Section: Pediatrics

Original Research Article

NEUROLOGICAL COMPLICATIONS OF REPEATED BLOOD TRANSFUSION IN BETA THALLASSEMIA MAJOR PATIENTS WITH REFERENCE TO NEUROPHYSIOLOGICAL EVALUATION AND NEUROIMAGING FINDINGS -A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Beta thalassemia major is a common hereditary blood disorder requiring lifelong blood transfusions. While transfusion therapy improves survival, it may lead to systemic complications including neurological abnormalities like cognitive impairment, peripheral neuropathies, focal neurological episodes. Early identification of such complications, especially subclinical findings, is crucial for timely intervention. Neurophysiological evaluation like Nerve Conduction Studies (NCS) and neuroimaging can serve as a valuable tool in detecting peripheral nervous system (PNS) and central nervous system (CNS) involvement earlier in these patients. This study was conducted with aim to identify and characterize neurological complications among pediatric patients with beta-thalassemia major who are receiving repeated blood transfusions. Specifically, it sought to assess cognitive deficits using standardized intelligence scales, detect peripheral neuropathies through nerve conduction studies, and identify cerebrovascular lesions via magnetic resonance imaging (MRI) and to correlate neurological findings with key clinical parameters, such as the number of transfusions and serum ferritin levels, to explore potential predictors of neurological morbidity in this population. **Materials and Methods:** This was a hospital-based, prospective, observational analytical study conducted over one year (June 2023 to July 2024) in the Department of Pediatric Thalassemia Ward, Calcutta National Medical College and Hospital, Kolkata, West Bengal. Total 77 Children aged 3 to 12 years with a confirmed diagnosis of beta-thalassemia major and a history of at least ten transfusions were enrolled after obtaining informed consent. Clinical evaluation focused on identifying neurological sign and symptoms such as numbness, paresthesia, motor or sensory deficits. Full-scale intelligence quotient (FSIQ) was assessed using age-appropriate Wechsler scales (Wechsler Preschool and Primary Scale of Intelligence-IV and Wechsler Intelligence Scale for Children-V). Nerve conduction studies (NCS) were performed and MRI brain imaging was undertaken in those presenting with focal neurological signs or severe headaches. **Result:** Out of 77 beta thalassemia major patients, 29.87% showed NCS abnormalities with predominant polyneuropathy (65.2%) affecting mainly lower limb (60.8%) and majority involved both sensory and motor component (56.5%) followed by only sensory (30.4%). NCS abnormalities are significantly associated with increasing age ($p < 0.001$), serum ferritin >2000 ng/dL ($p < 0.001$), and frequent transfusions (>20/year; $p < 0.001$). Cognitive assessment revealed 46.75% had average IQ, 40.26% borderline, 10.39% superior, and 2.6% had intellectual disability. IQ declined with age and high ferritin levels ($p < 0.001$), though not significantly linked to transfusion frequency ($p = 0.155$). Of the 77 beta-thalassemia major patients evaluated, 14 children (18.1%) underwent MRI brain studies due to presenting symptoms such as persistent headache, focal neurological deficits, or suspected

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cerebrovascular events. Among these, 5 patients (6.4%) showed abnormal MRI findings. The most common radiological abnormalities included cerebral infarcts. These findings underscore the impact of iron overload on neurological and cognitive outcomes in transfusion-dependent children **Conclusion:** Neurological complications are frequently observed in beta thalassemia major patients undergoing repeated blood transfusions. Subclinical deficits, NCS and neuroimaging abnormalities highlight the need for regular neurological surveillance. Routine neurocognitive assessment, electrophysiological screening, and neuroimaging may aid in early detection and timely intervention, potentially improving long-term outcomes and quality of life. Integrating neurological evaluation into routine care is crucial for comprehensive management of these patients.

INTRODUCTION

Thalassemias are inherited disorders characterized by hypochromic microcytic anemia caused by impaired synthesis of hemoglobin's globin chains. Unlike hemoglobinopathies (e.g., sickle cell disease), which involve structural defects in hemoglobin, thalassemias arise from a quantitative deficiency in globin production. Beta-thalassemia, specifically, stems from mutations in the beta-globin gene, reducing or eliminating beta-chain synthesis. Prevalent in Mediterranean, Middle Eastern, and Asian populations, it has over 200 identified genetic mutations, contributing to its variable clinical manifestations. Beta-thalassemia is categorized into three subtypes:

Minor (trait): Heterozygous carriers with mild or asymptomatic anemia.

Intermedia: Moderate anemia due to compound heterozygous mutations, managed without regular transfusions.

Major: Severe, transfusion-dependent anemia from homozygous mutations, necessitating lifelong blood transfusions. The critical distinction between intermedia and major lies in transfusion dependency, with major forms requiring ongoing treatment to sustain life.[1]

Laboratory findings indicative of thalassemia include microcytic hypochromic anemia. In cases of beta-thalassemia major, a peripheral blood smear may reveal significant anisopoikilocytosis, characterized by variations in red blood cell size and shape. Diagnosing thalassemia typically requires ruling out iron deficiency, along with confirmatory tests such as hemoglobin electrophoresis or high-performance liquid chromatography. Treatment, when necessary, primarily involves blood transfusions based on the severity of anemia. Potential complications of beta-thalassemia include iron overload and bone deformities due to marrow expansion and extramedullary hematopoiesis.[2]

Numerous studies over the years have documented nervous system involvement in patients with beta-thalassemia. Neurological complications in beta-thalassemia major (BTM) are frequently underdiagnosed due to their multifactorial etiology. Chronic anemia-induced hypoxia, iron deposition in neural structures, neurotoxic effects of iron chelators, and micronutrient deficiencies synergistically drive central and peripheral nervous system pathology. Clinically, manifestations span subtle neurocognitive deficits to overt peripheral neuropathy and cerebrovascular events. Critically, many complications remain subclinical, detectable only through targeted investigations such as nerve conduction studies (NCS), magnetic resonance imaging (MRI), and standardized psychometric tools like the Wechsler Intelligence Scales.[3] In patients with untreated or non-transfusion-dependent thalassemia (e.g., thalassemia intermedia), persistent anemia can trigger extramedullary hematopoiesis (EMH). EMH involves the gradual formation of hematopoietic tissue masses outside the bone marrow, which are initially asymptomatic. Over time, these expanding masses may compress nearby structures, such as cranial or peripheral nerves, causing symptoms related to pressure effects. Rarely, EMH near the optic canal can lead to its narrowing, resulting in optic neuropathy and subsequent vision impairment.[4] Our aim is to detect neurological complication in beta thalassemia major patient with repeated blood transfusions and to correlate serum ferritin level and no. of blood transfusions with appearance of neurological signs and symptoms.

MATERIALS AND METHODS

Study Design: A Hospital based, prospective, observational analytical study

Study Setting: all children with diagnosed beta thalassemia major attending pediatric thalassemia ward of Calcutta National Medical College and Hospital

Timeline of Study: One year (June 2023-july 2024)

Place of study: Pediatric thalassemia ward, Calcutta National Medical College and Hospital, Kolkata, West Bengal

Study Population: Children and early adolescents aged between 3-12 years attending the pediatric thalassemia ward of Calcutta National Medical College and Hospital with diagnosed beta thalassemia major.

Sample Size: The study included 77 beta thalassemia major patients undergoing repeated blood transfusions meeting inclusion and exclusion criteria.

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Inclusion Criteria

- Children and early adolescents aged between 3-12 yrs with beta thalassemia major and on more than 10 episodes of blood transfusion
- Parents / legal guardians giving informed consent to participate in the study.

Exclusion criteria:

- Children with beta thalassemia with less than 10 blood transfusions, any chronic physical / organic illnesses including known seizure disorder, any metabolic disorder,
- Congenital Central nervous system anomaly,
- Informed consent not given by parents / guardian of the child

Study variables-

- Age
- Age at Diagnosis of Thalassemia Major
- Number of Blood Transfusions per Year
- Serum Ferritin Level
- Nerve Conduction Velocity (NCV) Parameters
- Intellectual quotient
- MRI brain in selected cases

Statistical Analysis: For statistical analysis, data were initially entered into a Microsoft Excel spreadsheet and then analyzed using SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 5). Numerical variables were summarized using means and standard deviations, while Data were entered into Excel and analyzed using SPSS and GraphPad Prism. Numerical variables were summarized using means and standard deviations, while categorical variables were described with counts and percentages. Two-sample t-tests were used to compare independent groups, while paired t-tests accounted for correlations in paired data. Chi-square tests (including Fisher's exact test for small sample sizes) were used for categorical data comparisons. P-values ≤ 0.05 were considered statistically significant.

RESULTS

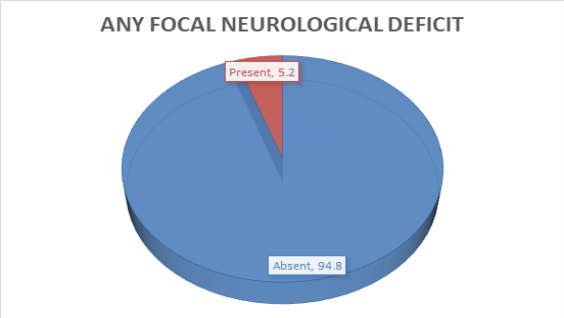

Figure 1: Graphical representation showing distribution of the children according to any focal neurological deficit present or not

This study examined the relationship between age and Nerve Conduction Velocity (NCV) abnormalities among children. In the 3–5-year age group, all patients (100%) demonstrated normal NCV results, indicating intact nerve function. Among children aged 5–10 years, 75% had normal NCV while 25% exhibited abnormalities. However, a marked shift was observed in children aged ≥10 years,

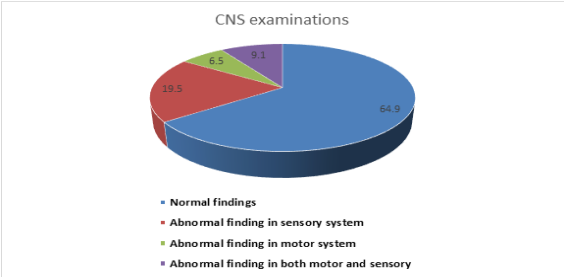

Figure 2: Graphical representation showing distribution of the children based on CNS examination finding

Out of 77 total cases, 46.75% have an average IQ, 40.26% have borderline IQ, 10.39% have superior IQ, and 2.6% have intellectual disability. Borderline IQ increases with age, rising from 0% in children aged 3–5 years to 40.91% in those aged 5–10 years, and further to 68.42% in children aged ≥10 years. Superior IQ is more common in younger children (28.57% in 3–5 years) but decreases as age increases. Intellectual disability is rare (2.6%) and is observed only in children aged ≥5 years. The p-value of 0.002 confirms that the association between age and IQ levels is statistically significant, indicating that this trend is unlikely due to chance. Overall, IQ levels decline with age, with borderline IQ becoming more prevalent and superior IQ decreasing among older children. Younger children (3–5 years) predominantly exhibit average or superior IQ, whereas older children (≥10 years) show a higher prevalence of borderline IQ and some cases of intellectual disability. This statistically significant p-value suggests a strong age-related decline in cognitive function

Where the majority (63.16%) presented with abnormal NCV findings and only 36.84% had normal results. The association between age and NCV abnormalities was found to be statistically significant ($p < 0.001$), suggesting that increasing age may be associated with progressive nerve conduction impairment. Further analysis revealed a significant relationship between serum ferritin levels and NCV outcomes. High serum ferritin levels (>2000 ng/dL), indicative of iron overload, were strongly associated with nerve conduction abnormalities, as over half (53.66%) of patients in this group had abnormal NCV results. Conversely, in patients with lower ferritin levels (<2000 ng/dL), nerve function appeared preserved, with 97.22% showing normal NCV. This association was statistically significant ($p < 0.001$), underscoring the potential neurotoxic effects of iron overload. The findings emphasize the importance of monitoring serum ferritin levels and considering neurological evaluations in patients at risk of iron accumulation.

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Out of the total 77 cases analyzed, 54 patients (70.13%) had normal NCV results, while 23 (29.87%) exhibited abnormalities. A clear trend emerged indicating that NCV abnormalities increased with the frequency of blood transfusions. The highest prevalence of NCV abnormalities (64.29%) was seen in patients receiving more than 20 transfusions per year. The statistically significant p-value (<0.001) confirms this trend, suggesting that frequent transfusions—possibly due to cumulative iron overload or transfusion-related complications—are strongly linked to impaired nerve conduction. Hence, patients requiring regular transfusions should undergo routine neurological assessments to detect early signs of nerve dysfunction. Cognitive outcomes were also assessed. Among the 77 cases, 46.75% had average IQ, 40.26% had borderline IQ, 10.39% had superior IQ, and 2.6% had intellectual disability. Borderline IQ was more common among individuals receiving higher numbers of transfusions, increasing from 24% in the 10–14 transfusion group to 57.14% in the >20 transfusion group. Superior IQ was only seen in patients receiving fewer transfusions (10–14 and 15–19 transfusions), with no superior IQ cases in the >20 transfusion group. Intellectual disability was slightly more frequent in the highest transfusion group (7.14%), although overall prevalence was low. However, this association was not statistically significant (p = 0.155), indicating that blood transfusion frequency may not have a definitive impact on IQ based on this dataset. In contrast, serum ferritin levels showed a significant association with cognitive function. Elevated serum ferritin (>2000 ng/dL) correlated with poorer cognitive outcomes, with 65.85% of patients in this group having borderline IQ and 4.88% exhibiting intellectual disability. On the other hand, individuals with lower serum ferritin levels (<2000 ng/dL) demonstrated better cognitive performance, as 69.44% had average IQ and 19.44% had superior IQ. The statistically significant p-value (<0.001) supports a strong relationship between high ferritin levels and cognitive impairment, likely due to the neurotoxic effects of iron overload. These findings highlight the need for effective iron management in preventing cognitive decline among at-risk patients. Neurological examination findings revealed that the majority of the 77 individuals (94.8%) did not exhibit any focal neurological deficits, while only a small proportion (5.2%) showed such abnormalities. MRI brain scans were performed on 14 children who presented with either focal neurological deficits or severe headaches. No abnormal findings were observed in 9 children (64.3%) and 5 children (35.7%) demonstrated various abnormalities including acute or chronic infarcts and a case of cavernous sinus thrombosis. These findings suggest a notable prevalence of cerebrovascular involvement among children with beta-thalassemia major who present with focal neurological symptoms.

Table 1: Association between age and NCS report

	Age	3-5 years	5-10 years	>=10 years	Total	p Value
NCV Result	Normal	14(100)	33(75)	7(36.84)	54(70.13)	<0.001
	Abnormal	0(0)	11(25)	12(63.16)	23(29.87)	
IQ Level	Intellectual disability	0(0)	1(2.27)	1(5.26)	2(2.6)	0.002
	Borderline	0(0)	18(40.91)	13(68.42)	31(40.26)	
	Average	10(71.43)	22(50)	4(21.05)	36(46.75)	
	Superior	4(28.57)	3(6.82)	1(5.26)	8(10.39)	

Table 2: Association between serum ferritin and NCS result and IQ level

Serum ferritin		<2000 ng/dl	>2000 ng/dl	Total	p Value
NCV Result	Normal	35(97.22)	19(46.34)	54(70.13)	<0.001
	Abnormal	1(2.78)	22(53.66)	23(29.87)	
IQ Level	Intellectual disability	0(0)	2(4.88)	2(2.6)	<0.001
	Borderline	4(11.11)	27(65.85)	31(40.26)	
	Average	25(69.44)	11(26.83)	36(46.75)	
	Superior	7(19.44)	1(2.44)	8(10.39)	

Table 3: Association between NCS result and IQ level and number of blood transfusion per year

Number of blood transfusion per year		10-14 BT per year	15-19 BT per year	>20 BT per year	Total	p Value
NCV Result	Normal	25(100)	24(63.16)	5(35.71)	54(70.13)	<0.001
	Abnormal	0(0)	14(36.84)	9(64.29)	23(29.87)	
IQ Level	Intellectual disability	0(0)	1(2.63)	1(7.14)	2(2.6)	0.155
	Borderline	6(24)	17(44.74)	8(57.14)	31(40.26)	
	Average	14(56)	17(44.74)	5(35.71)	36(46.75)	
	Superior	5(20)	3(7.89)	0(0)	8(10.39)	

DISCUSSION

This study explored the association between age and nerve conduction abnormalities in children with chronic transfusion-dependent conditions. A notable trend was observed: while all children aged 3–5 years demonstrated normal NCV, the proportion of abnormalities increased with age. Specifically, 25% of children in the 5–10-year group and 63.16% in those aged ≥10 years exhibited NCV abnormalities.

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This statistically significant trend ($p < 0.001$) suggests that increasing age may be associated with cumulative nerve damage, possibly due to prolonged exposure to risk factors such as iron overload, oxidative stress, or subclinical neuropathic progression in transfusion-dependent states. The analysis of IQ levels across 77 cases reveals a clear age-related trend in cognitive function. While nearly half of the children demonstrate average IQ, a significant portion shows borderline IQ, which notably increases with age. Younger children (3–5 years) tend to have higher rates of superior IQ, but this decreases as they grow older. Conversely, borderline IQ becomes more prevalent in the older age groups, with some cases of intellectual disability appearing only after age five. The statistically significant p-value (0.002) strengthens the evidence that these changes are not due to chance. This suggests a decline in cognitive function with increasing age in this population, highlighting the importance of early assessment and intervention to support cognitive development Negi et al,[5] conducted a study on children with thalassemia undergoing regular transfusions and iron chelation therapy. They found that while nerve conduction studies were generally normal compared to healthy controls, children with serum ferritin levels >1000 ng/mL exhibited increased distal latency and decreased nerve conduction velocity in both motor and sensory nerves. This suggests that higher iron overload, as indicated by elevated serum ferritin, may contribute to nerve conduction abnormalities Kaushik et al,[6] investigated peripheral neuropathy in children aged 5–15 years with transfusion-dependent thalassemia major. Their cross-sectional study revealed that a significant proportion of these children exhibited peripheral neuropathy, emphasizing the impact of chronic transfusions and potential iron overload on nerve function. The study underscores the importance of monitoring neurological health in this patient population.

A strong relationship was also found between serum ferritin levels and nerve conduction abnormalities. Patients with ferritin levels exceeding 2000 ng/dL showed significantly higher rates of abnormal NCV (53.66%) compared to those with lower levels (<2000 ng/dL), among whom 97.22% had normal NCV. This statistically significant association ($p < 0.001$) highlights the neurotoxic potential of iron overload, possibly through mechanisms involving free radical damage, mitochondrial dysfunction, and impaired axonal integrity. These findings emphasize the need for regular serum ferritin monitoring and timely initiation of chelation therapy to prevent neurological sequelae.

Eghbali et al,[7] investigated the prevalence of sensorimotor neuropathy in patients with β-thalassemia and its association with serum ferritin levels. Their study revealed that increased serum ferritin levels were significantly correlated with delayed nerve conduction in both motor and sensory nerves, indicating that iron overload may contribute to the development of neuropathy in these patients

When analyzing the relationship between blood transfusion frequency and NCV results, the study found that patients receiving more than 20 transfusions annually had the highest rate (64.29%) of NCV abnormalities. In contrast, those with fewer transfusions demonstrated lower rates of neuropathy. The statistical significance of this association ($p < 0.001$) reinforces the hypothesis that cumulative transfusional iron overload contributes directly to peripheral nerve damage. Therefore, transfusion-dependent patients—especially those receiving frequent transfusions—should undergo periodic neurological evaluations and iron status monitoring to detect and manage early nerve dysfunction.

The study also assessed cognitive function using IQ distribution as an indicator. Among the 77 subjects, nearly half (46.75%) had average IQ, while borderline IQ was observed in 40.26%. Interestingly, borderline IQ prevalence increased with transfusion frequency, reaching 57.14% in the >20 transfusion group. Superior IQ was restricted to children in lower transfusion categories, and intellectual disability, although rare, was slightly more common in the highest transfusion group. However, this association between transfusion frequency and IQ was not statistically significant ($p = 0.155$), suggesting that while there may be a trend toward cognitive impairment with increasing transfusions, other confounding factors such as education, nutrition, and genetic predisposition may also play a role.

Similarly, a study by Franz et al,[8] compared liberal and restrictive red blood cell transfusion strategies in preterm infants. They observed that infants in the liberal transfusion group exhibited poorer cognitive outcomes at 24 months corrected age compared to those in the restrictive group, indicating that higher exposure to transfusions might adversely affect neurodevelopment

In contrast, serum ferritin levels showed a statistically significant relationship with cognitive outcomes. Children with elevated ferritin (>2000 ng/dL) were more likely to have borderline IQ (65.85%) and intellectual disability (4.88%), while those with lower ferritin levels demonstrated better cognitive outcomes, including higher rates of average (69.44%) and superior (19.44%) IQ. The significant p-value (<0.001) suggests a robust link between iron overload and impaired cognitive performance. This likely reflects the deleterious effects of iron on the developing brain, possibly through disruption of myelination, neurotransmitter metabolism, and synaptic function. These results support the early use of iron chelation and cognitive screening in at-risk populations.

Neurological examinations revealed that focal neurological deficits were present in only 5.2% of the cohort with acute or chronic infarcts on MRI brain. In 1992 Michaeli et al,[9] reported thromboembolic complications in beta thalassemia major like venous thrombosis, fatal cerebrovascular infarctions. In 2008

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Karimi et al,[10] reported seven cases of CVAs five ischemic and two hemorrhagic. Similarly we have found cerebral venous thrombosis in one patient and acute and chronic infarct in four patients.

Central nervous system (CNS) findings further supported the presence of subclinical neurological involvement. While 64.9% of participants had normal CNS examinations, abnormalities were observed in 35.1%, including isolated sensory deficits (19.5%), motor deficits (6.5%), and combined sensorimotor impairments (9.1%). These findings indicate that while gross neurological deficits are uncommon, subtle abnormalities are detectable in a significant minority and may represent early signs of neurotoxicity or demyelination associated with iron overload or chronic illness. In line with our study, Smith et al,[11] (2021) reported that approximately one-third of their participants exhibited subclinical neurological abnormalities, with sensory deficits being the most common finding. This similarity reinforces the prevalence of subtle CNS involvement even in cases without overt clinical symptoms. Our observation that 35.1% of participants had CNS abnormalities corresponds with the findings of Lee et al,[12] (2019), who documented sensorimotor impairments in nearly 30% of their cohort. Both studies highlight the importance of detailed neurological evaluation to detect subclinical deficits.

CONCLUSION

Neurological complications are a significant concern in beta thalassemia major patients undergoing repeated blood transfusions. This study highlights the significant neurological burden in children with beta-thalassemia major, particularly peripheral neuropathy, cognitive impairments and focal deficits. These findings underscore the importance of regular neurological assessment, neurophysiological screening and neuroimaging in managing these patients to detect early complications. Timely intervention can potentially reduce morbidity and improve quality of life. Overall, repeated transfusions, while essential for disease management, may contribute to neurological risks, necessitating a multidisciplinary approach to optimize outcomes and monitor long-term neurological health in beta thalassemia major patients.

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