Original Article

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Cognitive Impairment in Children with Beta-Thalassaemia Major at a Tertiary Care Centre, Rajasthan, India: A Cross-sectional Study

Paediatrics Section

SANDEEP AVASARALA[1], ANUBHAV CHOUDHARY[2], KULDEEP SINGH BITHU[3], RENU AGRAWAL[4], GAJANAND SINGH TANWAR[5]

ABSTRACT

Introduction: Thalassaemia is one of the most common genetic disorders. Iron overload due to repeated blood transfusions and chelating therapy leads to oxidative stress and possible irreversible brain tissue damage, causing cognitive impairment in these children.

Aim: To study cognitive impairment in children with beta-thalassaemia major in a tertiary care centre in Bikaner, Rajasthan, India.

Materials and Methods: This was a hospital-based cross-sectional observational study conducted in the Department of Paediatrics, Sardar Patel Medical College, Bikaner, Rajasthan, India from September 2019 to August 2020. Sixty-five children with thalassaemia and 65 children without thalassaemia (as controls) were recruited and assessed using modified Mini-Mental State Examination (MMSE) for cognitive impairment.

Results: Majority of children belonged to age group 6-11 years (67.7% in cases and 68.8% in controls). The mean MMSE scores were significantly lower among children with thalassaemia (26.82±6.45) compared to the controls (29.08±5.71). There was a significantly higher prevalence of cognitive dysfunction in thalassaemia children (72.3%) as compared to controls (33.8%). Children who were compliant with chelation medications (n=30) were found to have a lesser prevalence of cognitive dysfunction (60%) than those who were not compliant (n=35) with medications (82.86%) (p-value=0.013). Among cases, the mean ferritin levels were higher in children with cognitive dysfunction (3399.00±1489.18) compared to those with normal cognitive function (2412.38±1117.26) (p-value=0.046). There was moderate positive correlation between thalassaemia child's Body Mass Index (BMI) and modified MMSE score.

Conclusion: This study highlights the higher prevalence of cognitive impairment in children with thalassaemia (72.3%). The key contributing factors were lack of compliance to chelation therapy, higher serum ferritin levels and low BMI.

Keywords: Body mass index, Chelation, Modified mini-mental state examination, Serum ferritin

INTRODUCTION

Thalassaemia was first described by Cooley and Lee in 1952, therefore, also named as Cooley's anaemia [1]. An estimated, 10,000-12,000 children are born every year with beta-thalassaemia major with an overall prevalence of beta-thalassaemia 3-4% [2]. The therapy regime of thalassaemia is complex, lifelong and inconvenient, as it requires repeated hospitalisations, which often affects the physical and mental health of children adversely [3]. The chronicity of the disease further affects the growth and development of the child [3,4].

Thalassaemia patients are dependent on regular blood transfusions to lessen complications of anaemia and expand bone marrow [5]. A study demonstrated, neurotoxicity in thalassaemia patients on chronic chelating therapy with deferoxamine [6]. In addition to neurotoxicity due to prolonged chelation therapy, repeated blood transfusions are associated with excessive iron absorption, iron overload and a chronic hypoxic state [6,7]. Increased iron in the brain leads to oxidative stress and possible irreversible brain tissue damage, causing cognitive impairment. All these events lead to brain dysfunction [8,9]. Metafratzi Z et al., stated that there was high iron deposition in the putamen, caudate nucleus, motor and temporal cortex of patients with beta-thalassaemia major [10]. These areas are as extremely imperative for cognitive function as much as they are for explicit and implicit memory.

In most cases, neurological involvement in thalassaemia major does not firstly present with relevant signs and symptoms (subclinical), and can only be perceived during neurophysiological and neuropsychological assessment [11]. A study by Gamyani U et al., concluded that patients with thalassaemia had lower cognitive function as compared to the control group [12]. Daar S et al., found that deficits were present in the domains of executive function and working memory among thalassaemia patients as compared to controls [13].

In India, unlike the developed countries, the care of these children is engrossed in medical management alone, and issues pertaining to mental health are not addressed [14]. Data strongly supports the need for an integrated psychosocial program that includes screening for neurocognitive problems to be part of the overall management of these patients [15]. Hence, this study has been undertaken to evaluate cognitive functions in children with thalassaemia and the factors influencing them, so as to accentuate the importance of accomplishing not only physical well-being but also the mental and social well-being among these children.

MATERIALS AND METHODS

This hospital-based cross-sectional observational study was conducted in the Department of Paediatrics, Sardar Patel Medical College and PBM Hospital, Bikaner, Rajasthan, India, between September 2019 and August 2020. Ethical approval was obtained from Institutional Ethics and Research Board {F.29(Acad) SPMC/2020/2797}. After taking consent from the caregivers, in children selected for this study, detailed history was taken and a thorough clinical examination was done on the day of admission. The entire findings were recorded on predesigned proforma.

Inclusion criteria: Children with beta-thalassaemia major who were admitted to the thalassaemia daycare centre during the study period and who had received chelation therapy atleast for four weeks

duration were taken as cases. Siblings (of cases) without beta-thalassaemia major or any other chronic illness and who are not traits for thalassaemia (in whom Haemoglobin electrophoresis was performed) were taken as controls. Controls were matched with cases for age and gender.

Exclusion criteria: Children whose caregivers refused to give consent to the study and children who were critically ill requiring intensive care at the time of study were excluded from the study.

Study Procedure

The modified Mini-Mental State Examination (MMSE) scale for children was used to study cognitive impairment [16]. The MMSE has 11 questions in five categories-orientation, attention-concentration, registration, recall, and language. The original categories of the test were used, but tests that can be performed in the paediatric age group from 6-17 years were chosen. Appropriate tests, which have been earlier standardised in an Indian setting, were used in the study. The tests were chosen after deliberation with a trained psychologist regarding its ability to test what it is purporting to test and the ability to be understood by Indian children of various socio-economic strata and education.

Cognitive dysfunction was defined as modified MMSE score less than two standard deviations below mean for age, i.e., below the cut-off value for age as mentioned in the [Table/Fig-1].

Age group (years)	Mean±Standard deviation	Score at two standard deviations (approximately)
6-8	34.72±3.03	28
9-11	34.90±2.77	30
12-17	36.80±0.63	35

[Table/Fig-1]: Mean and standard deviation of modified child MMSE scores in different age.

Socio-economic status was defined by modified Kuppuswamy scale 2019 [17]. For the purpose of this study, the immunisation of the child was considered complete, if child had received all due vaccine as per national immunisation schedule within first year age of child.

All cases were taking standard recommended dosage of deferasirox tablets as a part of chelation therapy starting within two years of initiation of blood transfusions and when their serum ferritin levels are above 1000 µg/dL. A child who missed more than two doses in a week for four consecutive weeks was categorised as non compliant to therapy.

STATISTICAL ANALYSIS

Data was entered in to Microsoft excel software and statistical analysis was done using Statistical Package for the Social Sciences (SPSS) software version 23.0. Data was analysed with the help of frequencies, figures, proportions and measures of central tendency, and appropriate statistical tests such as Wilcoxon-Mann-Whitney U test, Chi-square test, Fisher's-exact test, Kruskal-Waliis test, and t-test were used. A p-value <0.05 was considered statistically significant.

RESULTS

The age and gender distribution of the study population of cases and controls has been demonstrated. The gender distribution in cases was similar to that of controls, indicating that cases and controls were matched for gender without significant difference (p-value=0.0937) and significant difference was found in the age distribution (p-value <0.001) [Table/Fig-2].

The prevalence of cognitive dysfunction was higher in cases (72.3%) than controls (33.8%) (p-value= 0.009). But in cases, there was no significant difference in prevalence among different age groups [Table/Fig-3].

Variables		Cases n (%)	Controls n (%)	p-value
Gender	Male	36 (55.4%)	35 (53.8%)	0.0937[1]
	Female	29 (44.6%)	30 (46.2%)	
Age (years)	6-8 years	24 (36.92%)	21 (32.30%)	<0.001*[2]
	9-11 years	20 (30.77%)	24 (36.92%)	
	12-17 years	21 (32.30%)	20 (30.77%)	

[Table/Fig-2]: Age and gender distribution of cases (n=65) and controls (n=65). [1]Chi-square test; [2]Student's t-test; *p-value <0.05 was considered statistically significant

Parameter	Age (years)	Cases n (%)	Controls n (%)	p-value
Cognitive dysfunction present	6-8	19 (79.17%)	9 (42.86%)	0.1461
	9-11	12 (60%)	6 (25%)	
	12-17	16 (76.20%)	7 (35%)	
	Total prevalance	47 (72.3%)	22 (33.8%)	0.009*

[Table/Fig-3]: Prevalence of cognitive dysfunction in cases and controls. *p-value <0.05 was considered statistically significant (Chi-square test)

The prevalence of thalassaemia among cases was slightly higher in females (82.8%) compared to males (63.9%) but the difference was not statistically significant (p-value=0.091) [Table/Fig-4]. There was no significant difference in prevalence of cognitive dysfunction across different blood groups among thalassaemia children. Cognitive dysfunction was found to be little higher among children belonging to upper middle class (60%) and lower class (60%) but the difference was not significant (p-value=0.450). Factors like immunisation status and type of residence (rural/urban) did no show significant difference in prevalence among thalassaemia children. Children who were compliant with chelation medications were found to have lesser prevalence of cognitive dysfunction (60%) than those who were not (82.86%) (p-value=0.013).

Variables	Modified MMSE score (Mean±SD)	p-value	Cognitive Impairment present, n (%)	χ^2	p-value
Gender				2.856	0.0912[2]
Male	27.42±6.85	0.4513[1]	23 (63.9%)		
Female	26.07±5.95		24 (82.8%)		
Blood group				9.375	0.1463[3]
A-	28.50±0.71	0.0893[5]	0 (0.0%)		
A+	24.76±6.88		18 (85.7%)		
AB+	30.80±3.27		3 (60%)		
B-	21.67±2.52		3 (100%)		
B+	26.05±6.59		14 (70%)		
O-	27.00±7.07		1 (50%)		
O+	31.00±5.31		8 (66.7%)		
Socio-economic status				2.356	0.4503[3]
Upper Middle	28.60±6.92	0.6813[5]	6 (60%)		
Lower Middle	26.91±5.65		16 (34.0%)		
Upper Lower	26.00±6.13		22 (46.8%)		
Lower	27.20±11.21		3 (60%)		
Immunisation status				0.349	0.7133[3]
Complete	24.44±2.12	0.4113[1]	39 (70.90%)		
Incomplete	26.33±3.03		8 (80.0%)		
Residence				0.690	0.4062[2]
Rural	25.41±6.43	0.1413[4]	21 (77.78%)		
Urban	27.82±6.36		26 (68.42%)		
Formal school education				3.642	0.3453[3]
None#	22.50±6.32	0.002*[5]	20 (76.92%)		
Nursery	24.58±5.57		6 (75.0%)		
Primary	28.33±6.80		8 (53.33%)		
Secondary	31.19±4.76		13 (81.25%)		

Compliance with medications (chelation)					
Yes	27.31±3.33	0.044*[1]	18 (60%)	0.349	0.0133*[3]
No	22.66±4.11		29 (82.86%)		

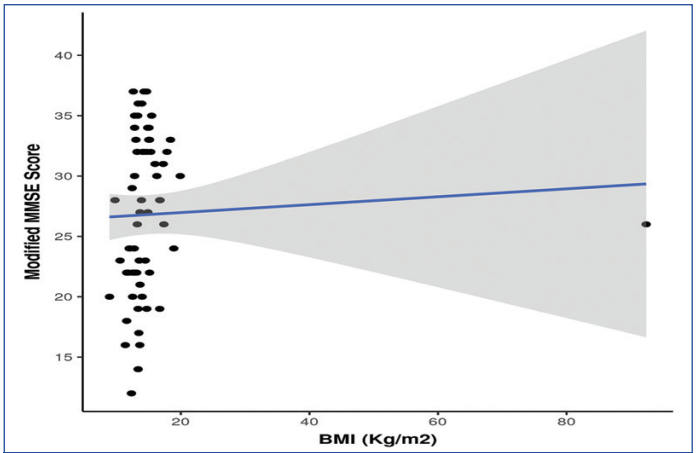
[Table/Fig-4]: Association between cognitive dysfunction and parameters among cases.
*p-value <0.05 was considered statistically significant; [1]Wilcoxon-Mann-Whitney U test; [2]Chi-square test; [3]Fisher's-exact test; [4]t-test; [5]Kruskal-Wallis test; [#]Percentage; [#]Percentage of children not received formal education is matched between cases and controls to avoid confounding

There was no significant difference in the mean age of the children, and their parents, among thalassaemia children with and without cognitive dysfunction. It was noticed that the mean age at which the diagnosis (of thalassaemia) was made was lower among children with cognitive dysfunction (8.50±3.07) as compared to children without it (12.13±4.22). Which suggests that, earlier the onset of disease, higher the chance for the child to develop cognitive dysfunction. It was also observed that the mean of total transfusions received by the child (153.89±52.45) (p-value=0.033) and the mean serum ferritin levels of the children (3399.00±1489.18) (p-value=0.046) was found to be higher in children with cognitive dysfunction compared to those with normal cognitive function [Table/Fig-5].

Parameters	Cognitive dysfunction		W	p-value (Wilcoxon-Mann-Whitney U test)
	Present (n=47) (Mean±SD)	Absent (n=18) (Mean±SD)		
Age (years)	9.57±3.76	9.44±3.31	391.500	0.642
Father's age (years)	36.09±6.91	35.44±7.57	469.500	0.495
Mother's age (years)	31.74±7.29	30.89±6.39	439.500	0.814
Age at diagnosis (months)	8.50±3.07	12.13±4.22	460.500	0.584
Number of transfusions till date	153.89±52.45	105.28±43.75	295.500	0.033*
Serum ferritin levels (µ/L)	3399.00±1489.18	2412.38±1117.26	407.500	0.046*

[Table/Fig-5]: Association between mean modified MMSE and parameters among the case group.
*p-value <0.05 was considered statistically significant (Wilcoxon-Mann-Whitney U test)

There was a moderate positive correlation between Body Mass Index (BMI) and modified MMSE Score, and this correlation was statistically significant (rho=0.33, p-value=0.007). This suggests adequate physical growth of the child is associated with improved cognitive function [Table/Fig-6].



[Table/Fig-6]: Correlation between Body Mass Index (BMI) (Kg/m^2) and Modified MMSE Score among cases (n=65).
For every 1 unit increase in BMI (Kg/m^2), the Modified MMSE Score increases by 0.03 units. Conversely, for every 1 unit increase in Modified MMSE Score, the BMI (Kg/m^2) increases by 0.08 units

DISCUSSION

In the present study, the modified mini-mental state examination was done to evaluate the cognitive function in children with beta-thalassaemia major. Cognitive function was evaluated in five domains namely-orientation, attention and concentration, registration and sensory perception, language, and recall. The mean MMSE scores and prevalence of cognitive dysfunction were significantly higher among controls as compared to those with thalassaemia. Similar findings were reported by El-Alameey IR et al., who evaluated cognitive function using Wechsler Intelligence Scale [18]. The study revealed that the mean total IQ (Intelligent Quotient) score (92.86±17.72) of cases was significantly lower than those of controls (101.42±6.47). The results were also consistent with that of Raafat N et al., who found marked lower performances and full-scale IQ scores in thalassaemic children compared to normal children [19]. Economou M et al., also claimed that children with beta-thalassaemia had increased impairments in cognitive performance [20]. A study by Duman O et al., also suggested that full-scale IQ, performance IQ, and verbal IQ were markedly lower in thalassaemia children (p-value<0.05) [21]. Conversely, Karimi M et al., found no significant difference in IQ between patients with thalassaemia compared to controls [22]. Their study indicated that, although abnormalities in affective state, behaviour, and character were seen, the intellectual functions remain generally within the expected normal range. This could be because of other protective factors such as adequate chelation therapy, normal growth (BMI) and comparatively lower serum ferritin levels in their study population. The mean age of controls and mean BMI were higher; and mean serum ferritin levels of the controls were lower in their study as compared to the present study. These factors could have probably resulted in difference in outcome of their study.

A study by Daar S et al., in Oman revealed that cognitive functions such as executive functions, working memory, auditory and visual attention functions score were affected in adults with beta-thalassaemia major compared to healthy controls. Attention is a primary cognitive function critical for perception, language and memory. The mechanism of attention and executive impairment in beta-thalassaemia children was thought to be the result of chronic hypoxia, and related to the chronic anaemic condition [13].

In the present study, thalassaemic children who were not compliant with chelation medications were at higher risk of having cognitive dysfunction compared to their counterparts. The risk of cognitive dysfunction was found to increase in children in whom thalassaemia was diagnosed at later age, children with higher serum ferritin values and children who underwent more blood transfusions. The cognitive function correlation with other variables such as child's education status, child's residence (rural/urban), and socio-economic status of the child's family, was not found to be statistically significant and was not evaluated by other studies (to the best of our knowledge).

The present study also demonstrated higher mean serum ferritin levels in thalassaemia children with cognitive dysfunction compared to children without cognitive dysfunction. This finding was in agreement with Monastero R et al., which suggested that cognitive function was affected more in thalassaemia children with haemosiderosis [23]. Similar observations were found in studies by El-Alameey IR et al., and Duman O et al., which suggested a negative correlation between IQ scores and Serum ferritin levels [18,21]. A study by Qurbani SN et al., found no correlation between serum ferritin levels and cognitive function in children with thalassaemia major, possibly due to the lack of signs of haemosiderosis in the brain caused by iron overload [24]. Another study reported that the neuropsychological scores were significantly lower in beta-thalassaemia major patients aged >16 years with signs of systemic haemosiderosis [21]. In addition, the specificity of serum ferritin levels as a marker of haemosiderosis is low owing to its susceptibility to infections and inflammatory conditions [5]. High serum ferritin levels can be prevented by ensuring timely start of chelation therapy and making sure the child is compliant with the therapy. Educating caregivers of

the children regarding the importance of chelation therapy can also be an important step in ensuring child's compliance to therapy.

This study also demonstrated positive correlation between child's BMI and cognitive function. Similarly, El-Alameey IR et al., also established a positive correlation between BMI and performance IQ [18]. Timely monitoring of growth of these children and ensuring normal growth through optimum nutrition can be helpful in improving their BMI and therefore their cognitive function as well.

Limitation(s)

The study was conducted on a small sample of children with thalassaemia. This limits the generalisation of the results. Magnetic resonance imaging was not performed in the cases to correlate cognitive impairment radiologically.

CONCLUSION(S)

This study highlights the prevalence of cognitive impairment in children with thalassaemia. The factors that were found to have an association with cognitive impairment were inadequate chelation therapy and subnormal physical growth. For proper cognitive development in children with thalassaemia, the present study strongly recommends timely screening; and the need for competent behavioural and cognition therapy, proper schooling, adequate chelation therapy, and consistent growth monitoring.

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PARTICULARS OF CONTRIBUTORS:
1. Medical Officer, Department of Paediatrics, Government District Hospital Kekri, Ajmer, Rajasthan, India.
2. Senior Resident, Department of Paediatrics, Sardar Patel Medical College, Bikaner, Rajasthan, India.
3. Principal Specialist, Department of Paediatrics, Sardar Patel Medical College, Bikaner, Rajasthan, India.
4. Senior Professor, Department of Paediatrics, Sardar Patel Medical College, Bikaner, Rajasthan, India.
5. Professor, Department of Paediatrics, Sardar Patel Medical College, Bikaner, Rajasthan, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Gajanand Singh Tanwar,
Professor, Department of Paediatrics, PBM Child Hospital, Bikaner, Rajasthan, India.
E-mail: avasarala.88@gmail.com

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