Short Communication

Prevalence of Peripheral Neuropathy in Children with Beta Thalassemia Major

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Abstract

Background: Thalassemia is a genetic disorder that results in abnormal hemoglobin structure. It has many complications; most is related to overstimulation of bone marrow, ineffective erythropoiesis, and iron overload from blood transfusions. Peripheral neuropathy one of neurological complications that is seen in adolescents and adults with thalassemia major. **Objectives:** this study the prevalence of peripheral neuropathy in thalassemia major and its relation to different sociodemographic, clinical, electrophysiological and laboratory Findings. **Materials and Methods:** a Case control study was conducted in hereditary blood disease center in Babylon Teaching Hospital for Maternity and Children and Al-Imam Al-Sadiq teaching Hospital, in Hilla city/ Iraq through the period of August. 2022 till August 2023. Patients with beta thalassemia major (51 patients) and control group (51 children) were randomly selected with age range from 4 to 18 years. Each of the study group will be assessed clinically by careful history and full examination, blood samples were taken for laboratory tests, and then the electrophysiological test was done. **Results:** In this study, there are six patients (12%) had peripheral neuropathy by clinical examination and NCS, while forty-five patients (88%) do not have peripheral neuropathy yet. The age of patient with beta thalassemia major ranged between (4-18) years with mean (12.2 ± 2.1) years, age of thalassemia patients who had peripheral neuropathy ranged (12-18) years with mean (15.8 ± 1.4) years, p-value = 0.021. **Conclusion:** Peripheral neuropathy was an anticipated future problem for patients with beta-thalassemia major increased serum ferritin levels, older age and decrease in hemoglobin level may cause mild changes in electrophysiological studies of motor nerves, and these changes may be early signs of future overt neuropathy.

Keyword: Beta-thalassemia major, Peripheral neuropathy, Children, Nerve conduction study, Serum ferritin, Iron overload

Introduction

Thalassemia is a genetic blood disorder that causes abnormal hemoglobin [1]. Globally it affects about (4.4/10,000) live births, approximately (200) million people all over the world [2]. Thalassemia is common in Iraq, the total number of registered thalassemia patients was (13063) in 2021, the number increased to (13737) in 2022 [3] B-Thalassemia major represented (73.9%) of all types of thalassemia in Iraq. Complications are related to overstimulation of bone marrow, ineffective erythropoiesis, and iron overload from blood transfusions [1]. Iron accumulates in the heart, causing heart failure, which is the most common cause of death in beta-thalassemia major (TM)

due to iron accumulation. Other complications include atrial fibrillation, hypothyroidism, hypoparathyroidism, adrenal insufficiency, diabetes mellitus, and hypogonadism [4]. Thromboembolic events such as deep venous thrombosis, pulmonary embolism, and recurrent arterial occlusion are more common in thalassemia patients than in the normal population. [5] Other complications are chronic hepatitis (from blood transfusion infection of hepatitis B and C viruses), cirrhosis (iron overload), hypersplenism, HIV infection and osteoporosis. [6]

Neurological complications

Central and peripheral nervous system complications have been demonstrated in several reports. In most cases, these complications remained subclinical and were detected only during neurophysiological or neuroimaging evaluation. Chronic hypoxia, iron overload, desferrioxamine (DFO) neurotoxicity, and bone marrow expansion are implicated as possible causes, but sufficient explanatory evidence and biomarker development are lacking [7]. peripheral neuropathy have been described in adolescents and adults with thalassemia major. However, its prevalence in children and the impact of effective chelation on the development of peripheral neuropathy is mostly undetermined. The neurological complications have been attributed to various factors such as iron overload, chronic hypoxia, and drug-induced neurotoxicity with desferrioxamine [8]. This study aimed to find the prevalence of peripheral neuropathy in thalassemia children and it's relation to different socio-demographic, clinical, and electrophysiological and laboratory Findings

Materials and Methods

Study design and Participants

Case control study was conducted in hereditary blood disease center in Babylon Teaching Hospital for Maternity and Children and Al-Imam Al-Sadiq teaching Hospital, in Hilla city/ Iraq through the period of August, 2022 till August, 2023. Fifty one (27 males and 24 females) children with B thalassemia major were included as the patient group. Their age ranged from 4 to 18 years. Additional 51 (31 males and 20 females) children were also included as the control group whose their sex and ages were consistent with those of the patient group (4-18 years old). Oral consent were taken from parents and older children before doing the tests.

Exclusion criteria

1. Age less than 4 years and more than 18 years.
2. History of diabetes mellitus, history of thyroid.
3. Children with B12 deficiency.
4. Administration of drugs that cause or aggravate peripheral neuropathy like anti TB and chemotherapy.
5. History of traumatic nerve injuries. Patients with beta thalassemia major were randomly selected from the

Clinical assessment

The study group undergo detailed clinical examination including demographic data and history related to thalassemia like age of diagnosis ,numbers and frequency of blood transfusions and use of iron chelating agent and history of neurological manifestation such as numbness , pain , headache , weakness and abnormal walk . Neurological examination was done (power, tone , deep tendon refluxes , gait , light touch , joint position sense , vibration and pin prick) .

Laboratory analysis

Laboratory analysis included measurement of serum levels of ferritin and hemoglobin

Electrophysiological assessment

The electrophysiological test was done in the neurophysiology department in Al-Imam Al-Sadiq general hospital and includes nerve conduction study. Each of the study group was examined by sensory (median, ulnar and sural) and motor (median, ulnar peroneal and tibial nerves) responses along with F-wave study. The standard procedures were used [9] with supramaximal stimulation and care of temperature (32-35C) and cleaning of recording and stimulation sites.

Statistical analysis

Statistical analysis done by SPSS 22, frequency and percentage used for categorical data, mean, SD for continuous data. Chi-square used for assessed association between variables, person correlation show the correlation between continuous data. T test used for evaluation differences between mean and median of continues variables. P-value less or equal to 0.05 is consider significant [10].

Ethical consideration

The study was conducted in accordance with the Declaration of Helsinki. Verbal informed consent was obtained from all participants prior to sample collection. Ethical approval was granted by the Medical Ethical Committee of the Department of Pediatrics, Babylon Teaching Hospital for Maternity and Children, and Al-Imam Al-Sadiq Teaching Hospital, Babil Health Directorate.

Results

Demographic data

Demographic characteristics of the study group are summarized in table 1 and shows that there are no statistical differences between the patients and control regarding these variables.

Table 1: demonstrate differences in demographic data between study groups

Groups	Patient (N:51)	Control (N:51)
Age (years)	12.2 ± 2.1	11.2 ± 2.5
Male/female	27/24	31/20
Age at diagnosis (months)	7.2 ± 2.1	NA

Values are expressed as mean ± standard deviation for age and number and percentage for male/ female ratio, no significant differences are seen between study groups

Electrophysiological data

Analysis of electrophysiological parameters shows statistically significant differences between patients and controls in multiple nerve conduction study parameters of motor nerves mainly the latency and amplitude. These differences are explained in table 2 for motor nerves and table 3 for sensory nerves.

Table 2: shows the differences in nerve conduction study of motor nerves between study groups

Groups r	Latency (ms)		Amplitude (mv)		Conduction velocity (m/sec)	
	Patient	Control	Patient	Control	Patient	Control
Median	4.9± 1.45	3.7 ±0.6*	5.8±1.34	6.1± 1.18	53.3±5.55	56.7± 6.4*
Ulnar	4.7± 0.78	3.6±0.56*	7.01±1.6	7.60±0.9*	58.65±8.49	58.54±6.15
Peroneal	6.6± 2.27	5.2±0.60*	5.84±2.4	5.06±0.8*	50.0± 7.34	49.2± 6.33
Tibial	6.6± 2.27	5.2±0.60*	5.8± 2.47	5.0± 0.85	50.0± 7.34	49.2±6.33*

Values are expressed as mean ± standard deviation, * mean significant differences between study group at P < 0.05

Table 3: shows the differences in nerve conduction study of motor nerves between study groups

Groups	Latency(ms)		Amplitude (microvolt)	
	Patient	Control	Patient	Control
Median	1.94± 0.42	2.0± 0.48	33.50± 17.57	28.40± 5.80*
Ulnar	1.86± 0.33	1.65 ± 0.37*	53.14 ± 19.52	24.78 ± 6.41*
Sural	2.94 ± 0.91	2.15 ± 0.62*	14.44 ± 5.92	17.18 ± 5.81*

Values are expressed as mean ± standard deviation, * mean significant differences between study group at P < 0.05

Incidence of peripheral neuropathy

After careful analysis of nerve conduction study data and comparing them to the normal reference range corrected according to age, we found that, there are six patients (12%) had peripheral neuropathy by NCS, while forty-five patients (88%) do not have peripheral neuropathy yet as shown in figure 1.

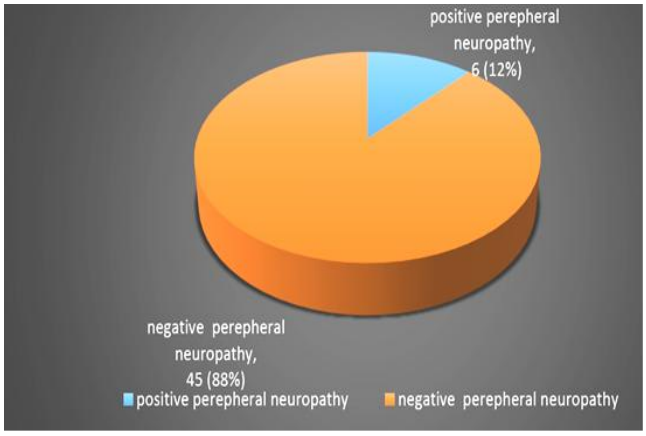

Figure 1: Prevalence of Peripheral Neuropathy by Nerve Conduction Studies in Children with Beta-Thalassemia Major

Distribution of study group according to ferritin and hemoglobin levels

The current study shows statistically significant differences between patients with thalassemia major and healthy control regarding ferritin and hemoglobin level in the following way: patients show lower levels of hemoglobin and higher levels of ferritin. These findings are shown in table 4.

Table 4: hematological values of thalassemia patients and healthy control

Parameter	Thalassemic patients	Healthy control	P value
Ferritin (ng/ml)	2820±900	42±5	0.001
Hb (g/dL)	7.62±0.97	12.69±0.44	0.001

On the other hand, the level of serum ferritin and hemoglobin were not different in patients with neuropathy compared to those without. These findings are shown in table 5.

Table 5: hematological values of patients with neuropathy and patients without

Parameter	Patient with Neuropathy	Patient without neuropathy	P value
Ferritin (ng/ml)	2820±900	3362±1103	0.059
Hb (g/dL)	7.62±0.97	7.51±0.98	0.69

Discussion

The results of study shows that there is six patients (12%) had peripheral neuropathy by NCS, while forty-five patients (88%) do not have peripheral neuropathy yet d as a complication of beta-thalassemia. This result disagree with reported data in that the incidence of peripheral neuropathy in thalassemic patients between 22.0-78.0% [11, 12]. The difference in these results is due to several factors, the most important of which is the ages of the patients included in the study, as ages from 4 to 18 years were included, while in the rest of the studies, older ages were included, this mean longer disease duration and then higher incidence of complications. Another important factor is the difference in environ-mental factors and the difference in patients'

compliance. Although we found both sensory and motor nerve abnormality in this study, Sawaya *et al.* [13] reported only sensory nerve abnormality in thalassemia patients. Stambolis *et al.* showed abnormalities in NCS results in about 52% of patients, while only 25% of patients were symptomatic [14]. Khosravi and colleagues reported the peripheral neuropathy in b-thalassemia major in 65 patients who received regular blood transfusion and DFO chelating therapy, at least for ten years [15]. Also, El-Tagui et al. reported that 63.3% of patients had motor neuropathy in the absence of sensory neuropathy or myopathy [16], whereas in this study, six patients (12%) had sensory and motor neuropathy. Our results reveal a statistically significant increase in the median, ulnar, tibial and peroneal nerve motor latencies in the patients with thalassemia than in the controls. On contrast, Aziz Eghbali et al. [17] in their study to evaluate the frequency of peripheral neuropathy in beta thalassemia patients, reported that their studied patients had a significant delay in the tibial motor latency, but no delay in the median, ulnar, and peroneal nerve motor latencies in the patients with neuropathy than in the controls, while Sawaya et al. [13, 11] reported that their studied patients had a no significant delay in the motor latencies. The result of current study showed that motor amplitude in thalassmic patients were difference from control (there is significant decrease in ulnar amplitude in thalassemic children than normal, there is significant increase in tibial amplitude in Thalassemic children than normal) this result was in agreement with Sawaya et al. [13]. The result is difficult to explain, we think that the neuropathy in these patients affects primarily the distal nerve endings. In the sensory fibers this presents as delayed distal latencies. In the motor fibers the neuropathy may cause degeneration followed by reinnervation via collateral sprouting. The latter phenomenon classically causes some increase in CMAP amplitude and area. The only way to confirm this hypothesis is by performing needle EMG examination of the distal muscles, which we found to be unethical in this group of patients. If the involvement of the motor fibers can be confirmed by later studies then the neuropathy may really be a sensory-motor polyneuropathy rather than only a sensory one [17].

Conclusion

Peripheral neuropathy was an anticipated future problem for patients with beta-thalassemia major in our study. Increased serum ferritin levels, older age and decrease in hemoglobin level may cause mild changes in electrophysiological studies of motor nerves, and these changes may be early signs of future overt neuropathy.

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Conflicts of interest: None

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