Hemoglobin

international journal for hemoglobin research

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ihem20

Polyneuropathy Associated with Age of Starting the Transfusion and Serum Ferritin Level in Iranian Patients with Thalassemia Major and Intermedia

Aziz Eghbali, Kazem Ghaffari, Roya shaykh Baygloo, Aygin Eghbali & Ali Ghasemi

To cite this article: Aziz Eghbali, Kazem Ghaffari, Roya shaykh Baygloo, Aygin Eghbali & Ali Ghasemi (2023) Polyneuropathy Associated with Age of Starting the Transfusion and Serum Ferritin Level in Iranian Patients with Thalassemia Major and Intermedia, Hemoglobin, 47:2, 42-48, DOI: 10.1080/03630269.2023.2208760

To link to this article: https://doi.org/10.1080/03630269.2023.2208760

Published online: 15 May 2023.

HEMOGLOBIN
2023, VOL. 47, NO. 2, 42–48
https://doi.org/10.1080/03630269.2023.2208760

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Polyneuropathy Associated with Age of Starting the Transfusion and Serum Ferritin Level in Iranian Patients with Thalassemia Major and Intermedia

Aziz Eghbali[a], Kazem Ghaffari[b], Roya shaykh Baygloo[c], Aygin Eghbali[d] and Ali Ghasemi[e]

[a]Clinical Research Development Center of Aliasghar Hospital, Iran University of Medical Sciences, Tehran, Iran; [b]Department of Basic and Laboratory Sciences, Khomein University of Medical Sciences, Khomein, Iran; [c]Department of Pediatrics, Amir Kabir Hospital, Arak University of Medical Sciences, Arak, Iran; [d]School of Medicine, Iran University of Medical Sciences, Tehran, Iran; [e]Department of Biochemistry and Hematology, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran

ABSTRACT

Considering the importance of managing patients with β-thalassemia and the importance of early detection of disease complications, we examined the rate of sensorimotor neuropathy in patients with β-thalassemia and the risk factors related to it. This cross-sectional study included 44 blood transfusion-dependent β-thalassemia patients aged 5 years and older. Nerve conduction studies (NCSs) were performed via standard procedures for both motor and sensory nerves. Neuropathy was observed in 14 patients (31.8%). NCS results for sensorimotor nerves in patients were within normal range. In motor NCS results, increased ulnar nerve amplitude was observed in patients with increasing age, and peroneal nerve delay in patients with an increase in serum ferritin level ($p < 0.05$). In sensory NCS results, delayed ulnar and sural nerves latencies were found in patients with an increase in serum ferritin level ($p < 0.05$). We provide data that sensorimotor neuropathy exists in thalassemia patients. It seems that with the increase of serum ferritin level and the age of patients, neuropathy becomes more obvious, while other factors such as gender, body mass index, and the number of transfusions may not be associated with neuropathy.

ARTICLE HISTORY
Received 24 January 2023
Revised 3 April 2023
Accepted 20 April 2023

KEYWORDS
β-Thalassaemic patients; polyneuropathy; chelation therapy; iron overload

Introduction

β-Thalassemias are heterogeneous disorders that develop secondary to congenital defects in the β-chain of hemoglobin (Hb). Decrease or absence of β-globin synthesis leads to imbalance of globin chains. β-Thalassemia is characterized by chronic hemolytic anemia, expansion of compensatory hematopoiesis and ineffective erythropoiesis [1,2]. One of the main methods of treating patients with thalassemia is regular packed red blood cell transfusions [3,4]. Under these conditions, iron accumulates in the heart, liver, spleen, and other tissues, which is responsible for many clinical complications in patients [2]. Serum ferritin greater than 300 ng/ml in males and greater than 150 to 200 ng/ml in menstruating females can be indicative of iron overload [5]. However, serum ferritin levels can also be elevated for a variety of reasons, including inflammation, infection, and liver disease; it is known as an acute phase reactant [6].

Accordingly, iron chelation is required to prevent or reverse iron overload in patients with transfusion-dependent thalassemia [7]. Today, oral deferasirox (DFX) and deferiprone (DFP) and parenteral deferoxamine mesylate (DFO) are available as the main iron chelating agents. Treatment of β-thalassemia patients with iron chelation has led to improved life expectancy and prognosis of patients, although clinical complications and functional disorders have also been reported in some patients [2,8]. These complications include neuroinflammation, neurodegeneration, endocrinopathies, peripheral neuropathy, renal disease, myopathy, and hepatic failure [9–11]. Even previous studies have shown that clinical complications differ between iron chelators [10]. A previous study done through journal search with determined MeSH term was done in PubMed and Scopus showed that DFP in reducing myocardial iron load and DFO in reducing liver iron load are superior to other iron chelators [12].

On the other hand, a wide range of eye complications including optic neuropathy, cataracts and visual field defects have been counted for DFO [13]. In addition, high doses of deferoxamine directly cause neurotoxicity in patients with thalassemia. For the reasons mentioned, there have been changes in the treatment of iron overload in the past decade, and today DFX is used as the first line of treatment in heavily iron-overloaded patients with β-thalassemia [14].

Considering the importance of managing patients with β-thalassemia and the high prevalence of β-thalassemia major in Iran and the importance of early detection of disease complications, we investigated the rate of sensorimotor neuropathy in patients with β-thalassemia, in addition to evaluating the risk factors associated with sensorimotor neuropathy such as age, age of starting blood transfusion,

CONTACT Dr. Ali Ghasemi a.qasemi2012@yahoo.com Department of Biochemistry and Hematology, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran

gender, chelation therapy, serum ferritin level, body mass index (BMI), height, and transfusion frequency. Nerve conduction study (NCS) results of patients with neuropathy were compared with normal control group data.

Materials and methods

This cross-sectional study included 44 blood transfusion-dependent β-thalassemia patients aged 5 years and older, which was conducted in Amirkabir Children's Hospital, Arak, Iran, between July 2018 and June 2019. Seventeen healthy people were selected as the control group. The NCS results in patients with neuropathy were compared with normal controls of the same age and gender who had visited our clinic and had not been diagnosed with any disease. Baseline characteristics were similar in both groups with regard to gender and age ($P > 0.05$, data not shown).

The local ethics committee, in accordance with the Declaration of Helsinki, approved the study protocol. Before data collection, informed consent was obtained from the parents of all patients. In addition, we also obtained informed consent from older patients. This study was approved by the Ethics Committee of Arak University of Medical Sciences (Ethical committee code number: IR.ARAKMU.REC.1394.101).

Exclusion criteria: patients less than 5 years old, any type of known neurological disease, family history of neurological disease, history of taking medications that may affect nerve conduction study results, acute fever in the last 3 weeks, infection, renal failure, history of chemotherapy, diabetes mellitus, patients with high creatinine kinase levels, vitamin B12 deficiency and folic acid deficiency. Patients did not receive antioxidant agents during the study. An experienced neurophysiologist retrieved the patients' clinical information by taking a detailed history through a direct interview and reviewing the patients' medical records, including the age of blood transfusion, sensory disorders such as numbness and paresthesia, BMI, height, weight, and deep tendon reflexes and the type of iron chelating agents.

NCSs were performed with an EMG device (Nemus, Biomedica, model number 00655, Galileo NT software version 3.71/00, Italy). Median, ulnar, peroneal and tibial nerves (both right and left) were used for motor NCSs. Surface electrode recordings were obtained from the abductor pollicis brevis (on testing the median nerve), the abductor digiti minimi (on testing the ulnar nerve), and the abductor hallucis (on testing peroneal nerve). Median (finger-wrist), ulnar, and sural nerves were used for sensory NCSs. Sensory NCS of the sural nerve stimulating at the calf and of median or ulnar nerve stimulating at the wrist and elbow were recorded. Distal sural delay was determined by stimulating the lateral edge of the foot and recording in the lateral malleolus, and distal latencies from the wrist or ankle to the corresponding muscles of the hand or foot in the motor nerves and to the digits in the sensory nerves [15]. Adhesive tape was used to fix the recording electrodes on the skin. The site of electrodes for stimulation and recording was determined based on previous studies [16,17]. In this study, surface electrodes were used that did not require skin preparation. The temperature of the room was maintained at 32 °C during the measurements. For action potential pick-up, the nerve-recording electrode was stimulated ultra-maximally using a square wave current with a duration of 0.2 milliseconds.

Neurological manifestations during the study included hypotonia of the lower and upper limbs, deep tendon reflexes, tremors in hands, headache, tingling, numbness, paresthesia, and pain in the hands and feet.

Hematological and biochemical profile in the last 6 months were calculated for all patients.

Data were expressed as mean ± SD for numerical variables. The Spearman rank-order correlation coefficient was used to evaluate the correlation of variables. One-way analysis of variance was used to compare the mean of the variables. The statistical significance of the differences in patients with and without neuropathy was calculated using Pearson's $\chi 2$ test or Fisher's exact test. Multivariate logistic regression model was carried out to evaluate variables that might have influenced sensorimotor NCSs. The data were analyzed using Package for the Social Sciences (SPSS) software, version 20 (Chicago, Illinois, USA). $P < 0.05$ was considered statistically significant.

Results

The mean ± SD age of the patients was 24.1 ± 4.2 years. The studied patients included 27 (61.4%) females and 17 (38.6%) males (Table 1). Male to female ratio was 0.6. Of the 44 patients studied, 39 (88.6%) had thalassemia major and 5 (11.4%) had thalassemia intermedia, and all of them were under repeated packed red blood cells (PRBCs) transfusion. All patients were treated with DFX. The mean ± SD duration of receiving iron-chelating agents was 12.3 ± 4.4 years with a range from 6 to 25 years. Mean serum ferritin levels was 2216.8 ng/ml with range from 143–9088 ng/ml. In our study, the highest prevalence of neuropathy was in patients with a transfusion starting age of over 5 years.

Ten patients (22.7%) had undergone splenectomy. All patients had a normal fasting blood sugar during the frequent routine testing over the past five years. Weights ranged from 29 to 65 kilograms, with a mean of 48.3 kilograms. The Hb concentrations in the patients, averaged over the last 5 years, ranged from 6.2 to 12.4 g/dL, with an average of 8.8 g/dL. Based on the Hb concentration, the transfusion of PRBCs was performed. All patients were transfused with 10–15 ml of PRBCs per kg of body weight. Seventy-one percent of patients received blood transfusion every 2 weeks and the rest of patients received blood every 3 or 4 weeks. All patients used Desferal as an iron-chelating agent in the past. In the present study, only one patient had extramedullary erythropoiesis.

In total, NCS results showed the occurrence of neuropathy in 14 (31.8%) patients, of which two (4.5%) patients had sensory neuropathy, and nine (20.4%) patients had motor neuropathy. Three patients (6.9%) showed motor and sensory neuropathy at the same time.

Table 1. Baseline clinical data among studied cases.

Data	Patients with neuropathy ($n = 14$)	Patients without neuropathy ($n = 30$)	p-value
Age at presentation, yrs	1.6 ± 0.4	1.5 ± 0.2	0.836
Age of starting the transfusion, yrs	1.9 ± 1.1	1.1 ± 0.8	**0.042**
Transfusion Frequency, times/year			
≥10	10	26	0.222
<10	4	4	
Female/male	9/5	18/12	0.786
Jaundice, n	9	21	0.868
Serum ferritin, ng/ml	2480.1 ± 84.8	2051.6 ± 49.4	**0.039**
BMI, kg/m^2	18.8 ± 3.7	20.1 ± 4.3	0.287
Height, (cm)	124.4 ± 9.1	126.7 ± 6.7	0.624
Weight (kg)	24.7 ± 4.3	25.6 ± 3.8	0.863

n: number of patients; BMI: body mass index; Bold indicates $p < 0.05$.

Table 2. Frequency of neurological manifestations.

Symptoms and signs	Number (%)
Hypotonia	5 (11.4)
Deep tendon reflexes	0
Tremors in hands	0
Headache	12 (27.3)
Tingling	15 (34.1)
Numbness	1 (2.3)
Paresthesia	1 (2.3)
Pain in the hands and feet	16 (36.3)

In total, 34.3% of all studied patients had neurological symptoms. Pain in the hands and feet (16, 36.3%), tingling (15, 34.1%) and headache (12, 27.3%) were the main neurological symptoms among the patients, respectively. Thus, some patients with normal NCS can have neurological manifestations. Deep tendon reflexes were absent, although five patients (11.4%) showed hypotonia (Table 2).

There were no statistically significant differences in age at presentation, gender, weight, height, BMI, transfusion frequency, type of iron-chelating agents, and clinical manifestations in the patients with and without neuropathy ($P > 0.05$). However, a significant difference was observed in terms of age at the start of blood transfusion and serum ferritin levels between patients with and without neuropathy based on NCS results ($P < 0.05$). A relationship was observed between the age of patients and the prevalence of neuropathy based on NCS results ($p = 0.03$). As the age of the patients increased, the prevalence of neuropathy based on NCS results in the patients increased, so that all patients over 40 years of age had neuropathy. NCS results for sensorimotor nerves in patients were within normal range. We also compared NCS results for sensorimotor nerves in patients grouped by age, sex, age at the start of transfusion, serum ferritin level, type of iron chelating agents, BMA, height, and the number of transfusions (Tables 3 and 4).

There was no significant difference in NCS results for motor nerves in patients grouped by gender, age of starting blood transfusion, type of iron-chelating agents, BMI, height, and the transfusion frequency ($p > 0.05$). However, in motor NCS results, increased ulnar nerve amplitude was observed in patients with increasing age, and peroneal nerve delay in patients with an increase in serum ferritin level ($p < 0.05$) (Table 3).

There was also no observed significant difference in sensory NCS results in patients grouped by age, gender, age of starting blood transfusion, type of iron-chelating agents, BMI, and height ($p > 0.05$). However, in sensory NCS results, delayed ulnar and sural nerves latencies were found in patients with an increase in serum ferritin level ($p < 0.05$) (Table 4).

Spearman's rank-order correlation coefficient of NCS data for sensorimotor nerves is shown in Figure 1. Peroneal motor nerve, ulnar sensory nerve and sural sensory nerve conduction latencies were found to correlate positively with serum ferritin ($r = 0.3$, $p = 0.036$; $r = 0.4$, $p = 0.040$; $r = 0.4$, $p = 0.043$; respectively). We also found a positive correlation between ulnar motor nerve conduction amplitude and age ($r = 0.3$, $p = 0.031$).

Multivariate logistic regression showed independent association between the serum ferritin and peroneal motor nerve conduction latency ($p = 0.031$; OR = 1.673, 95% CI = 0.153–15.701), independent of the age, gender, age of starting blood transfusion, type of iron-chelating agents, BMI, height, and transfusion frequency.

When we compared the NCS results of the patients with neuropathy and the control group there was no any statistically significant difference in the median, ulnar, and peroneal motor nerve conduction latencies (Table 5). However, in motor nerve studies, we found a statistically significant delay in the tibial nerve and lower velocities in the median nerve in patients with neuropathy compared to controls. No sensory abnormality was observed in the median, ulnar, and sural nerve conduction latencies and velocities of the patients. The sensory amplitudes in the ulnar nerve, but not the median and sural nerves, were lower in the patients with neuropathy than in the controls (Table 5). Interestingly, in the control group, 25% of subjects had asymptomatic neuropathy.

Discussion

We present results that support the existence of polyneuropathy in patients with thalassemia major. This study is the first reevaluation of neuropathy in the era of new iron chelators including DFX in Iran. In the current study, 13% of our patients had signs and/or symptoms that could be attributed to neuropathy and NCS data showed that 31.8% of patients had evidence of neuropathy. Although we found both sensory and motor nerve abnormality in this study, Sawaya *et al.* [15] reported only sensory nerve abnormality in thalassemia patients. In previous studies, the prevalence of neuropathy was reported between 22–78% [2]. Stambolis *et al.*

Table 3. The relationship between the results of motor NCSs and the studied variables.

		Median Nerve			Ulnar Nerve			Tibial Nerve			Peroneal Nerve		
	N, (%)	L (MS)	V (M/S)	A (μv)	L (MS)	V (M/S)	A (μv)	L (MS)	V (M/S)	A (μv)	L (MS)	V (M/S)	A (μv)
Age, yrs													
5-14	9 (20.5)	3.3	55.1	9.1	2.4	57.9	**5.3**	3.8	46.3	7.3	4.3	48.9	4.1
15-24	24 (54.5)	3.1	55.3	9.2	2.6	54.6	**6.2**	3.8	45.7	7.2	4.4	48.3	4.3
25-40	9 (20.5)	3.3	55.0	9.1	2.5	56.3	**7.8**	3.7	45.5	7.2	4.5	48.5	4.0
>40	2 (4.5)	3.2	55.2	9.1	2.3	55.5	**8.6**	3.8	46.1	7.2	4.4	48.7	4.4
Gender,													
Female	27 (61.4)	3.3	55.1	9.1	2.5	54.1	6.5	3.8	45.5	7.2	4.4	48.4	4.3
male	17 (38.6)	3.2	55.1	9.1	2.4	54.3	6.4	3.8	45.3	7.2	4.5	48.5	4.2
Age of starting blood transfusion, yrs													
<1	36 (81.8)	4.3	55.6	9.2	2.5	56.8	7.1	3.8	46.7	7.4	4.5	48.8	4.2
1-5	5 (11.4)	3.3	54.2	8.8	2.3	54.3	6.7	3.6	44.3	7.2	4.4	48.3	4.2
>5	3 (6.8)	3.2	55.3	9.1	2.4	55.5	6.2	3.7	42.6	7.3	4.2	47.2	4.1
Serum ferritin, ng/ml													
<1000	17 (38.6)	3.1	56.2	9.3	2.3	55.8	7.7	3.5	45.4	7.2	**2.7**	48.5	4.2
1000-2500	19 (43.2)	3.1	55.4	9.1	2.2	55.5	6.8	3.8	44.7	7.3	**3.3**	48.6	4.2
>2500	8 (18.2)	3.5	55.1	8.4	2.5	55.2	6.1	3.9	44.3	7.1	**4.6**	48.3	4.1
BMI, kg/m^2													
<20	25 (56.8)	3.3	55.1	9.1	2.2	55.5	6.5	3.8	45.4	7.2	4.4	48.5	4.1
>20	19 (43.2)	3.1	55.1	9.1	2.3	55.4	6.3	3.8	45.5	7.2	4.2	48.5	4.1
Height, (cm)													
<150	15 (34.1)	3.2	55.2	9.1	2.5	55.5	6.4	3.8	45.4	7.2	4.3	48.4	4.1
150-180	23 (52.3)	3.2	55.1	9.1	2.4	55.6	6.4	3.8	45.5	7.3	4.4	48.5	4.1
>180	6 (13.6)	3.3	55.2	9.2	2.5	55.6	6.5	3.8	45.4	7.3	4.4	48.4	4.1
Transfusion frequency, times/year													
≥10	36 (81.8)	3.4	55.4	9.1	2.6	55.8	6.4	3.9	45.3	7.1	4.6	48.3	4.2
<10	8 (18.2)	2.9	55.7	9.2	2.1	56.6	6.9	3.7	45.8	7.3	4.1	48.9	4.1

Data are mean values. NCS; nerve conduction study; N: number of patients; L: Latency; V: Velocity; A: Amplitude; BMI: body mass index; ms: millisecond; m/s: meter per second; μV: microvolt; Bold indicates $p < 0.05$.

Table 4. The relationship between the results of sensory NCSs and the studied variables.

		Median Nerve			Ulnar Nerve			Sural Nerve		
	N, (%)	L-FW (MS)	V –FW (M/S)	A-FW (μv)	L (MS)	V (M/S)	A (μv)	L (MS)	V (M/S)	A (μv)
Age, yrs										
5-14	9 (20.5)	2.8	56.5	20.5	2.6	53.7	15.8	2.5	48.7	19.8
15-24	24 (54.5)	2.7	57.3	20.4	2.7	54.1	15.9	2.6	48.5	19.9
25-40	9 (20.5)	2.9	55.4	20.5	2.5	53.9	15.8	2.4	48.4	19.8
>0	2 (4.5)	2.8	56.1	20.3	2.6	53.8	15.7	2.5	48.6	20.0
Gender,										
Female	27 (61.4)	2.8	56.3	20.5	2.6	53.8	15.8	2.5	48.5	19.8
male	17 (38.6)	2.8	55.5	20.5	2.5	53.8	15.8	2.5	48.5	19.8
Age of starting blood transfusion, yrs										
<1	36 (81.8)	2.8	56.4	20.3	2.9	53.8	15.8	2.7	48.6	19.9
1-5	5 (11.4)	2.7	55.7	20.5	2.5	53.8	15.9	2.6	48.7	19.7
>	3 (6.8)	2.7	55.5	20.5	2.1	53.6	15.2	2.4	48.6	19.7
Serum ferritin, ng/ml										
<1000	17 (38.6)	2.1	56.7	20.8	**2.4**	53.6	15.9	**2.5**	48.4	20.1
1000-2500	19 (43.2)	2.5	55.5	20.3	**2.7**	53.8	15.6	**2.7**	48.6	19.7
>500	8 (18.2)	3.2	53.3	19.4	**3.3**	54.0	15.1	**3.1**	48.9	19.1
BMI, kg/m2										
<20	25 (56.8)	2.8	55.5	20.5	2.4	53.5	15.7	2.4	48.5	19.7
>0	19 (43.2)	2.8	55.5	20.5	2.5	53.6	15.8	2.4	48.5	19.7
Height, (cm)										
<150	15 (34.1)	2.7	55.4	20.4	2.6	53.4	15.8	2.5	48.4	19.8
150-180	23 (52.3)	2.8	55.3	20.5	2.6	53.5	15.7	2.4	48.4	19.8
>180	6 (13.6)	2.8	55.4	20.5	2.5	53.4	15.8	2.5	48.5	19.7
Transfusion frequency, times/year										
≥10	36 (81.8)	2.8	55.3	20.4	2.8	53.0	15.7	2.6	48.5	19.7
<10	8 (18.2)	2.5	56.2	20.6	2.2	54.2	15.8	2.4	48.8	20.0

Data are mean values. NCS: nerve conduction study; N: number of patients; L: Latency; V: Velocity; A: Amplitude; BMI: body mass index; FW: finger-wrist; ms: millisecond; m/s: meter per second; μV: microvolt; Bold indicates $p < 0.05$.

showed abnormalities in NCS results in about 52% of patients, while only 25% of patients were symptomatic [18]. Khosravi and colleagues reported the peripheral neuropathy in β-thalassemia major in 65 patients who received regular blood transfusion and DFO chelating therapy, at least for ten years. The percentage of patients with peripheral neuropathy was 66.15%. The authors found that there was significant association between aging and peripheral neuropathy, but there was no significant association with gender, serum ferritin level and splenectomy [19]. Also, El-Tagui *et al.* reported that 63.3% of patients had motor neuropathy in the absence of sensory neuropathy or myopathy [17], whereas in this study, two patients (4.5%) had sensory neuropathy.

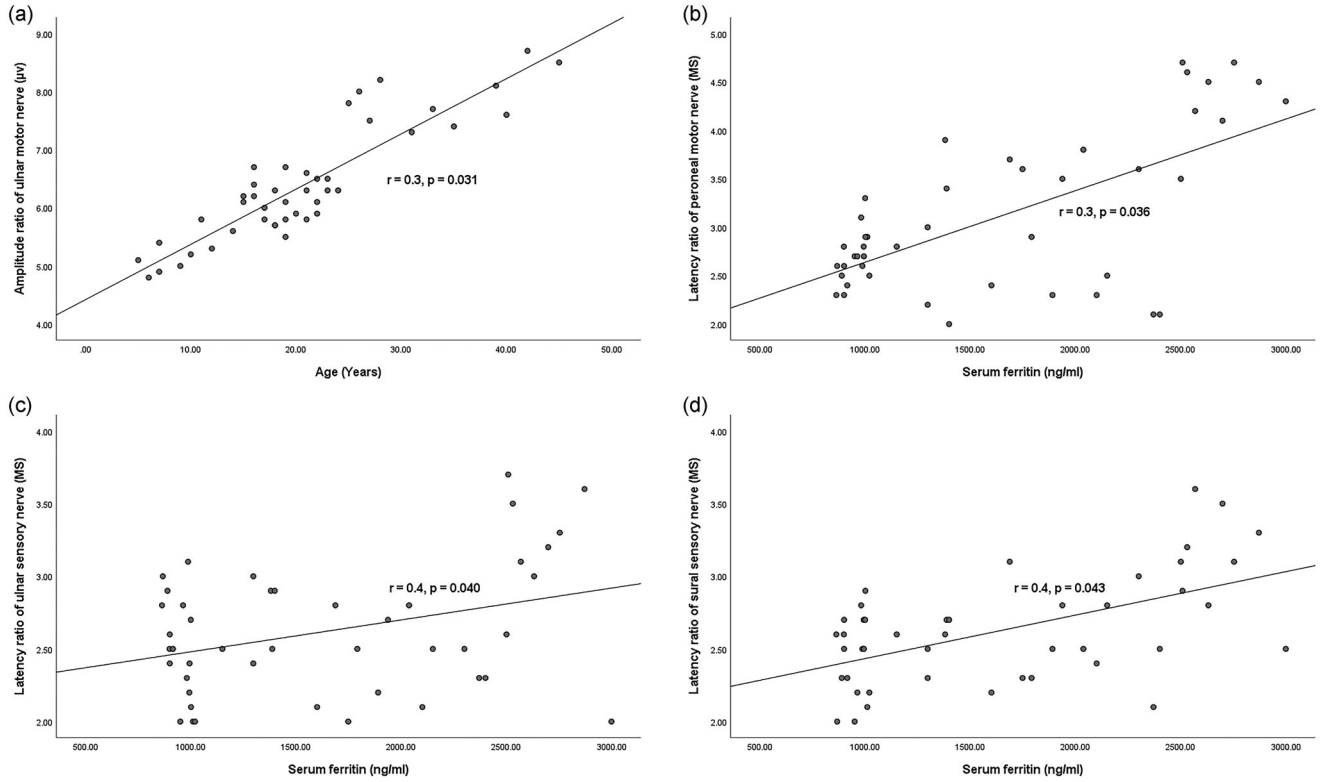

Figure 1. a) Significant positive correlation between age and amplitude ratio of ulnar motor nerve in patients with beta thalassemia, b) significant positive correlation between serum ferritin and latency ratio of peroneal motor nerve in patients with beta thalassemia, c) significant positive correlation between serum ferritin and latency ratio of ulnar sensory nerve in patients with beta thalassemia, d) significant positive correlation between serum ferritin and latency ratio of sural sensory nerve in patients with beta thalassemia.

Table 5. Sensorimotor NCS results in patients with neuropathy and healthy controls.

	Motor nerves				Sensory nerves		
Latency (ms)	Median	Ulnar	Tibial	Peroneal	Median	Ulnar	Sural
Patients (N = 14)	3.3 ± 0.3	2.5 ± 0.4	3.8 ± 0.7	4.3 ± 0.5	2.6 ± 0.4	2.5 ± 0.6	2.4 ± 0.3
MIN- MAX	2.7-4.4	1.8-3.1	2.6-5.7	2.5-5.3	1.6-4.2	1.7-4.2	1.6-3.3
Control (N = 17)	2.7 ± 0.2	2.2 ± 0.5	2.1 ± 0.7	3.8 ± 0.6	1.6 ± 0.7	2.0 ± 0.4	1.8 ± 0.7
MIN- MAX	2.3-3.5	1.3-2.6	1.2-3.7	1.9-4.0	1.1-3.1	1.3-2.9	1.2-2.7
P value	0.358	0.367	**0.021**	0.437	0.513	0.419	0.618
Velocity (m/s)							
Patients (N = 14)	55.1 ± 3.7	55.5 ± 4.8	45.4 ± 5.8	48.4 ± 2.4	55.4 ± 3.5	53.7 ± 5.2	48.4 ± 3.8
MIN- MAX	49-64	46-62	38-52	39-52	47-68	48-61	45-57
Control (N = 17)	58.1 ± 3.2	56.1 ± 5.5	47.5 ± 4.2	49.9 ± 3.3	57.3 ± 4.1	55.1 ± 4.3	49.1 ± 3.9
MIN- MAX	51-63	48-66	39-55	41-55	48-67	50-63	45-58
P value	**0.008**	0.568	0.637	0.461	0.715	0.563	0.891
Amplitude (μV)							
Patients (N = 14)	9.1 ± 0.7	6.5 ± 1.4	7.2 ± 2.1	4.2 ± 0.6	20.5 ± 3.8	15.8-2.8	19.7 ± 3.3
MIN- MAX	7.4-11.3	4.1-9.1	5.6-9.8	2.6-6.5	15.3-23.7	10.1-21.0	15.6-24.8
Control (N = 17)	11.2 ± 1.1	7.5 ± 1.1	7.5 ± 1.3	4.5 ± 0.5	21.2 ± 4.6	19.1 ± 2.4	20.5 ± 1.8
MIN- MAX	9.0-13.4	5.3-9.2	5.7-10.8	2.9-7.0	17.0-25.1	15.2-24.0	14.9-24.6
P value	0.234	0.368	0.412	0.778	0.891	**0.032**	0.697

Data are mean ± SD values. NCS: nerve conduction study; ms: millisecond; m/s: meter per second; μV: microvolt; N: number; MAX: maximum; MIN: minimum; Bold indicates $p < 0.05$.

Our results reveal a statistically 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. On contrast, Sawaya *et al.* [15] 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 sensory distal latencies.

The reason for the difference in the results can be attributed to the difference in the age of the studied patients, the type of thalassemia major or intermedia, transfusion frequency, the type of chelating drug, environmental effects and the more appropriate treatment of the underlying disease.

Considering that in our study, the highest prevalence of neuropathy was in patients with the age of starting

transfusion above 5 years, it is possible that the faster start of blood transfusion will delay the progression toward neuropathy in thalassemia patients and even have a protective effect. In a study from Lebanon, the authors claimed that the sensory amplitudes were significantly higher in thalassemia patients who had received blood transfusion. They stated that blood transfusion can delay or protect against the development of polyneuropathy in thalassemia patients [15].

Sensorimotor NCS results were in the normal range in all of the patients receiving DFX. Consistent with our results, in a study on the prevalence of neuropathy in 27 patients with beta-thalassemia major and intermedia, in which approximately 96% of patients received DFX, the authors reported that only 3% patients had motor neuropathy and sensorimotor NCS results were in normal range in all of the patients [11]. Studies have shown the relationship between peripheral neuropathy and some variables in patients with thalassemia major. Wong *et al.* found a high level of serum ferritin in thalassemia patients with neuropathy [20]. In a study from Greece, the authors claimed that age over 20 years and having hematocrit values less than 30.0% are risk factors for neuropathy [18]. In another study, Sawaya *et al.* revealed sensory neuropathy in beta thalassemia patients is related to aging and insufficient treatment. They reported that the hemoglobin level did not affect the status of the patients' nerves [15].

The difference in the prevalence of neuropathy in different studies can be due to the difference in the age of the studied patients, the type of chelating drug and the more appropriate treatment of the underlying disease. Ethnic and racial diversity and environmental effects can also be another reason for the difference in the prevalence of neuropathy in patients with thalassemia major in different studies. Thus, in a study in Turkey, no neuropathy was reported in patients with thalassemia major [21], which was contrary to the results of our study. Risk factors related to neuropathy in some diseases such as diabetes [22], ischemia [23], and sickle cell disease (SCD) [24] have been described, which may explain the risk factors of neuropathy in other conditions such as thalassemia major. In a study, the authors claimed that neuropathy in diabetic patients may be subclinical for several years and its late diagnosis leads to an increased risk of mortality [25]. Neuropathy risk factors in diabetes mellitus patients include age [26], hypertension [27], smoking, high triglyceride levels [28] and BMI [29]. In another study, Brandow *et al.* revealed neuropathy in SCD is related to older age, hydroxyurea use and female gender [30]. The effect of frequent blood transfusion and iron overload on the development and progression of neuropathy in SCD remains unknown [24].

In this study, we found that patients with older age had significantly longer motor ulnar nerve amplitude than younger patients. Our results were in agreement with Bayhan *et al.* [11] who reported that thalassemia patients over 20 years of age had longer motor ulnar nerve amplitude. Similar results have been reported in previous studies in thalassemic patients [15,18]. These data are consistent with previously published data in SCD patients where older age is a risk factor for the development of neuropathy [24,30]. The reason why the prevalence of neuropathy increases with age remains unknown and is also an area of active research.

The mean serum ferritin level in our study was 2216.8 ng/ml, which was different from the mean serum ferritin level in the study conducted by Ari *et al.* and Hesham *et al.* The current study showed that patients with higher ferritin levels had significantly longer peroneal motor nerve, ulnar sensory nerve and sural sensory nerve conduction latencies than patients with lower ferritin levels. Similar report has been shown in a previous study [11]. Iron overload should be considered in the etiology of these latencies; however, much is unknown and this is an active area of investigation. Anomalies in various other sensorimotor nerves have also been reported in other studies [15,31].

In patients with thalassemia major, it occurs due to iron overload; chronic hemolysis and frequent transfusion. These two events can cause cell damage and neurotoxicity through the production of free radicals. The increase of free iron and iron overload can cause the formation of reactive oxygen species and damage biological molecules such as lipids, proteins and DNA [32]. Additionally, it has been shown that deferoxamine administration may be associated with optic and vocal nerve complications in a dose-dependent manner [33].

In conclusion, we provide data that sensorimotor neuropathy exists in thalassemia patients. It seems that with the increase of serum ferritin level and the age of patients, neuropathy becomes more obvious, while other factors such as gender, BMA, and the number of transfusions are not associated with neuropathy. According to the results of our study, we recommend that a larger study be conducted considering the effect of different types of iron chelators as well as the type of thalassemia major and intermedia to provide a more reliable analysis. Considering the wide range of ferritin, we suggest to investigate this issue in other studies with larger sample size.

Acknowledgement

The authors thank to the Research Council of Arak University of Medical Sciences. We would like to thank all the staff of the Blood and Oncology, Department of Amirkabir Hospital, Arak, Iran.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Aziz Eghbali http://orcid.org/0000-0002-5118-0094
Kazem Ghaffari http://orcid.org/0000-0002-6077-3123
Roya shaykh Baygloo http://orcid.org/0000-0003-4451-548X

Aygin Eghbali http://orcid.org/0000-0002-6670-2270
Ali Ghasemi http://orcid.org/0000-0002-4996-7656

References

[1] Akif Yesilipek M. Stem cell transplantation in hemoglobinopathies. Hemoglobin. 2007;31(2):251–256.
[2] Nemtsas P, Arnaoutoglou M, Perifanis V, *et al.* Neurological complications of β-thalassemia. Ann Hematol. 2015;94(8): 1261–1265.
[3] Origa R. β-Thalassemia. Genet Med. 2017;19(6):609–619.
[4] Ghasemi A, Abbasian S, Ghaffari K, *et al.* Prevalence of alloantibodies and autoantibodies in transfusion dependent thalassemia patients. Iran J Blood Cancer. 2016;8(3):80–85.
[5] McDowell LA, Kudaravalli P, Sticco KL. Iron overload. Blood. 2018;118(16):421–30.
[6] Wang W, Knovich MA, Coffman LG, *et al.* Serum ferritin: past, present and future. Biochim Biophys Acta. 2010;1800(8):760–769.
[7] Morales NP, Rodrat S, Piromkraipak P, *et al.* Iron chelation therapy with deferiprone improves oxidative status and red blood cell quality and reduces redox-active iron in β-thalassemia/hemoglobin E patients. Biomed Pharmacother. 2022;145: 112381.
[8] Ginzburg Y, Rivella S. β-thalassemia: a model for elucidating the dynamic regulation of ineffective erythropoiesis and iron metabolism. Blood,. 2011;118(16):4321–4330.
[9] Ward RJ, Dexter DT, Crichton RR. Iron, neuroinflammation and neurodegeneration. IJMS. 2022;23(13):7267.
[10] Reddy PS, Locke M, Badawy SM. A systematic review of adherence to iron chelation therapy among children and adolescents with thalassemia. Ann Med. 2022;54(1):326–342.
[11] Bayhan T, Ünal Ş, Konuşkan B, *et al.* Assessment of peripheral neuropathy in patients with β-thalassemia via electrophysiological study: reevaluation in the era of iron chelators. Hemoglobin. 2018;42(2):113–116.
[12] Wahidiyat PA, Yosia M, Sari TT. Comparison of deferiprone to deferasirox and deferoxamine to cardiac and hepatic T2* MRI in thalassemia patients: evidence-based case report. Acta Med Indones. 2018;50(2):168–176.
[13] Keikhaei B, Farmani-Anooshe N, Bahadoram M, *et al.* An overview of complications associated with deferoxamine therapy in thalassemia. J Nephropharmacol. 2020;10(1):e05-e–e05.
[14] Taher A, El-Beshlawy A, Elalfy MS, *et al.* Efficacy and safety of deferasirox, an oral iron chelator, in heavily iron-overloaded patients with β-thalassaemia: the ESCALATOR study. Eur J Haematol. 2009;82(6):458–465.
[15] Sawaya RA, Zahed L, Taher A. Peripheral neuropathy in thalassemia. Ann Saudi Med. 2006;26(5):358–363.
[16] Awang MS, Abdullah JM, Abdullah MR, *et al.* Nerve conduction study among healthy Malays. The influence of age, height and body mass index on median, ulnar, common peroneal and sural nerves. The Malaysian Journal of Medical Sciences: MJMS. 2006;13(2):19.
[17] El-Tagui MH, Salama KM, El-Sabbagh MH, *et al.* Polyneuropathy Associated with Severe Iron Overload and Oxidative Stress in β-Thalassemia Patients. Indian J Hematol Blood Transfus. 2019;35(3):518–522.
[18] Stamboulis E, Vlachou N, Drossou-Servou M, *et al.* Axonal sensorimotor neuropathy in patients with β-thalassaemia. J Neurol Neurosurg Psychiatry. 2004;75(10):1483–1486.
[19] Khosravi A, Naderi M, Ardalani GF, *et al.* Evaluation of peripheral neuropathy and associated risk factors in patients with beta-thalasemia major. J Neurol Sci. 2017;381:612.
[20] Wong V, Li A, Lee A. Neurophysiologic study of β-thalassemia patients. J Child Neurol. 1993;8(4):330–335.
[21] Kardelen F, Tezcan G, Akcurin G, *et al.* Heart rate variability in patients with thalassemia major. Pediatr Cardiol. 2008;29(5): 935–939.
[22] Watterworth B, Wright TB. Diabetic peripheral neuropathy. Pain: Springer; 2019. p. 911–913.
[23] Teunissen L, Notermans N, Wokke J. Relationship between ischemia and neuropathy. Eur Neurol. 2000;44(1):1–7.
[24] Sharma D, Brandow AM. Neuropathic pain in individuals with sickle cell disease. Neurosci Lett. 2020;714:134445.
[25] Duque A, Mediano MFF, De Lorenzo A, *et al.* Cardiovascular autonomic neuropathy in diabetes: Pathophysiology, clinical assessment and implications. World J Diabetes. 2021;12(6): 855–867.
[26] Kaplan PW, Sutter R. Electroencephalography of autoimmune limbic encephalopathy. J Clin Neurophysiol. 2013;30(5): 490–504.
[27] Forrest KY, Maser RE, Pambianco G, *et al.* Hypertension as a risk factor for diabetic neuropathy: a prospective study. Diabetes. 1997;46(4):665–670.
[28] Tesfaye S, Chaturvedi N, Eaton SE, *et al.* Vascular risk factors and diabetic neuropathy. N Engl J Med. 2005;352(4):341–350.
[29] Meisinger C, Döring A, Thorand B, *et al.* Body fat distribution and risk of type 2 diabetes in the general population: are there differences between men and women? The MONICA/KORA Augsburg cohort study. Am J Clin Nutr. 2006;84(3):483–489.
[30] Brandow AM, Farley RA, Panepinto JA. Neuropathic pain in patients with sickle cell disease. Pediatr Blood Cancer. 2014; 61(3):512–517.
[31] Bertfield DL, Jumma O, Pitceathly RD, *et al.* Copper deficiency: an unusual case of myelopathy with neuropathy. Ann Clin Biochem. 2008;45(Pt 4):434–435.
[32] Jomova K, Valko M. Importance of iron chelation in free radical-induced oxidative stress and human disease. Curr Pharm Des. 2011;17(31):3460–3473.
[33] Olivieri NF, Buncic JR, Chew E, *et al.* Visual and auditory neurotoxicity in patients receiving subcutaneous deferoxamine infusions. N Engl J Med. 1986;314(14):869–873.