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# Cognitive Status In Thalassemia

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## Abstract

***Background:*** *Thalassemia is one of the most common chronic and genetic hematological disorder. This chronic disease challenges the individual at the physical, emotional, cognitive level and disrupts the quality of life because of persistent anemia and hypoxia. The aim of study is to assess the cognitive status in thalassemia.*

***Material and methods:*** *This is a cross-sectional observational type of study that was performed in Autism and Child Development Center of Chattagram Maa Shishu–O–General Hospital. Children aged 6 to 16 years with thalassemia of different catagories were enrolled as study subjects. Study period was six months. Cognitive status of this study subject was assessed by WICS-IV equipment.*

***Results:*** *Among the 50 study subjects, Hb E β thalassemia was the most common type of thalassemia 39(78%). 2(4%) patient took oral chelating agent, 18 (36%) were under injectable, 20(40%) were found taking both oral and injectable and 10(20%) were observed not under any iron chelation therapy. Regular iron chelation therapy was found in 22(44%) cases.10(20%) cases had normal intelligence,19(38%) cases had mild mental retardation and 21 (42%) had moderate mental retardation. Among the 10 patients who do not use any chelation therapy,8(80%) patients had moderate retardation and 2(20%) had mild mental retardation. On the other hand, among the 40 patients who were having iron chelation therapy, 10(25%) patients showed normal level of intelligence, 17(42.5%) had mild mental retardation and 13(32.5%) had moderate mental retardation. In different score of WISC-IV, it was found that working memory and processing speed were poorer than verbal comprehension and perceptual reasoning in different type of thalassemia. This study also showed poor cognition is more prominent in thalassemia major and Hb E beta thalassemia.*

***Conclusion:*** *Cognitive status of the study subjects who take regular iron chelation therapy is much better than those who do not take iron chelation therapy. Hence, iron chelation therapy is proved to have better cognitive outcome for thalassemia patients with iron overload.*

**Key words:** Chelating agent; Cognitive status; Thalassemia.

## INTRODUCTION

Thalassemia is one of the most common chronic and genetic hematological disorders encountered globally.[1] It refers to genetic disorders in globin chain production. The primary pathology in thalassemia stems from the quantity of globin chain production.[2] There are approximately 240 million people worldwide who are heterozygous for beta thalassemia while approximately 200,000 affected homozygotes are born annually.[1] Bangladesh is situated in the thalassemia belt where about 3% of the total population (i.e. about 3.6 million people of our country) has Beta Thalassemia trait.[3] More than two thousand thalassemia children are born every year in our country.[4] This high prevalence causes a significant burden on health resources.[5]

Bone marrow transplantation may offer the possibility of a cure in young people who have an HLA-matched donor.[6] Success rates have been in the 80-90% range. Mortality from the procedure is about 3%.[7] Multiple blood transfusions can result in iron overload. The iron overload related to thalassemia may be treated via chelation therapy with the medications deferoxamine, deferiprone or deferasirox. These treatments have resulted in improved life expectancy in those with thalassemia major.[8]

This is a major health problem not only for the patients and their families, but also for the public health system of each country due to the cost of treatment involving regular blood transfusion, iron chelation, frequent hospitalization and general medical follow-up.[9]

Given the often unpredictable and fluctuating course of thalassemia, it is apparent that the disease is related with frequent re-hospitalizations and repeated absences from school and therefore low school performance. Numerous other factors responsible for low school performance include impaired abstract reasoning, deficits of language, attention, memory or visual spatial skills and executive functions which are more prominent in hemosiderotic patients.[10-15] Moreover, silent brain infarcts may be responsible for neurological and cognitive impairment mainly attributed to the chronicity of the disease.[16] Chronic hypoxia, increased oxidative stress possibly associated with hemoglobinopathies or chronic hemolysis also can be blamed in the etiology of neurological findings.[17,18]

Cognition includes memory, language, orientation, judgment, conducting interpersonal relationships, performing actions and problem solving.Cognitive disorders reflect disruption in one or more of the above domains and are also frequently complicated by behavioral symptoms.[19]

Some study reported that the neuro-psychological tests were significantly impaired especially in patients with signs of hemosiderosis.[20] Modern treatments have greatly increased the life expectancy of patients with thalassemia. 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.[21]

The high prevalence of β thalassemia and the fact that it hinders psychosocial adjustment in affected children is markedly alarming. This dictates the importance of integrating a multi-dimensional psychosocial battery in the regular follow-up and clinical assessment of thalassemia patients in order to detect and manage any psychosocial disturbance in the early stages. Adopting the bio psychosocial approach in managing such lifelong medical conditions may add considerably to compliance and quality of life of these patients and their families. It also may help in reducing the cognitive handicap and hence the social and economic burden.[22]

## MATERIALS AND METHOD

This study was a cross sectional observational study carried out in Autism and Child Development Center of Chattagram Maa-Shishu O General Hospital during the period of July to December 2014. The patient aged 6-16 years, thalassemia proven by Hb-electrophoresis and no history of other chronic disease were enrolled. The thalassemia patients who were not attending school and very sick children were excluded from this study. All subjects were assessed by the Wechsler Intelligence Scale for Children – Fourth edition (WISC-IV). By this scale following domains were assessed- verbal comprehension, Perceptual Reasoning, working Memory and processing speed. Different items appropriate for age were used for assessment of particular domains. Mild, moderate and severe grading was applied according to the abilities of subject to perform various tasks. Score >70 is assigned as normal, 55 to 69 is mild, 40 to 54 is moderate and <40 is severe.

## RESULTS

A total 50 children aged 6-16 years, who attended Chattagram Maa- Shishu O General Hospital, during the period of July to December 2014 were enrolled as study subjects. The patient group consisted of 23 (46%) male and 27(54%) female patients. The most common type of thalassemia was Hb E beta thalassemia which was 39 (78%), beta thalassemia major 9 (18%) and Hb-E disease was 2 (4%).Among the thalassemia patients who had iron overload used iron chelating agent, 2 (4%) of them were on oral agents ,18 (36%) on injectable,20 (40%) on both oral and injectable and 10 (20%) did not use any chelating agents. Within these patients, 22 (44%) was on regular iron chelating agents and 18(36%) used irregularly. The study shows 21(42%) thalassemia patients had moderate mental retardation, 19(38%) had mild mental retardation and 10(20%) had normal intelligence level. According to WICS- IV scoring ,working memory and processing speed score were poorer than verbal comprehension and perceptual reasoning score in different types of thalassemia. Among the 10 patients who did not use any chelation therapy, 8 (80%) patients had moderate mental retardation and 2 (20%) had mild mental retardation. On the other hand, among the 40 patients who were having iron chelation therapy,10(25%) patients showing normal level of intelligence, 17(42.5%) had mild mental retardation and 13(32.5%) had moderate mental retardation. 18 patients who used only injectable chelation therapy, 11 (61.1%) of them had moderate mental retardation, 5 (27.8%) had mild mental retardation and 2(11.1%) had normal intelligence level. Those thalassemia patients who used both injectable and oral chelation therapy, 6 (30%) patients had normal intelligence level, 12 (60%) had mild mental retardation and 2 (10%) had moderate mental retardation. Among the 9 patients with thalassemia major, 4 (44.4%) had moderate mental retardation, 3 (33.3%) had mild mental retardation and 2 (22.2%) had normal intelligence level. Among the 39 Hb E beta thalassemia

patients, 17 (43.5%)patient had moderate mental retardation, 14 (36%) had mild mental retardation and 8 (20.5%) hads normal intelligence level.

**Table I** Sex of the respondents

| Sex | Frequency (n = 50 ) | Percent (%) |
|---|---|---|
| Male | 23 | 46.0 |
| Female | 27 | 54.0 |
| Total | 50 | 100.0 |

**Table II** Type of Thalassemia

| Types | Frequency (n = 50 ) | Percent (%) |
|---|---|---|
| beta- thalassemia major | 9 | 18.0 |
| Hb-E disease | 2 | 4.0 |
| Hb E beta thalassemia | 39 | 78.0 |
| Total | 50 | 100.0 |

**Table III** Type of Iron chelating agent

| Types | Frequency (n = 50 ) | Percent (%) |
|---|---|---|
| Oral | 2 | 4.0 |
| Injectable | 18 | 36.0 |
| Both | 20 | 40.0 |
| Not used | 10 | 20.0 |
| Total | 50 | 100.0 |

**Table IV** Regularity of iron chelating agent

| | Frequency (n = 50 ) | Percent (%) |
|---|---|---|
| Regular | 22 | 44.0 |
| Irregular | 18 | 36.0 |
| None | 10 | 20.0 |
| Total | 50 | 100.0 |

**Table V** Level of intelligence

| IQ Level | Frequency (n = 50 ) | Percent (%) |
|---|---|---|
| Normal (>70) | 10 | 20.0 |
| Mild mental retardation (55-69) | 19 | 38.0 |
| Moderate mental retardation (40-54) | 21 | 42.0 |
| Total | 50 | 100.0 |

**Table VI** Different Scores of WISC-IV

| Type of Thalassemia | | Score: Verbal comprehension | Perceptual Reasoning | Working Memory | Processing Speed |
|---|---|---|---|---|---|
| Beta- Thalassemia major | Mean | 75.44 | 73.00 | 58.56 | 55.67 |
| | N | 9 | 9 | 9 | 9 |
| | Std. Deviation | 13.135 | 24.042 | 2.877 | 35.135 |
| Hb-E disease | Mean | 71.00 | 96.00 | 62.00 | 50.00 |
| | N | 2 | 2 | 2 | 2 |
| | Std. Deviation | .000 | .000 | .000 | .000 |
| Hb E Beta Thalassemia | Mean | 74.70 | 70.92 | 63.23 | 63.10 |
| | N | 39 | 39 | 39 | 39 |
| | Std. Deviation | 28.96 | 23.32 | 8.59 | 18 |
| Total | Mean | 74.30 | 72.30 | 62.34 | 61.24 |
| | N | 50 | 50 | 50 | 50 |
| | Std. Deviation | 18.039 | 16.883 | 5.812 | 17.635 |

In different score of WISC-IV showing working memory and processing speed score are poorer than verbal comprehension and perceptual reasoning score in different type of thalassemia.

**Table VII** Relation of types of iron chelation with level of intelligence

| IQ Level | | On Iron Chelation Therapy: Oral Injectable n=2 | Injectable n=18 | Both n=20 | Total n=40 | No Iron Chelation Therapy n=10 |
|---|---|---|---|---|---|---|
| Level of intelligence | Normal (>70) | 2 | 2 | 6 | 10 | 0 |
| | | 100.0% | 11.1% | 30.0% | 25.0% | 0.0% |
| | Mild mental retardation (55-69) | 0 | 5 | 12 | 17 | 2 |
| | | 0.0% | 27.8% | 60.0% | 42.5% | 20.0% |
| | Moderate mental retardation (40-54) | 0 | 11 | 2 | 13 | 8 |
| | | 0.0% | 61.1% | 10.0% | 32.5% | 80.0% |
| Total | | 2 | 18 | 20 | 40 | 10 |
| | | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |

Chi square value=24.486, p=0.001 (p<0.05 is considered significant).

**Table VIII** Relation of types of thalassemia and level of intelligence

| IQ Level | | Type of Thalassemia: beta- thalassemia major n=9 | Hb-E disease n=2 | Hb E beta thalassemia n=39 | Total n=50 |
|---|---|---|---|---|---|
| Level of intelligence | Normal(>70) | 2 | 0 | 8 | 10 |
| | | 22.2% | 0.0% | 20.5% | 20.0% |
| | Mild mental retardation (55-69) | 3 | 2 | 14 | 19 |
| | | 33.3% | 100.0% | 36.0% | 38.0% |
| | Moderate mental retardation (40-54) | 4 | 0 | 17 | 21 |
| | | 44.4% | 0.0% | 43.5% | 42.0% |
| Total | | 9 | 2 | 39 | 50 |
| | | 100.0% | 100.0% | 100.0% | 100.0% |

Chi square value-= 12.924, p value= 0.044.

## DISCUSSION

Cognition includes memory, language, orientation, judgment, conducting interpersonal relationships, performing actions and problem solving. Cognitive disorders reflect disruption in one or more of the above domains and are also frequently complicated by behavioral symptoms.[19] Some study reported that the neuro-psychological tests were significantly impaired especially in patients with signs of hemosiderosis.[20] Of all available cognitive tests for children, the Wechsler series is the most popular to the clinicians and the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) is most widely used measure of children's intelligence.[23]

In this study regarding sex distribution male was (46%) and female was (54%). A study by Uddin et al. showed that 50.1% were male and 49.3% were female, which gives an equal incidence in both male and females.[24] Hb E beta thalassemia was found to be the most common (78%) type of thalassemia syndrome, followed by beta thalassemia major(18%) in this study. M Uddin et al. found that beta thalassemia minor (21.3%) was the most prevalent than E-β thalassemia (13.5%), Hb E trait (12.1%) and Hb E disease (9.2%) in Bangladesh.[24] Samir Palit et al. found 77.4% E-β thalassemia in greater Chittagong which is consistent with this study.[25]

In terms of iron chelation, it was found that (4%) received oral therapy, (36%) injectable, (40%) both Oral & Injectable and (20%) took neither oral nor Injectable. There were 44% patients on regular iron chelation therapy. As regard to the method of taking chelation therapy Samra et al. observed that 19.6%, 32.4%, 17.9% and 23.1% of the studied thalassemia children took the medicines via oral, intravenous, subcutaneous infusion and combined methods respectively.[26] Chelation is a routine practice among thalassemic patients, but some of the patients are not taking iron chelation due to financial inability and other reasons; these patients are potentially vulnerable to risks of high iron overload which causes hemosiderosis, an important cause of poor cognition.[15] This study also showed that among patients who did not use any type of iron chelation therapy, (80%) had moderate mental retardation and (20%) had mild mental retardation. On the other hand, among the 40 patients who were having iron chelation therapy, (25%) patients showed normal level of intelligence, (42.5%) had mild mental retardation and (32.5%) had moderate mental retardation. In the patients who were using only Injectable chelation therapy, 61.1% showed moderate mental retardation; while 27.8% of them developed mild mental retardation, 10% of patients using both oral and injectable chelation therapy had moderate mental retardation while 60.0% of them had mild mental retardation. In a study by M. S. Elalfy et al. neurophysiological tests among cases were significantly impaired as compared to control group, especially in those receiving injectable (Desferrioxamine). In terms of total IQ levels using oral chelating agent showed better outcome than isolated injectable (DFO) and combination therapy (Oral and injectable).[27]

This study revealed (20%) had normal intelligence (38%) had mild mental retardation and (42%) had moderate mental retardation. This is almost similar to the study of M.S.Elafy et al which showed 40% of cases were borderline mental function as regards to total IQ, while 41% had average IQ, compared to 65% of controls with average IQ and 22.5% were normal.[27]

In the different score of WISC- IV, working memory and processing speed score were poorer than verbal comprehension and perceptual reasoning score. Similar to our study Sabry N et al. had found uniform poor performance among cases except for vocabulary and picture completion.[22]

This study shows that among beta thalassemia major 44.4% patient have moderate mental retardation, 33.3% patient have mild mental retardation and 22.2% have normal intelligence score. Among Hb E-beta thalassemia patients 43.5% have moderate mental retardation, 36% have mild mental retardation and 20.5% have normal intelligence score. Mahmoud M. Elhabiby et al found that in β thalassemia major patients cognition was affected with no significant difference despite the differences in severity and the onset of blood transfusion and chelation therapy.[28] As regards intelligence scores, in a cross- sectional study by Teli A et al to evaluate subclinical involvement of the central nervous in young patients with thalassemia intermedia showed 11.7% of patients demonstrating IQ below 85. The study results confirm subclinical central nervous system involvement starting at childhood.[29]

Our study results indicate that thalassemia is associated with neuropsychological impairment involving multiple cognitive domains and those who are regular under iron chelation therapy have better cognitive status.

## LIMITATIONS

The study conducted was a single center study with a small sample size and without long term follow up. Also there was no control group in this study.

## CONCLUSION

This study was conducted to assess memory, language, processing speed as well as intelligence of a thalassemic child. The outcome shows that thalassemia is associated with neuropsychological impairment involving multiple cognitive domains. Cognitive status of the study subjects who were taking regular iron chelation therapy was much better than those who were not taking iron chelation therapy.

## RECOMMENDATION

Iron chelation therapy in a patient with thalassemia who have iron overload is mandatory for better cognitive outcome.

## DISCLOSURE

All the authors declared no competing interest.

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