Cognitive dysfunction in β-thalassemia major and intermedia patients and its clinical correlates

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Background
In Egypt, thalassemia is considered one of the most common genetically determined hemolytic diseases. Its high prevalence causes a significant burden on health resources. Few studies conducted on thalassemia patients have shown a heightened risk for cognitive function affection, and hence affects the patient's quality of life.

Objective
The aim of this study was to assess the cognitive functions and its clinical correlates in β-thalassemia major and β-thalassemia intermedia patients in comparison with healthy controls.

Patients and methods
This study included 40 β-thalassemia patients who were divided into two groups: 20 β-thalassemia major patients and 20 β-thalassemia intermedia patients. 20 controls matched for age and sex participated in the study. Cases were collected from the Hematology Outpatient Clinic, Internal Medicine Department of Ain Shams University. All participants were subjected to a full neuropsychological battery.

Results
Compared with controls, both β-thalassemia patient groups were equally and significantly impaired on most of the neuropsychological battery domains. Serum hemoglobin, serum iron, heart abnormalities, and liver functions were nonsignificant correlates, and hepatitis C virus infection and vaccination history were significant correlates.

Conclusion
Our findings suggest that both thalassemia types are equally affected as regards multiple cognitive domains, with no correlation with blood transfusion or serum iron levels, questioning any role for hemosiderosis as a cause for cognitive impairment.

Keywords:
clinical correlates, cognitive dysfuction, thalasemia

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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].

There is an increase in survival rates among β-thalassemia patients after the recent advances in the management of these patients with chelation therapy. This will lead to dramatic changes in the life requirements of thalassemia patients, which now is to improve quality of life in contrast to only trying to survive in the past [2].

Thalassemia is considered a significant issue for health professionals as they have to not only accommodate the demanding care including blood transfusions and iron chelation therapy but also screen and treat psychiatric disorders and increase the psychosocial adaptation toward the disease, and hence many researchers are targeting this area nowadays [3].

In Egypt, it is considered the most common genetically determined hemolytic disease [4]. The carrier rate varies from 6 to 10%, and gene frequency is 0.03. It was estimated that 1000 per 1.5 million live birth infants per year are born with thalassemia. Patient numbers are steadily increasing, reaching more than 2000 in the year 2003 at the largest Hematology Center in Cairo University. Sixty percent of the patients are less than 10 years of age, 30% of patients are 10–18 years of age, and 10% of patients are older than 18 years [5]. This high

prevalence causes a significant burden on health resources. The need to ameliorate the associated psychosocial burden thus becomes even more important. The scarcity of data on the psychosocial life aspects of thalassemia patients limits the implementation of proper intervention strategies [6].

Our study aimed to demonstrate the range of cognitive deficits in thalassemia major and intermedia patients and whether they differ in the degree of cognitive affection, to estimate the role of blood transfusion and hemosiderosis in cognitive impairment, using a full neuropsychological battery, and to correlate these cognitive deficits with clinical features. This can help in future implementation of proper intervention strategies for the disease.

Patients and methods

This cross-sectional study was conducted after approval of the Ethical and Research Committee of Ain Shams University. Informed written consent was taken from all patients after explaining the full study procedure to them.

Participants

All cases of β-thalassemia major and intermedia attending the Hematology Outpatient Clinic at the Internal Medicine Department, Ain Shams University Hospital, for follow-up and medication during the period from December 2012 to December 2013 were included in the study. Their ages ranged from 18 to 50 years (both male and female). Patients with no other medical disorders and those who can at least read and write were included. The participants were organized into three major groups, two patient groups and one control group. Group I included 20 β-thalassemia major patients, group II included 20 β-thalassemia intermedia patients, and group III included 20 healthy controls matched for age and sex. None of them had a history of any neuropsychiatric disorder, drug problems, or head trauma.

Measures

Assessment of thalassemia

Full history taking, including sociodemographic data, and physical and neurological examination were carried out. Laboratory investigations, including evaluation of mean Hb plasmatic levels (to assess chronic hypoxic states), serum iron level, mean serum ferritine level, and total iron binding capacity (to assess iron overload/progress of chelating treatment), were carried out. In addition, serum bilirubin and liver enzyme evaluation, together with evaluation of viral markers for hepatitis B and C and HIV infection, was carried out (to assess complications). Among the patient groups, there was no evidence of focal neurological signs or any complaint related to cognitive or behavioral disorders during assessment. Patients were considered as having β-thalassemia major if they had been receiving blood transfusion from the age of 2 years or younger regularly. Patients were considered as having β-thalassemia intermedia if Hb level was between 6 and 8.5, with no blood transfusion needed before the age of 18 years.

Assessment of cognitive functions

All patients and controls were subjected to full neuropsychological battery assessment by a trained psychologist who was blinded to diagnosis.

The battery included the following:

(1) The Wechsler Adult Intelligence Scale (WAIS) with all its verbal and performance subsets was used to assess intelligence quotient (IQ) and executive functions [7].
(2) The Wechsler Memory Scale-Revised subsets used were information and orientation, digit span backward, digit span forward, visual memory span backward, visual memory span forward, visual paired association I, visual paired association II, verbal paired association I, and verbal paired association II [8].
(3) Wisconsin Card Sorting Test, the computerized version, was used to assess abstraction ability and the ability to shift cognitive strategies in response to changing environmental contingencies. It is considered a measure of executive function in that it requires strategic planning, organized searching, the ability to use environmental feedback to shift cognitive sets, goal-oriented behavior, and the ability to modulate impulsive responding. It provides information on several aspects of problem-solving behavior [9].
(4) The Benton Visual Retention Test was used to assess visual perception, visual memory, and visual constructive abilities [10].
(5) In addition, the Hamilton Depression and Anxiety Rating Scale was used to exclude depression and anxiety.

Statistical analysis

Data were analyzed with SPSS (version 18; SPSS Inc., Chicago, Illinois, USA). Continuous variables such as age were expressed as mean ± SD, whereas categorical variables such as sex were presented as frequencies. The Pearson χ^2-test was used to detect significant associations between categorical variables. The independent-sample *t*-test (Student's *t*-test) was used to compare means of different groups. The level of significance was set as *P* value less than 0.5.

Results

The patient group consisted of 17 (42.50%) male and 23 (57.50%) female patients. The mean patient age was 28.100 ± 7.705 years. There was no statistically significant difference among the three groups as regards age and sex; however, the education level was less in patients (groups I and II) in comparison with controls (group III)

with statistical significance ($P = 0.000$), as shown in Table 1.

As regards the WAIS with its different subtypes, there was no statistical significance between group I (thalassemia major) and group II (thalassemia intermedia); however, there were a statistically significant difference between the patient group (I and II) and the control group (III) in all subsets, except for digit span, as shown in Table 2.

On the Wisconsin Card Sorting Test, there was no statistical significance on comparing group I (thalassemia major) and group II (thalassemia intermedia); however, on comparing the patient group with the control group, all were statistically significant, except for total correct, nonpreservative error, conceptional level response, number of trials to complete one category, failure to maintain set, and learning to learn, as shown in Table 3.

On the Benton Visual Retention Test, there was no statistical significance on comparing group I (thalassemia major) and group II (thalassemia intermedia); however, on comparing the patient group with the control group, all domains were statistically significantly affected, as shown in Table 4.

On correlation, it was found that, among thalassemia major patients (group I), most of the WAIS subsets correlate negatively with hepatitis C virus (HCV) infection, except for digit span and block design; thus, having HCV worsened the cognitive functions, as shown in Table 5.

Moreover, among β-thalassemia major patients, there was a correlation between liver functions and performance IQ and similarities. Another negative correlation was found between history of vaccination and all subsets, except for comprehension and digit span; being vaccinated rendered better performance on assessment. Pretransfusion Hb and heart abnormalities were of no significant correlation to cognitive functions, as shown in Table 5.

Among β-thalassemia intermedia patients, there was a negative correlation between history of vaccination and verbal IQ, total IQ, similarities, picture completion, and block design. Moreover, HCV infection was correlated with all Wechsler subsets, except for digit span and block design. Serum iron level was of no significance; age of splenectomy correlated weakly with digit span, similarities, and picture completion, as shown in Table 6.

Discussion

In recent studies conducted on β-thalassemia major patients, abnormal iron deposition was evident on MRI of

Table 1 Comparison of sociodemographic data between the three groups

	Major ($n=20$) (mean ± SD)	Intermedia ($n=20$) (mean ± SD)	Patients (mean ± SD)	Controls ($n=20$) (mean ± SD)	*P* value
Age (years)	25.05 ± 2.61	31.15 ± 9.77	28.100 ± 7.705	30.70 ± 5.53	P_1 0.01 P_2 0.03 P_3 0.98 P_4 0.184
Years of education	6.30 ± 3.50	7.90 ± 3.50	12.350 ± 2.368	12.35 ± 2.37	P_1 0.24 P_2 <0.001* P_3 <0.001* P_4 0.000*

P_1, major versus intermedia; P_2, major versus control; P_3, intermedia versus control; P_4, all patients versus control.
*P value is significant if <0.05.

Table 2 Comparison of the Wechsler Adult Intelligence Scale between the three study groups

WAIS	Major ($n=20$) (mean ± SD)	Intermedia ($n=20$) (mean ± SD)	Patients (mean ± SD)	Control ($n=20$) (mean ± SD)	*P* value
Verbal IQ	84.55 ± 5.25	87.50 ± 8.82	86.025 ± 7.319	102.50 ± 5.31	P_1 0.35 P_4 0.000*
Performance IQ	84.10 ± 7.33	88.30 ± 10.22	86.200 ± 9.033	107.20 ± 4.29	P_1 0.20 P_4 0.000*
Total IQ	83.70 ± 5.75	87.10 ± 9.11	103.85 ± 3.99	103.85 ± 3.99	P_1 0.25 P_4 0.000*
Digit span	5.95 ± 2.01	6.05 ± 2.21	6.000 ± 2.088	12.65 ± 15.23	P_1 1.00 P_4 0.067
Arithmetic	5.60 ± 0.88	5.95 ± 1.10	8.60 ± 2.48	8.60 ± 2.48	P_1 0.78 P_4 0.000*
Similarities	7.60 ± 1.76	7.70 ± 1.92	10.25 ± 1.25	10.25 ± 1.25	P_1 0.98 P_4 0.000*
Picture completion	7.80 ± 1.67	8.00 ± 1.56	9.95 ± 0.89	9.95 ± 0.89	P_1 0.90 P_4 0.000
Block design	7.40 ± 1.98	6.90 ± 2.02	9.20 ± 1.15	9.20 ± 1.15	P_1 0.65 P_4 0.000*
Digit symbol	7.45 ± 2.04	8.85 ± 2.46	13.30 ± 1.75	13.30 ± 1.75	P_1 0.10 P_4 0.000*

IQ, intelligence quotient; WAIS, Wechsler Adult Intelligence Scale.
P_1, major versus intermedia; P_4, all patients versus control.
*P value is significant if <0.05.

Table 3 Comparison of the Wisconsin Card Sorting Test between the three study groups

WCST	Major ($n=20$) (mean ± SD)	Intermedia ($n=20$) (mean ± SD)	Patients (mean ± SD)	Control ($n=20$) (mean ± SD)	*P* value
Trial administrated	97.90 ± 21.41	96.75 ± 23.23	97.325 ± 22.055	81.00 ± 7.47	P_1 0.98
					P_4 0.000*
Total correct	64.60 ± 9.49	63.40 ± 10.03	64.000 ± 9.658	67.15 ± 4.90	P_1 0.90
					P_4 0.099
Total error	33.30 ± 28.24	33.35 ± 29.24	33.325 ± 28.373	13.85 ± 3.87	P_1 1.00
					P_4 0.000*
% Error	30.10 ± 19.44	29.95 ± 20.22	30.025 ± 19.577	16.80 ± 3.41	P_1 1.00
					P_4 0.000*
Preservative response	30.00 ± 32.11	29.50 ± 32.04	29.750 ± 31.666	8.40 ± 3.39	P_1 1.00
					P_4 0.000*
% Perseverative response	23.500 ± 23.07	25.80 ± 23.39	24.650 ± 22.958	10.40 ± 3.08	P_1 0.92
					P_4 0.000*
Preservative error	21.95 ± 23.64	23.90 ± 24.88	22.925 ± 23.974	7.10 ± 2.10	P_1 0.95
					P_4 0.000*
% Preservative error	19.35 ± 17.06	12.00 ± 17.87	20.175 ± 17.268	8.65 ± 2.03	P_1 0.93
					P_4 0.000*
Nonpreservative error	11.35 ± 12.55	9.45 ± 9.83	10.400 ± 11.167	6.85 ± 2.81	P_1 0.80
					P_4 0.064
% Nonpreservative error	10.70 ± 9.21	9.10 ± 7.25	9.900 ± 8.224	8.25 ± 3.04	P_1 0.75
					P_4 0.391
Conceptional level response	58.30 ± 15.48	55.60 ± 18.35	56.950 ± 16.811	64.95 ± 4.37	P_1 0.82
					P_4 0.007*
% Conceptual level response	64.30 ± 24.37	63.40 ± 27.37	63.850 ± 25.520	80.65 ± 5.03	P_1 0.99
					P_4 0.000*
Categories completed	5.35 ± 2.30	4.80 ± 1.91	5.075 ± 2.105	6.00 ± 0.00	P_1 0.57
					P_4 0.008
Number of trials to complete 1 category	11.70 ± 1.42	11.70 ± 0.98	11.700 ± 1.203	13.15 ± 3.12	P_1 1.00
					P_4 0.057
Failure to maintain set	0.45 ± 0.89	0.25 ± 0.55	0.350 ± 0.736	0.15 ± 0.37	P_1 0.59
					P_4 0.165
Learning to learn	−8.35 ± 13.01	−7.64 ± 13.53	−8.005 ±	0.89 ± 173	P_1 0.98
					P_4 13.094

WCST, Wisconsin Card Sorting Test.
P_1, major versus intermedia; P_4, all patients versus control.
*P value is significant if <0.05.

brain structures, cortex, putamen, and caudate nucleus. In most of the cases, the neurological involvement is subclinical. A comparative study was carried out evaluating cognitive functioning in β-thalassemia major and intermedia patients and healthy controls using a full neuropsychological battery including tests of abstract reasoning, attention, executive functions, language, constructional/visuospatial skills, and memory. Our study was one of the scarce studies in Egypt to assess cognitive functions in thalassemia patients and to target a less studied group, thalassemia intermedia patients.

The study group consisted of 17 (42.50%) male and 23 (57.50%) female patients. The mean patient age was 28.100 ± 7.705 years (range: 20–36 years). There was a significant difference in years of education between the patient group and the control group. This may be explained by the frequent absence from school due to regular blood transfusion or due to weakness associated with this chronic illness, besides the negative effect of chronic anemia and disease complications on the learning ability of the patients. This finding is in agreement with the results noted by other researchers on thalassemic patients. An Indian study found that 90% of students with thalassemia take multiple days off from school, which affects more than 70% of their academic achievement. Moreover, thalassemia affected the scholastic performance of 70% of Indian adolescents adversely, as they had to take 1–3 days off from school every month to get their regular red cell transfusions, and complained that their academic performance was average or less because of their disease and its related problems. Over two-thirds of adolescents in the Indian study were unable to engage in outdoor play at the same level as their peers because of physical weakness related to their illness [11].

Our study demonstrated that there was a statistically significant impairment in all cognitive domains in thalassemia patients in comparison with controls. The striking finding was that in both β-thalassemia major and β-thalassemia intermedia patients cognition was affected with no significant difference despite the differences in severity and the onset of blood transfusion and chelation therapy. In a cross-sectional study by Teli *et al.* [12] to evaluate subclinical involvement of the central nervous system in young patients with thalassemia intermedia, 24 young patients with thalassemia intermedia were evaluated. As regards intelligence scores, the mean IQ was 100 ± 19.1, with 11.7% of patients demonstrating IQ below 85. The study results confirm subclinical central nervous system involvement starting at childhood [12]. Moreover, Duman *et al.* [13] found in a study of cognitive function in thalassemia major patients that all of the participants had normal IQ scores, but the patient group

Table 4 Comparison of the Benton Visual Retention Test between the three study groups

Benton Visual Retention Test	Major ($n=20$) (mean ± SD)	Intermedia ($n=20$) (mean ± SD)	Patients (mean ± SD)	Control (mean ± SD)	P value
Difference	6.30 ± 4.19	7.50 ± 4.25	6.900 ± 4.211	1.10 ± 0.79	P_1 0.52 P_4 0.000*
Expected error score	4.65 ± 0.88	4.50 ± 1.76	4.575 ± 1.375	2.85 ± 1.04	P_1 0.93 P_4 0.000*
Obtained error score	10.85 ± 4.73	11.50 ± 4.55	11.175 ± 4.590	3.35 ± 1.57	P_1 0.86 P_4 0.000*
Difference	3.25 ± 2.24	3.70 ± 2.15	3.475 ± 2.184	1.05 ± 0.83	P_1 0.73 P_4 0.000*
Estimated corre tedscore	6.65 ± 0.49	6.90 ± 0.79	6.775 ± 0.660	8.00 ± 0.56	P_1 0.42 P_4 0.000*
Obtained corre ted score	3.35 ± 2.23	3.20 ± 2.09	3.275 ± 2.136	7.15 ± 1.35	P_1 0.97 P_4 0.000*

P_1, major versus intermedia; P_4, all patients versus control.
*P value is significant if <0.05.

Table 5 Clinical correlates of cognitive functions in β-thalassemia major patients

	Clinical correlates								
	Liver functions (P value)			History of vaccination T-test		HCV infection T-test		Heart abnormalities	
Cognitive functions	ALT	AST	Pretransfusion Hb (P value)	t	P value	t	P value	t	P value
Verbal IQ	0.455	0.719	0.131	2.956	0.005	3.435	0.001	−0.439	0.663
Performance IQ	0.026	0.045	0.766	1.838	0.071	3.155	0.003	−1.775	0.084
Total IQ	0.843	0.472	0.237	2.675	0.010	3.318	0.002	−0.593	0.557
Comprehension	0.411	0.867	0.894	1.416	0.162	2.177	0.034	−1.509	0.140
Digit span	0.269	0.178	0.364	1.984	0.052	0.923	0.360	−0.664	0.511
Arithmetic	0.106	0.147	0.131	2.454	0.017	2.778	0.007	−0.777	0.442
Similarities	0.016	0.147	0.023	3.486	0.001	1.928	0.059	0.010	0.992
Picture completion	0.943	0.771	0.282	2.322	0.024	2.855	0.006	−0.835	0.409
Block design	0.135	0.514	0.486	2.271	0.027	1.237	0.221	−2.108	0.042

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; HCV, hepatitis C virus; IQ, intelligence quotient.

Table 6 Clinical correlates of cognitive functions in β-thalassemia intermedia patients

	Clinical correlates					
			History of vaccination T-test		HCV infection T-test	
Cognitive functions	Age of splenectomy (P value)	Serum iron levels (P value)	t	P value	t	P value
Verbal IQ	0.108	0.033	2.675	0.010	3.318	0.002
Performance IQ	0.246	0.113	1.838	0.071	3.155	0.003
Total IQ	0.61	0.098	2.956	0.005	3.435	0.001
Comprehension	0.154	0.421	1.416	0.162	2.177	0.034
Digit span	0.01	0.113	1.984	0.052	0.923	0.360
Arithmetic	0.063	0.218	2.639	0.011	2.778	0.007
Similarities	0.021	0.364	2.271	0.027	1.928	0.059
Picture completion	0.006	0.644	2.322	0.024	2.855	0.006
Block design	0.246	0.128	3.486	0.001	1.237	0.221

HCV, hepatitis C virus; IQ, intelligence quotient.

had significantly lower full-scale, performance, and verbal IQs compared with the control group. Sabry and Salama [14] found statistically significant differences between cases of thalassemia major and the control group as regards total intelligence and its verbal and performance components. The results indicate that the mean IQ of controls is within the low average range, whereas that of cases is within the borderline range. The scatter of the performance through different subscales of intellectual abilities shows near uniform poor performance among the cases, except for vocabulary and picture completion. The latter are subtests that are known to be less liable to deterioration with illness [14]. It is therefore proposed that the lower intellectual performance is at least partly a consequence of thalassemia regardless of severity or the onset and frequency of blood transfusion, which questions the sole role for hemosiderosis in impaired cognitive functions.

On the Benton Visual Retention Test, a statistically high significant difference in the performance on almost all domains between the patient and control groups was

elicited, with the patient group showing a poorer performance. Duman *et al.* [13] found that the number of children with visuomotor dysfunction was higher in the thalassemia patient group compared with the control group.

On correlating, HCV was found to statistically significant affect performance in all subsets of the WAIS except digit span and block design in both thalassemia major and thalassemia intermedia patients. This could be due to the effect of HCV on cognitive impairment. In a study by Forton *et al*. [15], 27 viremic patients with biopsy-proven mild hepatitis due to HCV and 16 patients with cleared HCV were tested with a computer-based cognitive assessment battery and also administered depression, fatigue, and quality-of-life questionnaires. The HCV-infected patients were impaired on more cognitive tasks compared with the HCV-cleared group. A factor analysis showed impairments in power of concentration and speed of working memory, independent of depression, fatigue, or symptom severity [15].

We found no correlation with pretransfusion Hb, liver functions, serum iron levels, and heart abnormalities. A very low correlation between age of splenectomy and some cognitive domains were found, which can be explained by severity of thalassemia intermedia. In a study by Monastero *et al.* [1], they found that in β-thalassemia major all cognitive domains were affected in comparison with controls as in this study. They could not find a significant correlation between systemic hemosiderosis (hepatic dysfunction and heart abnormalities), serum ferritine levels and Hb levels, which questions the role for hemosiderosis in degree of cognitive impairment [1].

Conclusion

We believe that cognitive impairment in thalassemia arises from multiple factors such as chronic hypoxic state and burden of illness and not only systemic hemosiderosis. All forms of thalassemia need psychological attention and assessment as early as possible. Besides, better health enhancement can yield better cognition as vaccination was correlated to better cognitive functions. All these findings should be applied in future plans to target thalassemia patients and render them better quality of services and life.

Limitations

This study shed light on the cognitive impairment found in β-thalassemia patients and its possible clinical correlates. However, it was not a well-representative community sample due to the small sample size. Thus, further studies on a larger sample size and more than one Egyptian government are warranted.

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Conflicts of interest

There are no conflicts of interest.

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