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Frequency and potential risk factors of polyneuropathy in transfusion-dependent B-thalassemia major patients: a cross-sectional study

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Abstract

Background Neurological complications, including peripheral polyneuropathy, have been reported in β-thalassemia patients that negatively impact their quality of life. Chronic hypoxia, iron overload, average age, and iron chelators-induced neurotoxicity might contribute to the development of neuropathy. However, the leading offender of this complication remains not clear. We aimed to study the frequency and potential risk factors of polyneuropathy in β-thalassemia patients. We performed a cross-section study on 150 transfusion-dependent β-thalassemia major patients with a mean age of 16.44 ± 3.32 years. We performed electrophysiological studies for motor and sensory nerves.

Results We found that 31.3% of cases had neurological manifestations with significant relation to age, duration of the disease, and frequent transfusion. Out of 47 patients with neurological manifestations, 12 (25.5%) had abnormal nerve conduction velocity (NCV). Abnormal median, peroneal, and tibial nerve motor amplitudes were detected in 10.6%, 10.6%, and 14.9% of patients respectively. Abnormal median, peroneal, and sural nerve sensory amplitudes were detected in 4.3%, 2.2%, and 10.6% of patients respectively. Apart from a significant relation between abnormal NCV and older ages, no significant relation was detected with other studied clinical and laboratory parameters.

Conclusion We detected a high frequency of motor and sensory polyneuropathy in B-thalassemia patients. Polyneuropathy was predominately detected in older ages highlighting that neuropathy in thalassemia patients is probably age-dependent. Other factors including disease duration, transfusion frequency, and iron overload might have a contributing effect, however, that could not be confirmed in this study. Further studies are needed to verify the frequency and predictors of polyneuropathy in B-thalassemia patients.

Keywords β-thalassemia, Neurological complications, Polyneuropathy, Nerve conduction velocity

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Background

B-thalassemia is caused by beta-globin gene mutation. The absence or reduced formation of β-globin chains leads to ineffective erythropoiesis which leads to hemolytic anemia, iron overload, and multi-organ complications [1]. In Egypt, the most common hemoglobinopathy is β-thalassemia major and is associated with a significant public health problem with a great impact on the

quality of life of those patients [2]. Frequent blood transfusion is considered the standard of care of individuals with β-thalassemia and this leads to iron precipitation in vital organs of the body [3]. Several studies have reported nervous system involvement in β-thalassemia patients. In most cases, neurological complications remained subclinical and were demonstrated only during neuropsychological, neurophysiological, or neuroimaging evaluation [4]. Various factors such as chronic hypoxia, oxidative stress, age, iron overload, and deferroxamine-induced neurotoxicity, might be associated with the development of neurological complications [5]. Central nervous system involvement has been previously reported in both β-thalassemia major and intermedia [6]; however, the data are scarce regarding peripheral nerve system complications, also, the impact of chelation therapy on the development of peripheral neuropathy hasn't been fully compiled yet [7, 8]. In this study, we evaluated the frequency of polyneuropathy in children and adolescents with regularly transfused β-thalassemia major patients via electrophysiological studies and investigated the potential risk factors associated with the development of polyneuropathy in those patients.

Methods

We conducted this cross-sectional study on 150 transfusion-dependent β-thalassemia major patients aged 10 years or above, patients were recruited from the regular attendants of the Pediatric Hematology Clinic, Zagazig University. Open Epi program was used to calculate the sample size with a confidence level of 95% and power of test of 80%.

We included all patients diagnosed as transfusion dependent β-thalassemia major of both sexes, aged 10 years or above.

Patients who had anatomical causes of neuropathy, comorbidities like diabetes mellitus, thyroid disease, vitamin B12 deficiency, liver cell failure, renal impairment, or exposure to other known neurotoxic medications, those with a family history of neurological disease, patients with a chronic inflammatory condition not related to thalassemia, or a critical concurrent illness were excluded.

All patients were subjected to the following assessments; detailed medical history, thorough clinical examination, and detailed neurological examination including cranial nerves, muscle strength, superficial and deep reflexes, and sensations. We used the Medical Research Council grading system from 0 to 5 for the grading of muscle strength. Nerve conduction studies were carried out by the same investigator using NEMUS 2, Galileu Software for patients with abnormal clinical neurological findings. Motor nerve conduction studies of motor nerves (ulnar, median, and peroneal nerves) were performed. Surface electrode recordings were acquired from the abductor pollicis brevis (on median nerve testing), the abductor digiti minimi (on ulnar nerve testing), and the abductor hallucis (on peroneal nerve testing). Sensory nerve conduction of the sural, median, and ulnar nerve was recorded.

Blood transfusion frequency and chelation characteristics, laboratory investigations in the form of complete blood count, serum ferritin, and liver and kidney function tests were assessed. We used patients' medical records to assist with some of these estimations.

Statistical analysis

The collected data were tabulated and analyzed using IBM SPSS Statistics, version 26 (IBM; Armonk, NY, USA). Categorical data were presented as numbers and percentages while quantitative data were expressed as mean ± standard deviation, median, and range. The chi-square test ($\chi 2$) or Fisher's exact test (FET) was used to analyze categorical variables. Quantitative data were tested for normality using Kolmogorov-Smirnova test, assuming normality at $P > 0.05$. Student "t" test was used to analyze normally distributed variables among 2 independent groups. While non-parametric variables were analyzed using the Mann-Whitney U test. The accepted level of significance in this work was stated at 0.05 ($P \leq 0.05$ was considered significant).

Results

This study included 83 (55.3%) males, with a male-to-female ratio of 1.2. The age of participants ranged from 11 to 22 years with a mean of 16.44 ± 3.32, about 61.3% of them were ≥ 16 years old. About 31.3% of the studied cases had neurological manifestations. Tingling and numbness were the main neurological symptoms among cases (24.0% and 23.3% respectively) followed by headache (21.3%), joint and muscle pain (20.7%), hypotonia (20.6%) and tremors in hands (3.3%). Grade 4 muscle power was reported in 16 cases (10.7%) and normal (grade 5) muscle power was reported in 134 cases (89.3%). Deep tendon reflexes were normal in 89.3% of the cases, while 10.7% had brisk deep tendon reflexes.

All subjects with neurological manifestations were aged above 16 years old. Neurological manifestations were significantly higher among β-thalassemia patients with prolonged duration of the disease, frequent transfusion ≥ 10 times/year, and in those who had splenomegaly and hepatomegaly as shown in Table 1. However, there was no significant relation between the presence of neurological manifestations and laboratory data of the patients.

Out of 47 β-thalassemia patients with neurological manifestations, 12 (25.5%) had abnormal NCV.

Table 1 Relation between neurological manifestation and clinical data of β-thalassemia studied cases

Variables	Neurological manifestation				
	Absent (*N* = 103)		Present (*N* = 47)		*P*
	N.	%	*N*	%	
Sex					
Male	55	66.3	28	33.7	0.383
Female	48	71.6	19	29.4	
Age					
years	59	100	0	0	< 0.001
≥ 16 years	44	48.4	47	51.6	
BMI (kg/m^2)					
Mean ± SD	19.02 ± 2.37		21.99 ± 2.63		0.000
Duration of disease (years)	13.91 ± 3.30		17.58 ± 1.78		0.000
Mean ± SD					
Transfusion frequency					
timesyear	27	27.2	1	2.1	0.001
≥ 10 times/year	76	73.2	46	97.9	
Splenomegaly					
No	17	40.5	25	59.5	0.005
Yes	85	79.4	22	20.6	
Splenectomy					
No	73	68.9	33	31.1	0.928
Yes	30	68.2	14	31.8	
Hepatomegaly					
No	59	47.6	65	52.4	0.005
Yes	44	55.7	35	44.3	
Iron chelation therapy					
Deferoxamine	29	63.0	17	37.0	0.135
Deferasirox	55	82.1	12	17.9	
Deferiprone	16	72.7	6	27.3	
Combined	10	62.5	6	37.5	

P value < 0.05 is significant

Abnormal median, peroneal, and tibial nerve motor amplitudes were detected in 5 (10.6%), 5 (10.6%), and 7 (14.9%) patients respectively. Lower number of patients were found to have abnormal sensory amplitude, abnormal median, peroneal, and sural nerve sensory amplitudes were detected in 4.3%, 2.2%, and 10.6% of patients respectively as shown in Table 2.

No statistically significant difference as regards all clinical and laboratory data between cases with normal and abnormal nerve conduction studies except for a significant elevation of serum creatinine levels among cases with abnormal nerve conduction studies. The patients with abnormal nerve conduction studies are older than others with normal nerve conduction studies as shown in Tables 3 and 4.

Table 2 Frequency of abnormal nerve conduction studies (NCS) among studied cases with neurological manifestations

Variable	Cases with neurological manifestations	
	N.	%
NCV		
Normal	35	74.5
Abnormal	12	25.5
Median nerve (motor) amplitude		
Normal	42	89.4
Abnormal	5	10.6
Peroneal nerve (motor)		
Amplitude	42	89.4
Normal	5	10.6
Abnormal		
Tibial nerve (motor) amplitude		
Normal	40	85.1
Abnormal	7	14.9
Median nerve (sensory)		
Amplitude	45	95.7
Normal	2	4.3
Abnormal		
Ulnar nerve (sensory) amplitude		
Normal	46	97.8
Abnormal	1	2.2
Sural nerve (sensory) amplitude		
Normal	42	89.4
Abnormal	5	10.6

NCS nerve conduction studies

Discussion

In the present study, 31.3% of the studied β-thalassemia cases had neurological manifestations. Electrophysiological study findings for motor and sensory nerves were abnormal in 25.5% of the cases with neurological manifestations.

In the literature, there are only a limited number of studies that reported polyneuropathy in β-thalassemia patients. Incidence of neuropathy in those patients has been reported between 22.0 and 78.0% [9, 10].

In agreement with our results, El-Tagui et al. [11] reported that 35 patients (58.3%) showed abnormal neurological examination and their extended neurological evaluation score, total neuropathy score (TNSn) ranged from 1 to 4. In a study on 30 patients with thalassemia by Sawaya et al. [12], 40% of patients presented with complaints of neuropathy symmetrically and distally in the lower extremities, moreover, 78% were found to have mild sensory neuropathy.

Table 3 Relation between nerve conduction studies (NCS) and sociodemographic data among the studied cases with neurological manifestations

	Nerve conduction studies (NCS)				
Variables	Normal (*N* = 35)		Abnormal (*N* = 12)		*P*
	N	%	*N*	%	
Sex Male Female	24 11	82.6 68.8	5 5	17.4 31.2	0.449
Age (years) Mean ± SD	18.92 ± 1.33		20.10 ± 1.10		0.008
Age < 16 years ≥ 16 years	0 35	0 100	0 12	0 100	1.000
Duration of disease (years) Mean ± SD	17.28 ± 1.84		18.30 ± 1.49		0.090
Transfusion frequency < 10 times/year ≥ 10 times/year	1 34	100 73.9	0 12	0 26.1	1.000
Splenomegaly No Yes	19 16	76 72.7	6 6	24 27.3	0.066
Splenectomy No Yes	28 7	82.4 53.8	6 6	17.6 46.2	0.156
Hepatomegaly No Yes	6 29	50 82.9	50 17.1	52.4 44.3	1.000
Iron chelation therapy Deferoxamine Deferasirox Deferiprone Combined	13 13 4 5	72.2 86.7 66.7 63	5 2 2 3	27.8 13.3 33.3 37	0.414

Table 4 Relation between nerve conduction studies (NCS) and laboratory data of the studied cases with neurological manifestations

	Nerve conduction studies (NCS)				
Laboratory data	Normal (*N* = 35)		Abnormal (*N* = 12)		*P*
Hb (g/dl) Mean ± SD	7.46 ± 0.76		7.60 ± 1.06		0.622
Serum ferritin (ng/ml) Mean ± SD	2514.19 ± 1644.94		3554.97 ± 2514.71		0.108
Serum albumin (g/dl) Mean ± SD	4.34 ± 0.53		4.42 ± 0.34		0.628
ALT (U/L) Mean ± SD	32.99 ± 18.61		34.43 ± 20.04		0.822
AST (U/L) Mean ± SD	32.80 ± 14.94		37.15 ± 15.70		0.395
Urea (mg/dl) Mean ± SD	27.71 ± 7.47		27.30 ± 7.57		0.871
Serum creatinine (mg/dl) Mean ± SD	0.43 ± 0.14		0.54 ± 0.12		0.019
Serum ferritin < 2000 ng/ml ≥ 2000 ng/ml	*N* 15 20	% 83.3 69	*N* 3 9	% 16.7 31	0.715

Similar results that revealed positivity for neuropathy were reported by Papanastasiou et al. [13] since 22% of their patients suffered from mild motor peripheral neuropathy. In another study, Stamboulis et al. [14] reported abnormal electrophysiological studies in 52.7% of their studied patients, while 25% of patients revealed neurological

symptoms. In agreement with these results, Wong et al. [10] reported subclinical nervous system toxicity in 32% of patients.

In contrast, Işıkay et al. [15] did not detect any neurological abnormalities in any of the participants or any evidence of large-fiber neuropathy. Also, Kaushik et al. [16] conducted a study on transfusion-dependent thalassemia major children aged 5–15 years, and none of them revealed either clinical or electrophysiological evidence of peripheral neuropathy. A similar finding was reported in a Turkish study by Kardelen et al. [17], in which no signs of peripheral or autonomic neuropathy were observed in thalassemia major patients [17]. Beyhan et al. [18], found only one patient (3.0%) with mild difficulty in motor functions, and none of the other patients had peripheral neuropathy symptoms. Moreover, normal electrophysiological study results for both motor and sensory nerves were detected in all studied patients.

Indeed, several factors may contribute to this discrepancy between the studies such as different sample sizes, the age of the studied patients, and access to highly developed supportive care. Ethical and environmental factors may also contribute to the occurrence of neuropathy [18].

Interestingly, among our studied patients, all subjects with neurological manifestations were aged above 16 years old, moreover, a highly significant relation between abnormal NCV and older ages was detected. This can be explained by the fact that chronic ischemia and neuropathy have been associated, and older patients may have been exposed to ischemia for a longer duration. This finding is consistent with previous studies, Papanastasiou et al. [13] found that neuropathy develops during the second and third decades of life. Also, Stamboulis et al. [14], reported a significant positive correlation between neuropathy and the age of the patients.

The results of this study revealed that the presence of neurological manifestation is statistically higher among β-thalassemia patients with longer disease duration, more frequent blood transfusion, hepatomegaly, and splenomegaly, this could be explained by the theory that neuropathy is worsened with increasing age and other related complications as iron overload and hepatosplenomegaly as the disease progress. However, patients with electrophysiological proof of neuropathy did not show a significant relation with these parameters. So, we cannot consider any of these parameters as a reliable predictor of the occurrence of polyneuropathy. Also, we found no significant relation between serum ferritin level or iron chelation therapy and abnormal NCV. These findings are consistent with previous studies showing a lack of significant correlation of electrophysiological parameters with serum ferritin levels [13, 18].

This is contradictory to El-Tagui et al. [11] who reported that patients with electrophysiological proof of peripheral motor neuropathy had elevated levels of serum ferritin, and those with serum ferritin C 2000 ng/ml are at higher risk. Also, they reported a positive correlation between peripheral neuropathy score (TNSn) and transfusion frequency and serum ferritin; highlighting an association between severe iron overload and motor neuropathy [11].

Bayhan et al. [18] found that patients with average serum ferritin levels of more than 1000 ng/mL had longer motor peroneal nerve latency than patients with lower ferritin levels and concluded that older age, elevated serum ferritin levels, and copper deficiency may cause mild changes in electrophysiological studies of motor nerves, and these parameters may be early signs of upcoming clinical neuropathy. Sawaya et al. [12] reported that better nerve function was detected in thalassemia patients who received blood transfusions and deferrioxamine than those who did not receive, irrespective of deferrioxamine dose [12].

Interestingly, despite excluding thalassemic patients with renal impairment from our study, we detected a significant relation between serum creatinine level and abnormal NCV. Bekhit et al. [19] reported that the serum creatinine was higher in 40% of thalassemic patients compared with controls but within a normal range.

It is very well proven that peripheral nervous system involvement is very common in uremic patients, Bakre et al. [20] found a significant correlation between creatinine (Cr) and nerve conduction parameters of the median, ulnar, peroneal, tibial, and sural nerve in patients with chronic kidney disease [20]. So, the early detection of subclinical renal impairment as a contributing factor to the development of polyneuropathy is crucial in thalassemic patients.

Conclusion

Our study demonstrated a high frequency of motor and sensory polyneuropathy in transfusion-dependent β-thalassemia major patients. Polyneuropathy was predominately detected in older ages highlighting that neuropathy shown in thalassemia patients is probably age-dependent and does not occur until adolescence. Other factors including transfusion frequency, increased serum ferritin, and chelation therapy might have a contributing effect; however, that could not be proved in the current study.

Recommendations

Further studies with larger sample sizes and longer duration are required to verify the frequency and predictors of polyneuropathy in β-thalassemia patients, moreover,

exploring the possible cause of neuropathy in these patients with basic lab workups like thyroid profile, ESR, and vitamin B12. Also, further research studies are needed to evaluate therapies of neuropathies in thalassemic patients, to determine the reversibility of polyneuropathy, to achieve a better quality of life for this patient group.

Limitations

The small sample size was the major limitation of our study. Also, patients were from limited geographical areas and not representing the whole of Egypt. So, larger multicenter studies are still required to support our findings.

Abbreviations

Cr	Creatinine
NCV	Nerve conduction velocity
TNSn	Total neuropathy score

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Authors' contributions

Contributions to idea and design: M.H., U.E, and A.R.; methodology and acquisition of data: M.O., D.H., and A.R.; investigations: Y.E. and S.S.; analysis and interpretation of findings: M.H., A.R., M.O., and D.H.; writing original draft preparation: D.H. and A.R.; writing review and editing: M.H, U.E., A.R., and D.H. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the local ethical committee, Faculty of Medicine, Zagazig University as per the Helsinki Declaration of 2013. We obtained informed consent from each participant or legal guardian before enrolment in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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