ORIGINAL ARTICLE

Eastern Journal of Medicine
East J Med 30(4): 531-540, 2025
DOI: 10.5505/ejm.2025.29626

Investigation of Polyneuropathy In Transfusion-Dependent Thalassemia

Deniz Kamaci Sener[1*], Sevil Sadri[2], Vildan Gursoy[2], Ozden Kamisli[1]

[1]*Department of Neurology, Bursa City Hospital, Bursa, Türkiye*
[2]*Department of Hematology, Bursa City Hospital, Bursa, Türkiye*

ABSTRACT

Transfusion-dependent thalassemia patients neurological complications remained subclinical and were demonstrated only during neuropsychological, neurophysiological, or neuroimaging evaluation. The aim of this study was to investigate the incidence of peripheral and entrapment neuropathies in a patient group and determine whether these neurological complications correlate with liver and heart involvement.

The study included 28 patients with transfusion-dependent thalassemia and 32 healthy controls. Nerve conduction studies were performed in the upper and lower extremities and the findings were evaluated in terms of entrapment neuropathy and polyneuropathy. Demographic data, laboratory parameters, radiological images of the patients were compared with the nerve conduction findings.

In the patient group, 64.29% had polyneuropathy, 10.71% had carpal tunnel syndrome, and 3.5% had ulnar neuropathy at elbow. Polyneuropathy was significantly more prevalent in the patient group. No correlation was found between polyneuropathy and age, gender, splenectomy, or ferritin. Hemoglobin was positively correlated with sural amplitude and tibialis amplitude. Liver MR T2 sequence was negatively correlated with PNP, ulnar sensory latency and was positively correlated with ulnar sensory amplitude, ulnar sensory velocity. We didn't find relationship between heart MRI T2* and nerve conduction study.

The findings obtained in the present study indicate that in patients with transfusion-dependent thalassemia, PNP is associated with iron overload in tissues. Furthermore, neurologic complications may be associated with other organ involvement.

Keywords: Transfusion-dependent thalassemia complications, electrophysiological study, polyneuropathy, entrapment neuropathy, T2* MRI heart, T2* MRI liver

Introduction

Transfusion-dependent thalassemia (TDT) is among the most prevalent genetic disorders worldwide and it can result in high morbidity and mortality, particularly in the alpha and beta globin chain variants. It is an important public health problem in Turkey as it is all over the world (1). The most frequent cause of hemolytic anemia is TDT (2). In these TDT patients, chronic anemia and iron overload lead to organ damage and complications (3). In recent years, new treatment strategies for TDT patients have led to increased life expectancy, consequently resulting in a rise in complications (2). Several studies have reported nervous system involvement in TDT patients. In most cases, neurological complications remained subclinical and were demonstrated only during neuropsychological, neurophysiological, or neuroimaging evaluation (4,5). The reasons responsible for the occurrence of neurological complications are chronic hypoxia, increased iron load in nerve cells results in oxidative damage and neurotoxicity, neurotoxicity of agents used for chelation, and bone marrow enlargement (6). Excess iron overload in cells always results in the generation of reactive oxygen species (ROS). In essence, ROS controls the cell's regular functions. However, an abnormal increase in ROS levels can damage the cell (7). Due to iron overload in tissues, ROS are produced more frequently in TDT patients, which results in oxidative stress. Alpha-synuclein and amyloid beta proteins aggregate as a result of iron overload and oxidative stress, contributing to the etiology of neurodegenerative illnesses like Parkinson's and Alzheimer's Disease (8,9). In other words, iron overload in tissues can affect the central and peripheral nervous system. Iron chelators are an essential part of treatment to remove iron in TDT patients. Iron chelators primarily bind to iron, which cannot be excreted from the body through normal pathways, facilitating the excretion of the iron-drug complex via urine. Hence, chelation is necessary to prevent mortality and morbidity. However, these agents themselves can also cause peripheral

***Corresponding Author:** Deniz Kamaci Sener, Department of Neurology, Bursa City Hospital, Bursa, Turkey
E-mail: drdenizkamaci@gmail.com, Phone: +90 (505) 788 68 50, Fax no: +90.224 268 00 62
ORCID ID: Deniz Kamaci Sener: 0000-0003-3433-6859, **Sevil Sadri:** 0000-0002-6315-9620, **Vildan Gursoy:** 0000-0002-3645-9345, **Ozden Kamisli:** 0000-0003-1114-7860
Received: 06.03.2025, **Accepted:** 13.08.2025

neuropathy.

There are very few studies in the literature that report polyneuropathy (PNP) in TDT patients.

The prevalence of neuropathy in those individuals has been reported in the range of 22.0 to 78.0% (3,4). In some studies, only motor neuropathy, sensory neuropathy, both myopathy and PNP (5,10,11) were reported in patients with TDT. There is limited data in the literature entrapment neuropathy due to iron accumulation and regarding the relationship between peripheral neuropathy and heart and liver involvement. The aim of the present study was to investigate the frequency of neuropathy in patients with TDT, to determine whether factors such as age, gender, ferritin liver and heart magnetic resonance imaging (MRI), or splenectomy are associated with neuropathy and to effectively manage neurological complications in the early period.

Materials and Methods

This retrospective study included 28 patients (20 women, 8 men) aged 18–34 years under follow-up due to TDT at the Bursa City Hospital Thalassemia Center between September 2022 and September 2023, along with 32 healthy volunteer controls (24 women, 8 men) aged 19–35 years. Healthy controls were selected from individuals without known diseases or neurological complaints. Patients with vitamin B12 and folic acid deficiency, diabetes mellitus, thyroid dysfunction, previously known PNP and neurotoxic drug use were excluded from the study. The study protocol was approved by the ethics committee of Bursa City Hospital and was prepared in accordance with the Helsinki declaration of the World Medical Association (Ethical committee code number: E13012450-514.99-226762499). (NCS) of all patients and health controls was performed by the same person using the same electroneuromyography (ENMG) device at an average temperature of 32°C for both upper and lower extremities. The nerve conduction velocity, sensory peak latency, and sensory amplitude of the right median, ulnar, and sural sensory nerves, as well as the nerve conduction velocity, motor distal latency, and motor amplitudes of the right median, ulnar, peroneal, and tibial motor nerves were recorded. In terms of entrapment neuropathy, patients with decreased sensory conduction velocity and increased sensory peak latency of the median and ulnar nerves were classified as mild entrapment neuropathy, patients with decreased conduction velocity and prolonged motor distal latency of the motor fibers of the median and ulnar nerves in addition to median and ulnar sensory involvement were classified as moderate entrapment neuropathy, and patients with decreased conduction velocity and amplitude and increased latency of sensory and motor nerve fibers were classified as severe entrapment neuropathy. Patients with decreased sural sensory amplitude and conduction velocity and decreased velocity and amplitude of sensory fibers of the median and ulnar nerves were classified as sensory PNP, patients with decreased velocity and amplitude of motor fibers of the peroneal, tibial, median and ulnar nerves were classified as motor PNP, and patients where both sensory and motor fibers were affected were classified as sensorimotor PNP. The files of the patients were examined and hemoglobin and serum ferritin levels (the current ferritin value taken in the last 3 months was discussed) during their most recent visit, whether they received chelation or not, presence of splenectomy, findings of involvement in liver and heart MRI T2*, and the number of transfusions in the last year were determined. ENMG performed routinely on every adult thalassemia patient in our hospital's thalassemia center were retrospectively examined by the neurologist.

Statistical Analysis: Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). A post-hoc power analysis was performed for the group comparisons (independent samples t-test). Assuming a medium effect size (Cohen's d = 0.6), a total sample size of 60 (28 patients and 32 controls), and a significance level of 0.05, the calculated statistical power was approximately 0.80, indicating an adequate sample size for detecting medium-sized differences. The distribution of continuous variables was assessed using the Shapiro–Wilk test. Descriptive statistics were presented as mean ± standard deviation for normally distributed continuous variables, median (25th–75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables. For group comparisons, the independent samples t-test was used for normally distributed continuous variables, and the Mann–Whitney U test for non-normally distributed continuous variables. For categorical variables, the Chi-square test, Fisher's exact test, or Fisher–Freeman–Halton test was used, depending on the expected frequencies. Correlation analyses were performed using the Pearson correlation coefficient for normally distributed continuous variables, the Spearman rank correlation coefficient for non-normally

distributed or ordinal variables, and the point-biserial correlation for relationships between binary and continuous variables. Due to the exploratory nature of the study and the large number of comparisons (especially in correlation analyses), no correction for multiple comparisons (e.g., Bonferroni or False Discovery Rate) was applied. p-value of <0.05 was considered statistically significant in all analyses.

Results

Demographic Data: The study included 28 patients (20 women, 8 men) (18–34 years) and 32 healthy volunteer controls (24 women, 8 men) (19–35 years). The patients and health controls were age and gender matched. (p:0,237, p:0,920) All patients included in the study were receiving Deferasirox (DFX) chelation. The mean hemoglobin level was 8.41 ± 0.88 and the mean serum ferritin level was 1328.5 g/L (955.0–3106.5). Splenectomy was performed in 18 of 28 patients (64.29%). All patients had received chelation and 18 (64.29%) patients had splenectomy. Summary of disease-related characteristic was given in Table 1. We divided patients into two groups according to ferritin level (9 patients in the<1000 groups and 19 patients in the>1000 group). Summary of demographics and NCS results with regard to ferritin level in the patients group in Table 2.

NCS Data: NCS revealed PNP in 10 of 28 patients (64.29%). Two patients had mild carpal tunnel syndrome (CTS) (7.14%) and one patient had moderate CTS (3.57%). One patient had mild ulnar neuropathy at the elbow (UEN) (3.57%) 2 cm above the elbow. This patient also had moderate CTS and sensory and motor fibers were also affected in the lower extremities and sensorimotor PNP was found. In the control group, two patients had mild CTS (6.25%). Summary of demographics and EMG results with regard to groups in Table 3.

Age was negatively correlated with CTS (r=-0.395, p=.037), CTS severity (r=-0.391, p=0.040). Hemoglobin was positively correlated with sural amplitude (r=0.485, p=0.012), tibialis amplitude (r=0.460, p=0.018). Liver MR T2 sequence was negatively correlated with PNP (r=-0.389, p=0.041), , ulnar sensory latency (r=-0.485, p=0.009) and was positively correlated with ulnar sensory amplitude (r=0.422, p=0.025), ulnar sensory velocity (r=0.400, p=0.035). (Table 4).

Hemoglobin (p=0.010) was significantly higher in the <1000 group than in the >1000 group. We found no significant differences between ferritin groups in terms of heart MR T2*, liver MRI T2*, splenectomy and number of transfusion in a year (Table 5).

Discussion

In the present study, PNP was found in 64.29% TDT patients. Ten patients (35.71%) had normal NCS findings. Eight patients (28.57%) had sensory PNP and two patients (7.14%) had sensorimotor PNP. There were no patients with motor PNP affecting only motor fibers. Previous electrophysiological studies in TDT patients reported different rates of peripheral neuropathy. In their study, Mona H et al. (10) reported that 63% of patients had motor neuropathy, whereas in the present study, none of the patients had motor neuropathy affecting only the motor nerves. In another study, Sawaya et al. reported that 78% of the patients had mild sensory PNP (5). In a study conducted by Nemtsas et al., 27.8% of the patients had myopathy and 16.7% had both PNP and myopathy. We were unable to remark on the rate of myopathy because only NCS were conducted in this investigation (11). PNP was not found in any of the patients in a prior study carried out in Turkey (12). However, we discovered a high rate of PNP in our investigation. Varying rates and different findings in different studies may be due to ethnic and racial factors, age difference between the groups studied, underlying diseases, and environmental factors.

In patients with PNP, the involvement of neuropathy primarily affects the distal large sensory myelinated fibers, thus the expectation is for the sensory fibers in the lower extremities to be affected first, followed by the involvement of the sensory fibers in the upper extremities. Motor fibers are expected to be affected after sensory fibers. People with PNP are more likely to have entrapment neuropathy (13).

In previous studies related to peripheral neuropathy and TDT, entrapment neuropathy has not been widely discussed. We also evaluated the patients for entrapment neuropathy. We observed CTS in 10.71% and UEN in 3.57% of TDT patients. Despite the absence of any complaints in healthy controls, 6.25% CTS was an intriguing finding for us. Consequently, these individuals have been placed under observation for further investigation and treatment.

PNP and entrapment neuropathy are associated with aging (14). According to NCS among TDT patients, PNP is more prevalent in groups with higher average ages. PNP is less common in the pediatric age group. 53 TDT patients, with a mean age of 17, were studied by Papanastasiou et al., who determined that neuropathy manifested in the

Table1: Summary of Disease Related Characteristics of The Patients

Chelation	
No	0 (0.00%)
Yes	28 (100.00%)
Ferritin	1328.5 (955.0 - 3106.5)
Hemoglobin	8.41 ± 0.88
Heart MRI T2 sequence	21.84 ± 10.52
Liver MRI T2 sequence	3.7 (2.55 - 7.2)
Splenectomy	
Absent	10 (35.71%)
Present	18 (64.29%)
Number of transfusion in a year	20.41 ± 4.45

Descriptive statistics were presented by using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables.
MRI: Magnetic resonance imaging

second and third decades of life (13). Therefore, because of the extended period of chronic ischemia, advanced age can be considered a risk factor for the development of PNP (5,13,15). The frequency of PNP and age did not correlate in the current investigation.

In the study by Sawaya et al., no relationship was found between hemoglobin levels and PNP. In the present study, we found that sural amplitudes and tibial motor amplitudes increased as hemoglobin levels increased. This finding supports the notion that chronic ischemia causes neuropathy (5). Exposure to chronic ischemia leads to endoneuronal ischemia, resulting in axonal damage and neuropathy. Neuropathy starts primarily in the large sensory myelinated fibers. Sensorimotor PNP is also common in diseases that may cause chronic ischemia such as lung disease, peripheral arterial disease, and polycythemia vera (16-18)

The long-term and high-dose use of DFX has been reported to have neurotoxic effects such as sensorineural hearing loss, ocular symptoms, and sensorimotor polyneuropathy (19). DFX treats heart hemosiderosis and also protects patients without siderosis (20). In our center, all patients were using iron chelation therapy (DFX). We evaluated the patients at an adult age; chelation treatment was started in childhood. Therefore, how long they had been receiving chelation was not evaluated in the study, and no comparison could be made and we could not compare the frequency of PNP with patients who did not receive chelation or with patients who received different agents (deferipon, or deferipon/defesirox combination).

In the present study, the mean serum ferritin level of the patients was 1328.5 g/L (955.0–3106.5). This value is lower than the mean serum ferritin level reported by Aziz et al. (21) In previous studies, it was found that peroneal motor nerve, sural sensory, and ulnar sensory peak latencies were longer in patients with higher ferritin levels (> 1000 □g/L) compared to those with lower levels (<1000 □g/L) (3) . In another study, it was mentioned that peripheral motor neuropathy was more common in patients with serum ferritin >2000 ηg/L. In the present study, the patients were divided into two groups as serum ferritin > 1000 □g/L and < 1000 □g/L to evaluate its relationship with neuropathy. We did not detect a correlation between serum ferritin levels and neuropathy as in the literature. This may be related to treatment compliance, patient age, and the type of chelation used.

Contradictory findings have been found between splenectomy and the frequency of neuropathy. While no relationship was found between splenectomy and neuropathy in the study conducted by Sawaya et al., in the study conducted by Mona et al. in Egypt, the frequency of motor neuropathy was found to be higher in patients who underwent splenectomy (5,10) In our study, no relationship between splenectomy and neuropathy reported . We think that this is an issue that should be investigated in the future.

The depth of anemia increases the number of transfusions. Both chronic ischemia and excessive iron overload due to transfusions may lead to higher complication rates as the duration and frequency of transfusion increases. Mona et al. identified a positive correlation between

Table 2: Summary of Demographics and EMG Results With Regard To Ferritin Level In The Patient Group

	Ferritin<1000(n=9)	Ferritin>1000 (n=19)	p
Age	22 (21 - 25)	24 (23 - 31)	p=0.216‡
Sex			
Female	7 (77.78%)	13 (68.42%)	p=1.000§
Male	2 (22.22%)	6 (31.58%)	
Diabetes mellitus			
Absent	7 (77.78%)	19 (100.00%)	p=0.095§
Present	2 (22.22%)	0 (0.00%)	
CTS			
Absent	7 (77.78%)	18 (94.74%)	p=0.234§
Present	2 (22.22%)	1 (5.26%)	
CTS severity			
Absent	7 (77.78%)	18 (94.74%)	p=0.234 ¥
Mild	1 (11.11%)	1 (5.26%)	
Moderate	1 (11.11%)	0 (0.00%)	
Severe	0 (0.00%)	0 (0.00%)	
UEN			
Absent	8 (88.89%)	19 (100.00%)	p=0.321§
Present	1 (11.11%)	0 (0.00%)	
UEN severity			
Absent	8 (88.89%)	19 (100.00%)	p=0.321 ¥
Mild	1 (11.11%)	0 (0.00%)	
Moderate	0 (0.00%)	0 (0.00%)	
Severe	0 (0.00%)	0 (0.00%)	
PNP			
Absent	4 (44.44%)	14 (73.68%)	p=0.210§
Present	5 (55.56%)	5 (26.32%)	
PNP type			
Absent	4 (44.44%)	14 (73.68%)	p=0.123 ¥
Sensory	3 (33.33%)	5 (26.32%)	
Motor	0 (0.00%)	0 (0.00%)	
Mixed	2 (22.22%)	0 (0.00%)	
Median sensory latency	2.08 (2.08 - 2.24)	2.08 (1.93 - 2.19)	p=0.197‡
Median sensory amplitude	39.50 ± 24.36	40.97 ± 15.81	p=0.848 †
Median sensory velocity	62 (58 - 62)	62 (57 - 66)	p=0.470‡
Ulnar sensory latency	1.82 (1.77 - 2.60)	1.98 (1.88 - 2.23)	p=0.693‡
Ulnar sensory amplitude	33.97 ± 24.47	37.35 ± 12.58	p=0.704 †
Ulnar sensory velocity	60 (50 - 62)	58 (53 - 61)	p=0.805‡
Sural latency	2.57 ± 0.38	2.45 ± 0.45	p=0.560 †
Sural amplitude	17.9 (10.8 - 32.1)	15.0 (9.9 - 23.0)	p=0.795‡
Sural velocity	54.57 ± 10.81	57.26 ± 10.83	p=0.579 †
Median motor latency	2.76 (2.34 - 3.02)	2.40 (2.24 - 2.71)	p=0.080‡
Median motor amplitude	8.97 ± 1.57	10.71 ± 2.74	p=0.090 †
Median motor velocity	60 (56 - 61)	64 (58 - 69)	p=0.104‡
Peroneal latency	3.85 (2.97 - 4.58)	3.54 (3.13 - 4.17)	p=0.583‡

Peroneal amplitude	5.26 (3.10 - 5.70)	5.00 (3.90 - 5.90)	p=0.840‡
Peroneal velocity	50 (44 - 51)	56 (45 - 63)	p=0.202‡
Tibialis latency	3.68 ± 0.63	3.72 ± 0.85	p=0.897 †
Tibialis amplitude	10.74 ± 4.86	8.35 ± 3.49	p=0.175 †
Tibialis velocity	44 (44 - 48)	48 (44 - 54)	p=0.139‡

p-values were calculated using independent samples † Student's t test, ‡ Mann Whitney U test, § Fisher Exact test, ¥ Fisher-Freeman-Halton
CTS: Carpal tunnel syndrome, UEN: ulnar neuropathy at elbow PNP: polyneuropathy

Table 3: Summary of Demographics and EMG Results With Regard To Groups

	Controls (n=32)	Patients (n=28)	p
Age	26 (24 - 29)	24 (22 - 27.5)	p=0.237 ‡
Sex			p=0.920§
Female	24 (75%)	20 (71.43%)	
Male	8 (25%)	8 (28.57%)	
CTS			
Absent	30 (93.75%)	25 (89.29%)	p=0.657§
Present	2 (6.25%)	3 (10.71%)	
CTS severity			
Absent	30 (93.75%)	25 (89.29%)	p=0.794 ¥
Mild	2 (6.25%)	2 (7.14%)	
Moderate	0 (0.00%)	1 (3.57%)	
Severe	0 (0.00%)	0 (0.00%)	
UEN			
Absent	31 (96.88%)	27 (96.43%)	p=1.000§
Present	1 (3.13%)	1 (3.57%)	
UEN severity			
Absent	31 (96.88%)	27 (96.43%)	p=1.000 ¥
Mild	1 (3.13%)	1 (3.57%)	
Moderate	0 (0.00%)	0 (0.00%)	
Severe	0 (0.00%)	0 (0.00%)	
PNP			
Absent	32 (100%)	18 (64.29%)	p=0.012§
Present	0 (0.00%)	10 (35.71%)	
PNP type			
Absent	32 (93.75%)	18 (64.29%)	p=0.006 ¥
Sensory	0 (0.00%)	8 (28.57%)	
Motor	0 (0.00%)	0 (0.00%)	
Mixed	0 (0.00%)	2 (7.14%)	
Median sensory latency	2.19 (2.01 - 2.40)	2.08 (1.96 - 2.24)	p=0.094‡
Median sensory amplitude	42.33 ± 16.89	40.50 ± 18.52	p=0.691 †
Median sensory velocity	58 (54 - 62)	62 (57.5 - 65)	p=0.051‡
Ulnar sensory latency	1.96 (1.85 - 2.08)	1.97 (1.82 - 2.24)	p=0.801‡
Ulnar sensory amplitude	34.19 ± 14.14	36.26 ± 16.90	p=0.607†
Ulnar sensory velocity	55 (52 - 59.5)	58.5 (53 - 61.5)	p=0.275‡

Sural latency	2.34 ± 0.38	2.48 ± 0.43	p=0.189†
Sural amplitude	26.0 (15.1 - 29.9)	15.15 (10.8 - 23.1)	p=0.053‡
Sural velocity	58.87 ± 7.77	56.54 ± 10.67	p=0.345†
Median motor latency	2.78 (2.53 - 3.05)	2.45 (2.27 - 2.74)	p=0.009‡
Median motor amplitude	10.45 ± 2.61	10.15 ± 2.53	p=0.653†
Median motor velocity	61.5 (56.5 - 66)	61 (57.5 - 66)	p=0.824‡
Peroneal latency	3.59 (3.07 - 4.64)	3.59 (3.13 - 4.27)	p=0.892‡
Peroneal amplitude	4 (2.6 - 5.5)	5 (3.7 - 5.7)	p=0.083‡
Peroneal velocity	50 (47 - 55)	50.5 (45 - 58)	p=0.785‡
Tibialis latency	4.00 ± 1.03	3.71 ± 0.78	p=0.222†
Tibialis amplitude	7.32 ± 3.31	8.99 ± 3.95	p =0.085†
Tibialis velocity	47.5 (43 - 51.5)	46.5 (44 - 50)	=0.944‡

p-values were calculated using independent samples † Student's t test, ‡ Mann Whitney U test, § Fisher exact test, ¥ Fisher-Freeman-Halton
CTS:Carpal tunnel syndrome, UEN: ulnar neuropathy at elbow PNP:polyneuropathy

Table 4: Correlations Between Disease Related Variables and Emg Results In Thepatients Group

		Age	Ferritin	Hemoglobin	Heart MRI T2 sequence	Liver MRI T2 sequence	Splenectomy	Number of Tx in a year
CTS	r	-0.395	-0.021	0.128	-0.107	-0.337	-0.224	-0.156
	p	0.037*	0.914*	0.515**	0.589**	0.079*	0.252*	0.437**
CTS severity	r	-0.391	-0.031	0.182	-0.119	-0.338	-0.206	-0.139
	p	0.040*	0.877*	0.353**	0.545**	0.079*	0.292*	0.490**
UEN	r	-0.323	-0.131	0.287	0.077	-0.275	-0.258	-
	p	0.093*	0.506*	0.138**	0.695**	0.157*	0.185*	-
UEN severity	r	-0.323	-0.131	0.299	0.072	-0.275	-0.258	-
	p	0.093*	0.506*	0.123**	0.717**	0.157*	0.185*	-
PNP	r	-0.144	-0.221	0.221	-0.012	-0.389	0.089	-0.156
	p	0.465*	0.257*	0.258**	0.953**	0.041*	0.653*	0.437**
PNP type	r	-0.198	-0.241	0.178	-0.088	-0.421	0.066	-0.174
	p	0.312*	0.216*	0.365**	0.657**	0.026*	0.740*	0.384**
Median sensory latency	r	0.010	-0.005	-0.167	0.025	-0.178	-0.168	-0.005
	p	0.960*	0.979*	0.397*	0.898*	0.364*	0.394*	0.979*
Median sensoryamplitude	r	-0.032	-0.308	0.170	0.063	0.259	0.099	0.115
	p	0.872*	0.111*	0.386	0.752	0.183*	0.615	0.569
Median sensory velocity	r	0.003	-0.039	0.123	-0.163	0.137	0.061	-0.072
	p	0.988*	0.842*	0.533*	0.408*	0.486*	0.759*	0.722*
Ulnar sensory latency	r	-0.122	0.128	-0.159	-0.025	-0.485	-0.217	-0.081
	p	0.537*	0.518*	0.419*	0.900*	0.009*	0.267*	0.690*
Ulnar sensory amplitude	r	0.191	-0.073	-0.034	0.051	0.422	0.047	-0.053
	p	0.329*	0.714*	0.865	0.797	0.025*	0.811	0.791
Ulnar sensory velocity	r	0.076	0.002	0.222	-0.012	0.400	0.176	-0.052
	p	0.700*	0.991*	0.257*	0.950*	0.035*	0.370*	0.795*
Sural latency	r	0.061	-0.075	0.030	-0.059	-0.260	0.163	-0.088
	p	0.769*	0.716*	0.883	0.775	0.199*	0.427	0.670
Sural amplitude	r	-0.019	0.074	0.485	-0.086	0.292	-0.075	-0.127
	p	0.927*	0.719*	0.012*	0.677*	0.147*	0.714*	0.536*

Sural velocity	r	-0.066	0.097	0.064	-0.075	0.324	-0.140	-0.057
	p	0.749*	0.639*	0.757	0.717	0.107*	0.494	0.782
Median motor latency	r	-0.118	-0.288	-0.154	0.276	-0.338	-0.171	0.286
	p	0.550*	0.137*	0.435*	0.155*	0.079*	0.384*	0.148*
Median motor amplitude	r	0.280	0.101	-0.102	0.237	-0.157	-0.019	0.183
	p	0.149*	0.608*	0.606	0.224	0.424*	0.923	0.362
Median motor velocity	r	-0.098	0.304	-0.154	-0.053	0.095	-0.287	0.191
	p	0.621*	0.115*	0.435*	0.790*	0.630*	0.139*	0.341*
Peroneallatency	r	0.328	-0.036	-0.211	0.112	-0.256	0.016	-0.125
	p	0.102*	0.863*	0.300*	0.587*	0.207*	0.937*	0.542*
Peroneal amplitude	r	0.097	0.053	-0.233	-0.003	-0.025	0.022	-0.142
	p	0.638*	0.797*	0.252*	0.989*	0.903*	0.917*	0.488*
Peroneal velocity	r	-0.327	0.132	-0.031	-0.126	-0.213	-0.324	0.255
	p	0.103*	0.519*	0.882*	0.540*	0.297*	0.106*	0.208*
Tibialis latency	r	0.183	0.182	-0.216	0.075	-0.045	-0.112	-0.113
	p	0.371*	0.374*	0.289	0.717	0.826*	0.586	0.584
Tibialis amplitude	r	-0.282	-0.076	0.460	-0.181	0.301	-0.089	0.127
	p	0.162*	0.714*	0.018	0.376	0.135*	0.667	0.536
Tibialis velocity	r	-0.383	0.259	0.064	-0.324	-0.111	-0.070	0.118
	p	0.054*	0.201*	0.757*	0.106*	0.591*	0.733*	0.566*

p values with * show Spearman correlation analysis, p values with ** show point biserial correlation analysis, while other p values show Pearson correlation analysis.
CTS: Carpal tunnel syndrome, UEN: ulnar neuropathy at elbow PNP: polyneuropathy MRI: Magnetic resonance imaging

Table 5: Summary of Disease-Related Characteristics With Regard To Ferritin Level In The Patient Group

	Ferritin<1000 (n=9)	Ferritin>1000 (n=19)	p
Hemoglobin	9.01 ± 0.83	8.13 ± 0.76	p=0.010†
Heart MRI T2 sequence	22.76 ± 9.63	21.41 ± 11.14	p=0.758†
Liver MRI T2 sequence	4.2 (4.0 - 10.0)	3.6 (2.3 - 7.0)	p=0.175‡
Splenectomy			
Absent	1 (11.11%)	9 (47.37%)	p=0.098§
Present	8 (88.89%)	10 (52.63%)	
Number of Tx in a year	19.50 ± 2.62	20.79 ± 5.04	p=0.393†

Descriptive statistics were presented by using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. p values were calculated using † Student's t test, ‡ Mann-Whitney U test, § Fisher exact test
MRI: Magnetic resonance imaging

transfusion frequency, serum ferritin levels, and peripheral neuropathy scores. The current investigation found no association between neuropathy and the amount of transfusions received in the previous 12 months. This might be because there were only a few patients in our trial and we did not include the peripheral neuropathy score. (5,7,10).

In TDT patients, organ damage occurs as a result of liver and heart iron overload. T2* MRI-guided chelation therapies resulted in a 71% reduction in iron overload-related mortality and a 62% reduction in all-cause mortality (22). In the present study, we compared the severity of iron overload involvement heart and liver MRI T2* with the presence and severity of neuropathy. The frequency of PNP decresed in correlation with the degree of iron overload in liver MRI T2*. This finding is unexpected and does not supports the increase in the frequency of PNP and myopathy

with iron load in liver MRI T2* in the study of Nemtsas et al. (11). The iron overload in liver MRI T2* increased; sensory peak latency of the ulnar nerve shortened,and sensory amplitude of the ulnar nerve decreased, and ulnar sensory conduction velocity decreased. These electrophysiological findings don't support PNP. These discordant findings may have been detected due to the small number of patients or coincidence.

In the literature, the study comparing the severity of iron accumulation on heart MRI T2* and neuropathy was not found. We compared these two parameters and found that as iron accumulation increases in heart MRI T2* and didn't find relationship between heart MRI T2* and NCS.

The results obtained in this study did not correlate with neuropathy in TDT patients with iron overload as assessed by liver and heart T2* MRI.

In the future, more meaningful results may be found if electrophysiological examinations are performed in multicenters with a higher number of patients.

As the life expectancy of TDT patients increases, many neurological complications can now be recognized. Early detection of these complications can enhance the quality of life and extend the lifespan of TDT patients without causing permanent damage. Consequently, iron overload may contribute to the pathogenesis of neuropathy.

The limitations of the study include its retrospective nature, the small number of patients and not performing muscle examination with ENMG and we did not include the peripheral neuropathy score in our study. If the number of patients had been larger, neuropathies and trap neuropathy data would have been more meaningful. Another significant limitation is that our center uses the oral chelator DFX tablet for iron chelation, and we are not aware of how the results might differ with other iron chelation methods such as intravenous or subcutaneous forms. NCS is performed on every patient followed in the thalassemia center of our hospital.

In the coming years, this study is planned to be multicenter, prospective, with a larger number of patients, and the patients will also be evaluated in terms of neurological disability.

Acknowledgment: The authors also acknowledge the staff in our institution who have assisted in data collection and data acquisition.

Competing Interests: The authors declare no conflict of Interest

All authors critically revised the manuscript, agree to be fully accountable for ensuring the Integrity and accuracy of the work, and read and approved the final manuscript. There are no conflicts of interest to disclose with companies.

Funding: The study was financially supported by the researchers and authors.

Availability of Data and Materials: The authors agree to share, copy, and modify the data used in this article, even for commercial purposes, so long as appropriate credit is given, and possible changes are indicated. Ethics approval and consent to participate.

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