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RESEARCH

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Cognitive impairment in beta thalassemia major and intermedia pediatric patients: a cross-sectional study

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Abstract

Background Thalassemia is a commonly occurring genetic hemoglobinopathy worldwide. Periodic and routine blood transfusions, iron chelation therapy and splenectomy procedures are all required for the treatment of thalassemia. Numerous organs and bodily systems could be impacted by thalassemia, particularly the nervous system, which could impede cognitive performance. The study aimed to assess cognitive abilities of pediatric patients diagnosed with beta thalassemia major and intermedia.

Patients and methods A total of 168 participants [54 β-thalassemic major children, 51 with β-thalassemia intermedia and 63 age-matched healthy controls from both genders (85 girls and 83 boys)] with age ranging from 8 to 16 years were participated in a cross-sectional study. Cognitive function was evaluated for all children by using the Wechsler Intelligence Scale For Children 4th edition.

Results Compared with control group, a significant decline was found in all Wechsler Intelligence Scale subtests as well as in verbal comprehension index, perceptual reasoning index, working memory index, processing speed index and full scale index scores of thalassemia major and intermedia patients ($p < 0.001$). When compared to children with thalassemia intermedia, the beta thalassemic major children showed a significant decrease in all Wechsler Scale subtests as well as in all its five index scores ($p < 0.001$).

Conclusions The study concluded that thalassemia negatively affects and impairs cognition and intellectual capacities.

Keywords Pediatric, Beta thalassemia, Major, Intermedia, Wechsler Scale 4th edition, Intelligence

Background

Globally, thalassemia is widely recognized as one of the most prevalent form of inherited anemia. It is featured by deficiency or absence of either the alpha or beta globin chains that are necessary to form hemoglobin tetramers [1].

In the Middle East, Mediterranean and Central Asia, beta thalassemia (βT) is one of the most prevalent autosomal recessive diseases [2]. It is the most common hemoglobinopathy in Egypt. The gene frequency for this condition is 0.03% and the carrier rate ranges from 5.3 to 9%. Thalassemia is thought to affect 1000–1.5 million live births annually [3].

βT has a wide range of clinical manifestations and has traditionally been categorized into three main types: beta thalassemia major (βTM), beta thalassemia intermedia

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(βTI) and beta thalassemia minor. Thalassemia minor refers to the less severe form of the condition and groups patients who exhibit mild anemia and a heterozygous condition (trait) for thalassemia. On the other hand, βTM encompasses patients who suffer from very severe anemia starting from a young age and need to transfuse blood frequently along with lifelong iron chelation therapy. βTI is a condition that combined a group of patients with varying clinical manifestations, ranging from mild to moderately severe anemia. Unlike βTM, patients with βTI do not need to transfuse blood regularly to maintain life [4]. However, they do experience a range of thalassemia-related complications such as iron overload, skeletal deformities and growth problems [5, 6].

Patients with βT must adhere to a strict treatment plan that begins in infancy and includes periodic blood transfusions and iron chelating therapy. Because of improvements in its treatment, patients with this condition currently experiencing longer life expectancies [7]. However, these longer life expectancies appear to be related to some difficulties and effects on their body systems, particularly the nervous system. They may experience deficits in language, attention, memory, visuomotor dysfunction, executive functions and abstract reasoning, all of which may have an impact on their quality of life and academic performance [8].

Several studies over the past few years have shown that βT patients can experience a wide range of neurological involvement, including cognitive impairment, abnormal evoked potential results, complications from extramedullary hematopoiesis, cerebrovascular disease and peripheral neuropathy. In the majority of cases, such problems were undetected and only discovered following a neuropsychological, neurophysiological or neuroimaging tests [9, 10].

There are few studies evaluating cognitive performance in children with chronic illnesses like thalassemia, particularly βTI and the results are inconsistent [8, 11–14]. It is crucial to evaluate cognitive and intellectual abilities regularly, especially in those who have chronic illnesses like thalassemia.

Aim of the study

The objective of the study was to test and determine the cognitive function of βTM and less targeted group βTI pediatric patients.

Methods

Subjects

From January 2022 to April 2023, a total of 168 children between the ages of 8 and 16 years were included in a cross-sectional study. Among them, 54 βTM children (29 girls and 25 boys), 51 βTI (24 girls and 27 boys) selected from Cairo University Children's Hospital and 63 healthy children with normal hemoglobin level (32 girls and 31 boys) were selected from governmental schools matching the age and sex of the thalassemia affected children. All children were enrolled in formal education, had no musculoskeletal deformities, free from any visual or auditory impairments, did not have any associated diseases with βT such as leukemia, sickle cell anemia or any other blood disorders and did not suffer from marked cognitive, mental or cardiac impairments. Prior to participation, the children and their parents were interviewed to explain the goal and procedural steps of the study.

Materials for assessment

To evaluate the cognitive function, the Arabic version of the Wechsler Intelligence Scale For Children 4th Edition (WISC-IV) was utilized. It is the revision of the WISC 3rd edition. The WISC-IV is an assessment tool which is administrated individually, consisting of 15 subtests that provides a detailed examination of intellectual capability. It is designed to be used with children aged 6 to16 years and 11 months old [15].

The 15 tests of the WISC-IV are divided into 10 main subtests and 5 supplementary subtests. The main subtests are as follows: similarities, vocabulary, comprehension, block design, picture concepts, matrix reasoning, coding, symbol search, digit span and letter–number sequencing. The supplemental subtests are as follows: information, word reasoning, picture completion, cancellation and arithmetic [15].

The WISC-IV provides 4 index scores including verbal comprehension, perceptual reasoning, working memory and processing speed. Additionally, it gives full scale intelligence quotient [15].

Procedures

The objective and procedural steps were elucidated to both the children and their caregivers.

Anthropometric measurements By utilizing a calibrated floor scale (ZT-120 model), weight (kg) and height (cm) were measured. Weight was recorded to the nearest 100 g and height was measured to the last completed 0.1 cm. The body mass index (BMI) of each child was calculated, BMI = Weight (kg)/Height $(m)^2$.

Cognition

- All the participants were assessed using the Arabic version of WISC-IV.
- Every child was individually evaluated in spacious and quiet room free from any visual and auditory distractions.

1. In the Similarities subtest: the child was required to recognize and articulate the commonalities between sets of distinct objects that pertain to the same group (Ex: recognizing that both a banana and an apple are fruits).
2. The Vocabulary subtest is divided into:

- Pictured items in which a number of pictures were showed to the child and he/she was required to identify and describe each image.
- Verbal items in which the child was asked about something and he/she had to give a description or a definition of it (Ex: What does the word "umbrella" mean ?).

3. In the Letter–Number Sequencing subtest, the child was given a combination of letters and numbers in a mixed sequence, which must be recalled in two different ways. He/she was required to repeat the numbers in numerical order and then the letters in an alphabetical order.
4. In the Comprehension subtest: the child had to answer some questions related to general and social concepts (Ex: Why do people use toothbrush to clean their teeth?).
5. In the Matrix Reasoning subtest, the child was presented with a matrix which was missing one of its parts and he/she was required to complete the matrix by selecting the item that properly filled the missing piece.
6. The Symbol Search subtest: the child was required to determine within a time limit whether the symbol in the target group was located in the search group or not.
7. The Digit Span subtest: the child had to repeat strings of digits recited by the examiner. The series began with 2 digits and kept increasing in length, with two trials at each length. It is subdivided into: digit span forward and digit span backward.

- In digit span forward: the child had to repeat the digits in the exact same order that the examiner did in a loud voice.
- In digit span backward: the child had to repeat the digits in a reverse order (in a sequence opposite to that said by the examiner).

8. The Picture Concepts subtest: From the stimulus book, two or three rows of pictures were showed to the child and he/she had to choose one picture from the first line which had a common property with a picture from the second line (Ex: both are trees Or both are animals).
9. In the Block Design subtest, the child was presented with red and white blocks and was required to use them to construct specific designs within a specific time limit. The designs were typically shown in a stimulus book and the child had to replicate them using the blocks.
10. The Coding subtest: during a specific time limit and as fast as possible, the child had to draw a symbol inside a square or a specific figure according to a code.
11. In the Picture Completion subtest, the child was presented with images with missing parts and was required to complete the pictures by identifying the missing elements within a specific time limit (Ex: a picture of a car with the door handle missed).
12. The Cancellation subtest: divided into random cancellation and structured cancellation.

- In random cancellation: the child had to label particular animal pictures that were distributed randomly during a time limit. A page is covered with pictures of animals and other common objects randomly scattered on the page and the child had to mark through or cancel the animals as quickly as possible.
- In structured cancellation: the child had to draw a line under a number of specific animal pictures placed in a structured manner during a time limit.

13. The Information subtest: the child was supposed to answer some questions related to general topics (Ex: How many days in the week ?).
14. The Arithmetic subtest: the child needed to solve a series of mathematical problems within a specified time limit.
15. The Word Reasoning subtest: the child had to define something after giving him/her a description and successive clues (Ex: the child might identify a bicycle after describing its shape and function).

- The administration time of the test was 60 to 90 min and the child was permitted to finish the test in two different sessions.

Statistical analysis

MANOVA test for numerical data and chi-squared (Fisher exact) test for categorical data were used to compare subjects' characteristics between groups. Shapiro–Wilk test was used to check the normality of data. Levene's test for homogeneity of variances was conducted to test the homogeneity between groups. One-way MANOVA was conducted for comparison of WISC-IV between groups. For subsequent multiple comparison, Post-hoc tests using Tukey's test were carried out. The level of significance for all statistical tests was set at $p < 0.05$. Statistical analysis was performed through the statistical package for social studies (SPSS) version 25 for windows.

Results

Subject characteristics

Table 1 shows the subject characteristics of control, βTI and βTM. There was no significant difference between groups in sex distribution and age ($p > 0.05$). There was a significant decrease in weight, height, BMI, Hemoglobin (Hb) concentration and non-consanguineous marriage of children with βTI and βTM compared with that of control group ($p < 0.001$) with no significant difference between βTI and βTM children ($p > 0.05$). There was a significant decrease in attending school on regular basis of βTM and βTI children compared with that of control group ($p < 0.001$) and a significant decrease in attending school regularly of βTM children compared with that of βTI ($p < 0.001$).

There was no significant difference in splenectomy and use of iron chelating therapy between βTI and βTM groups ($p > 0.05$) (Table 1).

Comparison of WISC-IV between control, βTI and βTM

MANOVA test revealed a significant group effect (($F = 296$), ($p = 0.001$), ($\eta^2 = 0.86$)). There was a significant difference in WISC-IV between control, βTI and βTM ($p < 0.001$) (Table 2) (Fig. 1, 2).

There was a significant decrease in all WISC-IV subtests and in its five index scores of (VC, PR, WM, PS and full scale score) of βTI and βTM compared with that of control group ($p < 0.001$) (Table 3).

When compared to βTI children, βTM children showed a significant decrease in all WISC-IV subtests as well as in all its five index scores ($p < 0.001$) (Table 3).

Table 1 Participants' characteristics

	Control group ($n = 63$)	Thalassemia intermedia ($n = 51$)	Thalassemia major ($n = 54$)	*F* value	*p*value
Age (years), mean ± SD	11.73 ± 2.51	11.78 ± 2.61	11.80 ± 2.65	0.01	0.98
Weight (kg), mean ± SD	54.29 ± 11.80	42.36 ± 9.28	42.54 ± 7.83	28.11	0.001
Height (cm), mean ± SD	148.85 ± 16.65	141.34 ± 17	142.01 ± 16.21	3.68	0.02
BMI (kg/m^2), mean ± SD	18.02 ± 2.13	14.80 ± 1.73	14.87 ± 1.23	63.89	0.001
Hb (g/dl), mean ± SD	10.93 ± 1.92	6.74 ± 0.84	6.96 ± 0.81	180.39	0.001
Sex, n (%)					
Girls	32 (50.8%)	24 (47.1%)	29 (53.7%)	$\chi^2 = 0.46$	0.79
Boys	31 (49.2%)	27 (52.9%)	25 (46.3%)		
Consanguinity, *n* (%)					
Positive	20 (31.7%)	34 (66.7%)	38 (70.4%)	$\chi^2 = 21.69$	0.001
Negative	43 (68.3%)	17 (33.3%)	16 (29.6%)		
Splenectomy, *n* (%)					
Yes	–	34 (66.7%)	38 (70.4%)	$\chi 2 = 0.16$	0.68
No	–	17 (33.3%)	16 (29.6%)		
Use of iron chelating therapy, *n* (%)					
Yes	–	37 (72.5%)	42 (77.8%)	$\chi^2 = 0.38$	0.53
No	–	14 (27.5%)	12 (22.2%)		
Regular school attendance					
Yes	60 (95.2%)	39 (76.5%)	19 (35.2%)	$\chi^2 = 53.23$	0.001
No	3 (4.8%)	12 (23.5%)	35 (64.8%)		

SD standard deviation, *p* probability value

Table 2 Mean values of Wechsler Intelligence Scale of control, thalassemia intermedia and thalassemia major

Wechsler Intelligence Scale	Control group	Thalassemia intermedia	Thalassemia major	*F*-value	*p* value
	Mean ± SD	Mean ± SD	Mean ± SD		
Block design	11.79 ± 0.94	6.51 ± 0.58	5.44 ± 0.77	1097.98	0.001
Similarities	12.48 ± 0.86	7.08 ± 0.63	5.91 ± 0.98	1035.98	0.001
Digit span	12.06 ± 1.20	6.73 ± 0.85	5.13 ± 1.20	640.03	0.001
Picture concepts	11.73 ± 0.94	6.96 ± 0.77	5.17 ± 0.93	867.07	0.001
Coding	12.94 ± 1.00	6.92 ± 0.69	5.48 ± 0.88	1226.03	0.001
Vocabulary	11.67 ± 1.09	6.61 ± 0.72	5.24 ± 0.85	806.06	0.001
Letter–number sequencing	11.44 ± 1.09	6.80 ± 0.69	5.61 ± 0 0.71	740.25	0.001
Matrix reasoning	12.14 ± 1.19	6.75 ± 0.63	5.31 ± 0.95	811.20	0.001
Comprehension	12.06 ± 1.08	6.22 ± 0.76	4.98 ± 0.88	987.19	0.001
Symbol search	12.10 ± 0.95	6.75 ± 0.44	5.70 ± 0.77	1183.92	0.001
Picture completion	11.48 ± 1.13	6.35 ± 0.80	5.37 ± 1.22	548.18	0.001
Cancellation	10.60 ± 1.37	5.75 ± 0.74	5.04 ± 0.87	481.88	0.001
Information	11.43 ± 1.10	6.14 ± 0.67	4.48 ± 0.95	879.91	0.001
Arithmetic	10.62 ± 1.17	5.45 ± 0.81	4.31 ± 1.04	626.64	0.001
Word reasoning	10.87 ± 1.01	6.63 ± 0.87	5.37 ± 1.03	512.38	0.001
Verbal Comprehension Index	35.68 ± 4.55	19.90 ± 1.45	16.13 ± 2.19	636.86	0.001
Perceptual Reasoning Index	35.67 ± 2.16	20.22 ± 1.24	15.93 ± 2.10	1751.70	0.001
Working Memory Index	23.51 ± 1.60	13.53 ± 1.21	10.74 ± 1.44	1287.94	0.001
Processing Speed Index	25.03 ± 1.41	13.65 ± 0.82	11.19 ± 1.36	2086.58	0.001
Full scale score index	120.41 ± 5.45	67.31 ± 2.61	53.98 ± 5.89	2977.10	0.001

SD standard deviation, *p* probability value

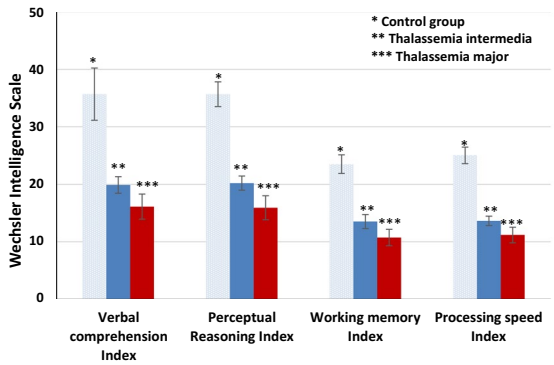

Fig. 1 Mean verbal comprehension, perceptual reasoning, working memory, processing speed of control, βTI and βTM

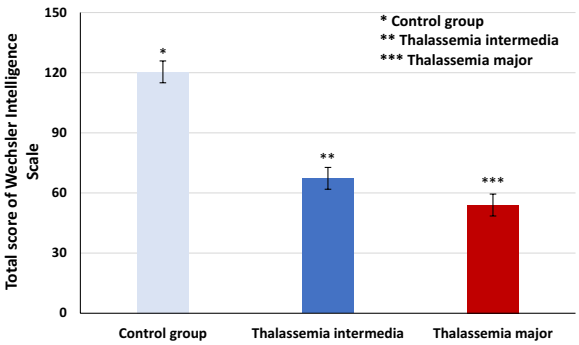

Fig. 2 Mean total score of Wechsler Intelligence Scale of control, βTI and βTM

Discussion

The aim of our study was to assess the cognitive abilities of pediatric patients with βTM and βTI and to compare the results with age and sex matched healthy controls. Our findings revealed that patients with βT scored less than controls in all WISC-IV subtests as well as in all its five index scores including verbal comprehension, perceptual reasoning, working memory, processing speed and full scale score.

Intellectual impairment among thalassemics was first described by Orsini et al. [16]. The cognitive abilities of patients with βTM were then assessed in several studies conducted across different parts of the world [17–21]. In Egypt, the majority of the studies conducted in that domain [22–25] revealed deficient cognitive function among patients with βT than controls. The former studies used the WISC 3rd edition whereas in our study the 4th edition was used. Elalfy et al. [23] echoed our findings and had related these findings with chelation use in

Table 3 Pairwise comparison of Wechsler Intelligence Scale between groups

Outcome	Control versus thalassemia intermedia		Control versus thalassemia major		Thalassemia intermedia versus thalassemia major	
	MD (95% CI)	*p* value	MD (95% CI)	*p* value	MD (95% CI)	*p* value
Block design	5.28 (4.94–5.65)	0.001	6.35 (6.00–6.70)	0.001	1.07 (0.69–1.42)	0.001
Similarities	5.40 (5.04–5.79)	0.001	6.57 (6.20–6.94)	0.001	1.17 (0.76–1.54)	0.001
Digit span	5.34 (4.81–5.80)	0.001	6.93 (6.45–7.42)	0.001	1.60 (1.12–2.14)	0.001
Picture concepts	4.77 (4.39–5.19)	0.001	6.56 (6.17–6.95)	0.001	1.79 (1.36–2.18)	0.001
Coding	6.01 (5.59–6.36)	0.001	7.46 (7.07–7.84)	0.001	1.44 (1.08–1.88)	0.001
Vocabulary	5.06 (4.66–5.48)	0.001	6.43 (6.02–6.83)	0.001	1.37 (0.93–1.78)	0.001
Letter–number sequencing	4.64 (4.25–5.03)	0.001	5.83 (5.45–6.22)	0.001	1.19 (0.78–1.59)	0.001
Matrix reasoning	5.40 (4.97–5.84)	0.001	6.83 (6.40–7.25)	0.001	1.43 (0.97–1.88)	0.001
Comprehension	5.85 (5.45–6.28)	0.001	7.08 (6.68–7.49)	0.001	1.23 (0.79–1.65)	0.001
Symbol search	5.35 (5.01–5.70)	0.001	6.39 (6.06–6.73)	0.001	1.04 (0.68–1.39)	0.001
Picture completion	5.12 (4.63–5.60)	0.001	6.11 (5.63–6.58)	0.001	0.98 (0.49–1.49)	0.001
Cancellation	4.86 (4.37–5.32)	0.001	5.57 (5.10–6.03)	0.001	0.71 (0.23–1.21)	0.001
Information	5.29 (4.87–5.71)	0.001	6.95 (6.53–7.36)	0.001	1.66 (1.22–2.09)	0.001
Arithmetic	5.17 (4.72–5.64)	0.001	6.30 (5.85–6.76)	0.001	1.14 (0.65–1.60)	0.001
Word reasoning	4.25 (3.81–4.69)	0.001	5.50 (5.07–5.93)	0.001	1.26 (0.79–1.70)	0.001
Verbal Comprehension Index	15.78 (14.41–17.24)	0.001	19.55 (18.17–20.94)	0.001	3.77 (2.26–5.20)	0.001
Perceptual Reasoning Index	15.45 (14.63–16.34)	0.001	19.74 (18.90–20.58)	0.001	4.29 (3.37–5.14)	0.001
Working Memory Index	9.98 (9.30–10.59)	0.001	12.77 (12.14–13.40)	0.001	2.79 (2.15–3.49)	0.001
Processing Speed Index	11.38 (10.80–11.91)	0.001	13.85 (13.30–14.39)	0.001	2.46 (1.92–3.07)	0.001
Full scale score index	53.10 (50.89–55.33)	0.001	66.43 (64.26–68.60)	0.001	13.33 (11.02–15.62)	0.001

MD mean difference, *CI* confidence interval, *p* probability value

patients. Raafat et al. [24] showed that verbal IQ was not affected in βTM unlike the full scale and performance IQ. El-Alameey et al. [25] showed that the scores of similarities, comprehension and digit span (verbal subsets) and the coding, mazes and object assembly (performance subsets) of thalassemic cases were significantly less than those of healthy controls. He also revealed that performance and total IQ scores of cases were considerably less than those of controls, while there was no marked difference regarding verbal IQ score.

Another study conducted by Duman et al. [26] among the Turkish population used the Turkish version of the WISC-revised and reported a decline in full scale, performance and verbal IQ of 20 βTM compared with controls. In addition, in Iran, Meymandi et al. [27] concluded that the verbal subtests scores of (information, digit span, arithmetic and comprehension) and the performance subtests scores as (picture completion, symbol search and mazes) of βT children were notably less than that of healthy controls. According to Elbahy et al. [28], the βTM children had significantly lower IQ scores when assessed by the WISC-IV than healthy children, including the mean of the full scale IQ as well as the mean scores of the VCI, PSI, PRI and WMI.

Contrarily, other studies claimed that there was no marked discrepancy in IQ between βTM patients and healthy ones [29, 30].

On the other hand, few studies had been carried out on βTI pediatric patients, a study done by Teli et al. [11] examining the subclinical involvement of CNS in 24 young βTI patients and concluded that 11.7% of the patients had IQ below 85, indicating subclinical CNS dysfunction that started in childhood.

Several explanations can be attributed for our findings. We proposed that our results are due to chronic hypoxic state brought on by chronic anemia which may cause decrease mental alertness and consequently affect the learning ability of these children. The chronicity of the disease and its complications and consequences on body systems including the CNS as well as the disease affects the parents psychological state and makes their focus not the children's education and scholastic performance. In addition, abnormal iron deposition in brain structures, cortex, putamen and caudate nucleus, could affect their cognition. These confirmed by a study done by Kharat and Waghmare [31] who declared that persons suffering from anemia were more susceptible to inattention, slowed down interpretation of information,

late decision-making and sluggish working memory processing in comparison with the control individuals. Chronic hypoxia and iron overload, according to Nemtsas et al. [32] contribute to neurological symptoms in βT. Iron is engaged in a variety of cell processes and is required for optimal neuronal development. However, the transition metal can produce neurotoxic reactive oxygen species, if it is not properly managed [33, 34].

Our study also compared the cognitive function between βTM and βTI patients and found a significant decline in cognitive performance among patients with βTM. Studies that examined the difference between both groups are limited [8, 35]. One study by Tartaglione et al. [35] studied 53 βTM and 21 βTI adult patients and compared them to healthy controls and showed that βTM scored the least followed by βTI followed by controls. In contrast to our study, ELhabiby et al. [8] who investigated 20 βTM and 20 βI patients found no difference between both groups.

To the best of our knowledge, this is the first study to investigate cognition among a larger number of βTI pediatric patients. Tartaglione et al. [35] proposed that the disease itself and its severity has a role in determining cognitive abilities. Besides, cognition can be affected according to environment and treatment related factors. A possible explanation for our results, according to our study, could be that patients with βTM do not attend school as regular and frequent as patients with βTI. Causes could be attributed to feeling fatigued and fear of psychological trauma and bullying. Additionally, the psychological side effects of this long-term illness, the limitations placed on the physical and social development of children and the overly protective parental attitude that hinders the psychosocial development of the children, are all potentials factors that could affect their cognition and learning capabilities.

Limitations of this study

The nutritional status was not evaluated in our study as factor that could affect cognition. The risk factors associated with cognitive impairment were not assessed as well in our study. Further studies that are designed to assess risk factors of cognitive impairment among patients with βT especially the βTI could be conducted on a large number of patients with different age range to allow for a definitive conclusion to be done.

Conclusion

Thalassemia as a chronic disorder profoundly affects cognition. Our study shows that there is a significant difference in cognitive abilities between βTM and βTI pediatric patients. As cognition is essential to the individuals everyday life, cognitive deficits can have a significant impact on the psychosocial life of βT children. Therefore, it is crucial to routinely evaluate the cognitive function of these children for early identification and revelation of intellectual impairment. This would enable proper handling and support to achieve better scholastic and academic achievement and ultimately improving these children's quality of life.

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Author contributions
EEAE contributed to study design, methodology, data collection, data analysis and interpretation, writing original draft and editing the final manuscript. AME contributed to revision, editing of the final manuscript and study supervision. MHE contributed to revision, editing the final manuscript and study supervision. MSN contributed to data collection, revision and editing the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study has received the approval of the Faculty of Physical Therapy Cairo University, Cairo, Egypt (No:P.T.REC/012/003783). Informed consent was obtained from all participants engaged in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Aydinok Y (2012) Thalassemia. Hematology 17(sup1):s28-31
2. Hakeem GL, Mousa SO, Moustafa AN, Mahgoob MH, Hassan EE (2018) Health-related quality of life in pediatric and adolescent patients with transfusion-dependent ß-thalassemia in upper Egypt (single center study). Health Qual Life Outcomes 16:1–9
3. El Beshlawy A, Mohtar G, Abd El Ghafar E, Abd El Dayem SM, El Sayed MH, Aly AA, Farok M (2008) Assessment of puberty in relation to L-carnitine and hormonal replacement therapy in β-thalassemic patients. J Trop Pediatrics 54(6):375–381
4. Weatherall DJ (2012) The definition and epidemiology of non-transfusion-dependent thalassemia. Blood Rev 26(Suppl 1):S3–S6
5. Asadov C, Alimirzoeva Z, Mammadova T, Aliyeva G, Gafarova S, Mammadov J (2018) β-Thalassemia intermedia: a comprehensive overview and novel approaches. Int J Hematol 108(1):5–21
6. Viprakasit V, Ekwattanakit S (2018) Clinical classification, screening and diagnosis for thalassemia. Hematol Oncol Clin 32(2):193–211
7. Hamdy M, Draz IH, El Sayed IT, Ayyad AA, Salemd MR (2021) Assessment of quality of life among beta-thalassemia major patients attending the hematology outpatient clinics at Cairo university hospital. Open Access Maced J Med Sci 9(E):156–160

8. Elhabiby MM, ElSalakawy W, Khalil SA, Hassan DI, Hjislam SG (2016) Cognitive dysfunction in β-thalassemia major and intermedia patients and its clinical correlates. Middle East Curr Psychiatry 23(3):128–133
9. Dessoki HH, Soltan MR, Ezzat AA (2018) Cognitive deficits in patients with β-thalassemia major. Middle East Curr Psychiatry 25(3):127–130
10. Rund D, Rachmilewitz E (2005) β-Thalassemia. N Engl J Med 353(11):1135–1146
11. Teli A, Economou M, Rudolf J, Tzovaras F, Gourtsa V, Kondou A, Kontopoulos E, Gombakis N, Athanassiou-Metaxa M, Zafeiriou D (2012) Subclinical central nervous system involvement and thrombophilic status in young thalassemia intermedia patients of Greek origin. Blood Coag Fibrinol 23(3):195–202
12. Mousa SO, Abd El-Hafez AH, Abu El-ela MA, Mourad MA, Saleh RN, Sayed SZ (2022) RANK/RANKL/OPG axis genes relation to cognitive impairment in children with transfusion-dependent thalassemia: a cross-sectional study. BMC Pediatr 22(1):435
13. Bu M, Deng X, Zhang Y, Chen SW, Jiang M, Chen BT (2023) Brain iron content and cognitive function in patients with β-thalassemia. Ther Adv Hematol. https://doi.org/10.1177/204062072311670
14. Adly A, Ismail E, Salah N, Ibrahim G, Ahmed S (2023) P1462: neurocognitive function and psychological assessment in transfusion-dependent beta-thalassemia patients: relation to brain iron content. HemaSphere 7(S3):e185302c
15. Flanagan DP, Alfonso VC, Mascolo JT, Hale JB (2011) The wechsler intelligence scale for children–fourth edition in neuropsychological practice. In: Handbook of pediatric neuropsychology. Springer Publishing Company, pp 397–414
16. Orsini A (1967) Nervous manifestations associated with thalassemia (critical study of the concept of thalassemic neurohemolytic syndrome). Pediatrie 22:771–784
17. Qurbani SN, Reniarti L, Chairulfatah A (2017) Serum ferritin, serum nitric oxide, and cognitive function in pediatric thalassemia major. Paediatr Indones 57(3):148–152
18. Economou M, Zafeiriou DI, Kontopoulos E, Gompakis N, Koussi A, Perifanis V, Athanassiou-Metaxa M (2006) Neurophysiologic and intellectual evaluation of beta-thalassemia patients. Brain Dev 28(1):14–18
19. Kurian AK, Sharma M, Varughese PV, Aggarwal N (2023) Cognitive Function in children with β-thalassemia major. Indian Pediatr 60(4):294–297
20. Gamayani U, Gartika P, Meidha LP, Cahyani A, Aminah SA, Panigoro R (2018) Attention and executive function impairment in children with beta-thalassaemia major. J Biomed Clin Sci (JBCS) 2(2):57–59
21. Avasarala S, Choudhary A, Bithu KS, Agrawal R, Tanwar GS (2023) Cognitive impairment in children with beta-thalassaemia major at a tertiary care centre, Rajasthan, India: a cross-sectional study. J Clin Diagn Res. 17(2):4–7
22. Sabry N, Salama KH (2009) Cognitive abilities, mood changes and adaptive functioning in children with β thalassaemia. Curr Psychiatry 16:244–254
23. Elalfy MS, Aly RH, Azzam H, Aboelftouh K, Shatla RH, Tarif M, Abdatty M, Elsayed RM (2017) Neurocognitive dysfunction in children with β thalassemia major: psychometric, neurophysiologic and radiologic evaluation. Hematology 22(10):617–622
24. Raafat N, Safy UE, Khater N, Hassan T, Hassan B, Siam A, Youssef A, Shabrawy AE (2015) Assessment of cognitive function in children with beta-thalassemia major: a cross-sectional study. J Child Neurol 30(4):417–422
25. El-Alameey IR, Alzaree F, Shehata MA, Shady MM, Atti MA, El-Khonezy MI (2019) Neurocognitive function and its related potentials in children with beta thalassemia major: an Egyptian study. Open Access Maced J Med Sci 7(3):322
26. Duman O, Arayici S, Fettahoglu C, Eryilmaz N, Ozkaynak S, Yesilipek A, Hazar V (2011) Neurocognitive function in patients with β-thalassemia major. Pediatr Int 53(4):519–523
27. Meymandi SH, Seyednezhad-Golkhatmi SH, Meymandi MH (2015) A comparison of intelligence quotient in children with and without β-thalassemia major. Galen Med J 4(4):132–138
28. Elbahy SM, Ayad SH, Elsayed RA, Nawar E (2023) Cognitive Function assessment in paediatric patients with beta-thalassemia major. Egypt J Hosp Med 90(2):2634–2642
29. Karimi M, Yarmohammadi H, Cappellini MD (2006) Analysis of intelligence quotient in patients with homozygous beta-thalassemia. Saudi Med J 27(7):982
30. Khairkar P, Malhotra S, Marwaha R (2011) Growing up with the families of B-thalassaemia major using an accelerated longitudinal design. Eur Psychiatry 26(S2):381
31. Kharat P, Waghmare P (2015) Could anemia be the reason for dysfunctional cognition. Int J Res Med Sci 3(3):663–669
32. Nemtsas P, Arnaoutoglou M, Perifanis V, Koutsouraki E, Orologas A (2015) Neurological complications of beta-thalassemia. Ann Hematol 94(8):1261–1265
33. Schipper HM (2004) Brain iron deposition and the free radical-mitochondrial theory of ageing. Ageing Res Rev 3(3):265–301
34. Schipper HM (2012) Neurodegeneration with brain iron accumulation—clinical syndromes and neuroimaging. Biochim Biophys Acta Mol Basis Dis 1822(3):350–360
35. Tartaglione I, Manara R, Caiazza M, Carafa PA, Caserta V, Ferrantino T, Granato I et al (2019) Brain functional impairment in beta-thalassaemia: the cognitive profile in Italian neurologically asymptomatic adult patients in comparison to the reported literature. Br J Haematol 186(4):592–607

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