FSIQ was significantly lower in patients than in controls, as well as the mean scores of the VCI, the PSI, the WMI and the Perceptual Reasoning Index (PRI).

Many studies have demonstrated the impact of βTM on the cognitive function and the neurological development of thalassemic patients; *Orsini et al.* were the earliest to report intellectual impairment in thalassemic children [15], which has been attributed to various risk factors, either directly or indirectly, related to the nature of the disease. Direct risk factors include the chronic hypoxic state created by chronic anemia, asymptomatic brain infarctions, iron overload-related organ toxicity, and deferoxamine neurotoxicity. *Metafratzi et al*. reported higher iron deposition in the caudate nucleus, putamen, and temporal and motor cortex of patients with βTM [16]. Other risk factors indirectly related to the disease include repeated school absences to attend hospital appointments, the psychic adverse effects of chronic illness, the restrictions implemented on the physical and social development of children, and the overly protective family attitude that impairs the psychosocial development of thalassemic children [7,8,10,17,18]**.** The cognitive functions of thalassemic children have been previously assessed by different scores such as the WISC-III [7–12], computerized Wisconsin's card sorting test (WCST) [17], and Stanford Binet fourth edition Scales [18].

The psychometric properties of the WISC-IV score are superb, and psychometric evidence of its construct validity is excellent, with emerging evidence supporting that it has a greater diagnostic and treatment validity than WISC-III. WISC-IV data are more likely to be related to the natural environment of the child (i.e., ecological

validity) and could lead to intervention (i.e., treatment validity), which is the ultimate goal of effective cognitive and neuropsychological assessment [19].

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 [8,17].

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 [20,21]. The retarded growth in thalassemic patients has been attributed mainly to iron overload and high serum ferritin, which impairs bone growth and contributes to short stature and decelerated growth rate through impairment of bone metabolism and endocrine glands [22,23]. Moreover, as chronic anemia, thalassemia impairs patients' weight gain [8].

**IQ scores among patients and controls**

In this study, thalassemic children had lower mean scores on different IQ tests than healthy children; however, this was not reflected in their school performance, which was not significantly different between the two groups. This was also reported in the study that compared 74 thalassemic adults to 45 healthy controls using the Fourth edition of the Wechsler Adult Intelligence Scale (WAIS-IV) [14]

WISC-III was used previously in multiple studies; two had similar results to ours. One study compared 100 βTM patients to 100 normal children [12], and the other compared 20 βTM to 21 healthy controls [7]. All subtests of WISC-III were significantly lower in thalassemic patients.

On the other hand, one study compared 40 children with βTM and 40 healthy children [9]. βTM children had lower scores on both Full Scale and Verbal Scale; nevertheless, the difference between the two groups' scores on Performance Scale was non-significant.

Moreover, in the studies that compared the cognitive function of 50 βTM children to 50 healthy children [8],100 βTM children to 100 healthy controls [11], and 32 patients to 40 normal subjects [6], βTM patients were found to have marked lower FSIQ and performances scores compared to controls, while Verbal scores showed no difference between patients and controls.

Other cognitive function tests were used formerly. WCST was used to compare the cognitive function in 100 βTM patients to 50 healthy controls [17], and Stanford Binet fourth edition scale was used to compare 30 βTM to 40 healthy controls [18]; both reported cognitive functions were significantly lower in βTM children. This was in contrast to the study that investigated 294 βTM patients in comparison to 294 controls, using the Ravin test [24]. This score revealed no statistically significant difference among the two groups.

The variation in IQ scores among thalassemic patients in different studies may be attributed to different tests and other factors that could have influenced the IQ, including disease severity, iron overload status, and psychosocial factors [5]. We believe that as our study group was from low and low-middle socioeconomic classes, the disease burden overwhelms families and puts education at the tail of the priority list.

**Correlation between IQ scores and onset of disease and transfusion frequency.**

In this study, The IQ mean scores did not correlate with age of onset of disease or transfusion frequency, which was in line with previous reports [7,16]. In contrast to our study, a third study found no significant association between cognitive variables and age at onset of βTM and illness duration, while the blood transfusion frequency was significantly positively correlated with some of the IQ scores [18]. Also, another one found that some IQ subsets were negatively correlated with duration of illness and age of onset of disease. However, IQ scores had no significant correlation with transfusion frequency [8].

**Correlation between IQ scores and pretransfusion Hb**

In this study, we found IQ scores were positively correlated with pretransfusion Hb; this was similar to one study [17] and contrary to another study [7]. The adverse effect of anemia on children's cognitive functions has been investigated by *Ai et al.*, who explained that areas of brain associated with performance IQ components might have been affected by low Hb level during development [25]. Moreover, lower intelligence scores than normal children were reported in children with thalassemia minor or iron deficiency anemia [26,27].

**Correlation between IQ scores and serum ferritin, onset, duration, and type of chelation**

The mean IQ scores did not correlate with serum ferritin, onset and duration of chelation, and type of chelation; this was in line with other studies [7,11] and in contrast to one study [8], where serum ferritin negatively correlated to onset of chelation therapy and some IQ subsets. The recorded serum ferritin value in our study was the most recent value, and this does not give an overall impression of the iron overload status; in addition to the poor correlation between serum ferritin level and tissue iron level [28], which is a significant factor for the development of neuropsychological impairment [7].

**Correlation between IQ scores and anthropometric measurements**

There was a positive correlation between the VCI, WMI, PSI, and FSIQ and weight and height of patients, also between FSIQ and BMI, and between WMI, PSI, and FSIQ and HC, which is consistent with one study [8]. Patients with lower weight, height, BMI and HC might have more severe or inadequately treated disease, impairing their IQ scores [8]. Also, as theoretically, there is a strong negative correlation between iron overload status and growth parameters, patients with lower growth parameters would have higher iron overload, which subsequently will impair the IQ scores [22,23].

**Correlation between IQ scores and education and school performance**

In thalassemic children, all IQ subsets were positively correlated with school performance; the VCI, WMI, PSI, and FSIQ were positively correlated with education, while there was no correlation with parents' education or socioeconomic status, this was in agreement with a former study [17].

**IQ distribution among patients and controls**

In this study, regarding the mean FSIQ score, there was a significant difference between patients and controls, as most patients fell in the average subset (60%), while the major group of healthy children fell in the very superior subset (36%). This was consistent with former studies [7,8], where the major group of patients had average full IQ scores by a percentage of 34% and 44%, respectively.

This study has some limitations, the small study group; we did not compare transfusion-dependent to non-transfusion-dependent thalassemia, the lack of presence of the high-middle and high socioeconomic class, and only serum ferritin was recorded as a marker of iron overload.

## CONCLUSION

Thalassemic children had significantly lower IQ scores on cognitive function assessment than healthy children. The IQ mean scores were positively correlated with pretransfusion Hb, weight, height, BMI, HC, education, and school performance of patients. There was no correlation with the serum ferritin, onset, duration, and type of chelation.

**Conflict of Interests:**

The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

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