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Original Article

Exploring Neuropathy and Myopathy in Mitochondrial Diseases: Insights from Nerve Conduction Studies and Electromyography

Mitokondriyal Hastalıklarda Nöropati ve Miyopatinin İncelenmesi: Sinir İleti Çalışmaları ve Elektromiyografi Bulguları

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ABSTRACT

Objective: Mitochondrial diseases (MDs) are characterized by significant genetic and clinical heterogeneity. Although they are frequently investigated for potential central nervous system involvement, they can also affect the peripheral nervous system, leading to neuropathy and myopathy. The aim of this study is to determine the role of nerve conduction study (NCS) and electromyography (EMG) in the diagnosis of MD and the monitoring of peripheral nervous system involvement in patients with MD.

Method: This retrospective study examined data from 25 patients with MD. Clinical and laboratory parameters were compared between groups with and without abnormal electrophysiological findings. Additionally, subtypes of neuropathy were classified, and correlations between genotypes and phenotypes were analyzed.

Results: Neuropathy was detected at a considerable rate of 40%. The findings were predominantly consistent with the expected axonal neuropathy in MD, particularly in cases with lower limb-onset MD, although demyelinating patterns were also frequently observed. Notably, neuropathy was more prevalent in patients with mitochondrial variants than previously reported. Furthermore, physical examination findings and motor symptoms failed to predict neuropathy. Similarly, myopathic findings identified on EMG were observed even in cases without corresponding neuropathy-specific physical examination findings, motor symptoms, or elevated muscle enzyme levels.

Conclusions: The routine use of NCS and EMG serves as a valuable guide in the diagnostic process of MD. They are considered important tools for both diagnostic evaluation and ongoing monitoring of peripheral nervous system involvement.

Keywords: Mitochondrial diseases, neuropathy, nerve conduction studies, mitochondrial DNA, nuclear DNA, pediatric population

ÖZ

Amaç: Mitokondriyal hastalıklar (MH), belirgin genetik ve klinik heterojenite ile karakterizedir. Genellikle santral sinir sistemi tutulumu açısından araştırılsalar da periferik sinir sistemini de etkileyerek nöropati ve miyopati gibi bulgulara yol açabilirler. Bu çalışmanın amacı, MH'de periferik sinir sistemi tutulumunun değerlendirilmesinde ve tanı sürecinde sinir ileti çalışması ve elektromiyografinin (EMG) rolünü belirlemektir.

Yöntem: Bu retrospektif çalışmada, MH tanılı 25 hastanın verileri incelendi. Elektrofizyolojik olarak anormal bulguları olan ve olmayan gruplar arasında klinik ve laboratuvar parametreleri karşılaştırıldı. Ayrıca, nöropati alt tipleri sınıflandırıldı ve genotip-fenotip korelasyonları analiz edildi.

Bulgular: Nöropati %40 gibi yüksek bir oranda saptandı. Bulgular, özellikle alt ekstremite başlangıçlı olgularda, MH'de beklenen aksonal tip ile büyük ölçüde uyumluydu; ancak demiyelinizan nöropati de sıklıkla gözlendi. Mitokondriyal varyant taşıyan hastalarda nöropati daha önce bildirilen oranlardan daha yüksek bulundu. Ayrıca, fizik muayene bulguları ve motor semptomlar nöropatiyi öngörmede yetersizdi. Benzer şekilde, miyopati tanısında da EMG klinik ve laboratuvar tetkiklerinden üstündü.

Sonuç: Sinir ileti çalışmaları ve EMG'nin rutin kullanımı, MH'lerin tanı sürecinde değerlidir. Bu yöntemler, hem tanısal değerlendirme hem de periferik sinir sistemi tutulumunun izleminde önemli araçlar olarak kabul edilmelidir.

Anahtar kelimeler: Mitokondriyal hastalıklar, nöropati, sinir ileti çalışmaları, mitokondriyal DNA, nükleer DNA, pediatrik popülasyon

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INTRODUCTION

Mitochondrial diseases (MDs) are the most common metabolic disorders, with an incidence of approximately one in 5000 live births[1]. They exhibit considerable heterogeneity in terms of genetic inheritance mechanisms and clinical presentations[2]. Mitochondria are crucial organelles in eukaryotic cells, responsible for generating the majority of cellular energy in the form of adenosine triphosphate (ATP) via oxidative phosphorylation (OXPHOS). Genetic testing has become the primary diagnostic approach for MDs when clinical uncertainty is present. The human mitochondrial genome is a circular DNA molecule encoding components of four OXPHOS enzyme complexes and comprises 37 genes[3]. Nuclear DNA (nDNA) is essential for the formation and assembly of all other subunits within the OXPHOS complexes. Consequently, the mitochondrial proteome comprises approximately 1500 nDNA-encoded mitochondrial genes in addition to 37 genes encoded by mitochondrial DNA (mtDNA)[4]. This dual origin leads to two patterns of inheritance, and genetic testing aims to identify mutations in both nDNA and mtDNA genes[5]. Consequently, any organ systems may be involved in MD[6]. Neurologic system involvement is common in MD, while peripheral neuropathy and myopathy have been described in addition to central nervous system involvement[7-10].

Nerve conduction studies (NCS) are being conducted to establish the diagnosis of neuropathy[11]. Although challenging to perform in pediatric populations, needle electromyography (EMG) is useful for detecting neuropathic changes that cannot be identified performing NCS[12]. Furthermore, EMG can also be used to diagnose myopathy[13]. In previous studies, subgroups of patients with an established diagnosis of MD who developed neuropathy have been presented as case series, and subtypes of neuropathy have been classified[8,14,15]. However, in this already rare and heterogeneous disease group, the prevalence of neuropathy and the diagnostic value of NCS remain unclear. Although electrophysiological studies are uncomfortable procedures[16] in clinical practice they may serve as important indicators for referrals to genetic testing in order to make the final diagnosis of MD by revealing the presence of neuropathy and myopathy.

Therefore, this study aimed to determine the role of performing NCS and EMG at initial presentation—before a confirmed definitive genetic diagnosis was made—regardless of the presence of symptoms, in the diagnostic process of MD.

MATERIALS and METHODS

The Publication Ethics Statement

This study was approved by the Ethics Committee of Dokuz Eylül University Non-Interventional Studies Ethics Committee (approval number: 2024/17-21, dated: 15.05.2024).

Study Design and Participants

A retrospective analysis was conducted on patient files covering the time interval from January 2013 to May 2024 at the Department of Pediatric Neurology, Dokuz Eylül University Faculty of Medicine. The study included patients with a confirmed genetic diagnosis of MD, meeting diagnostic criteria for pathogenic or likely pathogenic variants per American College of Medical Genetics and Genomics guidelines[13]. These variants were required to affect genes associated with human disease, corresponding with the participant's phenotype, and matching the disease's mode of inheritance. Age, sex, clinical symptoms, neurologic examinations, NCS and EMG findings, brain magnetic resonance imaging (MRI), laboratory parameters and genetic results were recorded. Patients were analyzed in two groups as those with nDNA and those with mtDNA variants.

NCS

NCSs were performed using Nihon Cohden EMG/evoked potentials Measuring System Model MEB-9400K SN 80853 2011. For the evaluation of sensory and motor nerves in the upper extremity, the median nerve was assessed. In the lower extremity, the sural nerve was evaluated as the sensory nerve, while the tibial and peroneal nerves were examined as the motor nerves. The measured values were compared with age-appropriate reference values[17].

The diagnosis of demyelinating neuropathy was made based on at least one of the following criteria: conduction velocity below 75% of the age-appropriate lower limit, distal latency above 130% of the upper limit, or proximal compound muscle action potential (CMAP) amplitude equal to or less than 50% of the distal CMAP amplitude. Axonal neuropathy was diagnosed in the absence of the criteria indicating the presence of demyelinating neuropathy and when CMAP amplitude was below 80% of the age-appropriate lower limit[18]. Cases that did not fully fit into either category were classified as mixed neuropathy. Myopathy is characterized by short-duration polyphasic motor unit potentials and a complete interference pattern of low amplitude on needle EMG, while high amplitude polyphasic waves are typically observed in neuropathic cases[19].

Statistical Analysis

IBM SPSS Statistics 27.0 (SPSS Inc., Chicago, IL, USA) program was used for statistical evaluation. Descriptive variables were reported as percentages (%), means ± standard deviation, or medians accompanied by interquartile ranges (IQRs) in parentheses. Chi-squared or Fisher's exact tests were applied for categorical variables, while Mann-Whitney U-test were used for quantitative data after testing normality of variables with the Shapiro-Wilk test. A p-value below 0.05 was deemed statistically significant.

RESULTS

In this study, data of 25 cases of MD from 21 different families were analyzed. The median age of the participants was 10 years (IQR:9, range: 1-17), with males constituting 56% (n=14) of the study population. Diagnosis of MD was established in 76% (n=19) of the cases by identifying variants in nDNA, while 24% (n=6) of the diagnoses were attributed to variants in mtDNA. In the nDNA variant group, one case underwent next-generation sequencing panel for cardiomyopathy-associated gene ie. tafazzin, while another patient underwent a targeted single-gene analysis for *SURF1* gene based on clinical findings and neuropathy type, while the remaining cases were diagnosed using whole exome sequencing. In the mtDNA variant group, mutations and deletions were tested from plasma samples. The variants were most frequently identified in the *MT-ATP6* gene, observed in three cases, followed by *SURF1*, *POLG*, *NDUFA12*, and *COQ8A* genes, where each of them were reported in two cases.

Neurological symptoms were predominant in the majority of the cohort. Cognitive impairment was the most common pathology present in 18 (72%) patients, followed by motor delay in 16 (64%) cases. Seizures were reported at the time of presentation in 11 (44%) cases. Additionally, skeletal deformities were observed in 7 (28%) and muscle atrophy in 6 patients (24%) (Table 1).

MRI of the brain was conducted in 23 cases, with 15 (69.6%) cases demonstrating pathological findings. Hyperintense lesions on the T2-weighted sequences involving the basal ganglia were observed in eight (34.8%), and cortical atrophy in seven (30.4%) cases. Magnetic resonance spectroscopy revealed abnormal findings in 8 (35%) cases. An increased lactate peak was present in seven cases, while a decreased N-acetyl aspartate peak was observed in one case (Table 1).

Clinical suspicion of neuropathy was not present in all cases, as NCS were routinely performed with a preliminary diagnosis of MD at our center. Muscle weakness, defined as reduced muscle strength in at least one extremity based on the Medical Research Council scale, was observed in 15 (65%) patients, two of whom also had hypoactive deep tendon reflexes (DTRs). Based on NCS, neuropathy was observed in 10 (40%) patients (Table 1). These patients had mixed-type neuropathy with axonal predominance (n=4), demyelinating neuropathy (n=2), and axonal neuropathy (n=4). In the groups with neuropathy, most commonly the tibial and peroneal nerves were affected (n=8: 80%), while the other evaluated nerves (medial—both sensory and motor—and sural nerves) were equally affected, in 70%

Table 1. Demographic, and clinical characteristics of study subjects

		n (%)
Gender	Male	14 (56)
	Female	11 (43)
Brain MRI	Normal	8 (34.8)
	Hyperintense lesions	8 (34.8)
	Cortical atrophy	7 (30.4)
MRS	Normal	6 (43)
	Increased lactate peak	7 (50)
	decreased NAA peak	1 (7)
Variant	mtDNA	6 (24)
	nDNA	19 (76)
Cognitive impairment		18 (72)
Muscle weakness		16 (64)
Dsymorphologic features		14 (56)
Ophthalmoparesis		12 (48)
Seizures		11 (44)
Skeletal deformities		7 (28)
Hearing loss		4 (16)
DTRs	Normoactive	15 (60)
	Absent	1 (4)
	Hypoactive	2 (8)
	Hyperactive	7 (28)
NCS	Normal	11 (60)
	Neuropathy	10 (40)
EMG	Normal	1 (25)
	Myopathy	4 (75)

DTRs: Deep tendon reflexes, EMG: Electromyography, MRI: Magnetic resonance imaging, MRS: Magnetic resonance spectroscopy, mtDNA: mitochondrial DNA, NAA: N-acetyl aspartate, nDNA: Nuclear DNA, NCS: Nerve conduction study

(n=7) of the cases. On the other hand, EMG performed revealed findings consistent with myopathy in four of five cases.

The median ages of the groups with and without neuropathy were within a similar range, without any statistically significant difference. The physical examination and clinical findings of these two groups including muscle weakness, abnormal DTRs, ophthalmoparesis, dysmorphologic features, hearing loss, skeletal deformities, and muscle atrophy did not also differ significantly between groups (Table 2).

In the group with the mtDNA variant, 4 (67%) patients exhibited muscle weakness. Examination of DTRs revealed hypoactive reflexes in 2 (33%), hyperactive reflexes in 1 (17%) patient, while remaining cases had normal DTRs. None of the patients showed elevated creatine kinase (CK) levels. NCS revealed axonal polyneuropathy, predominantly affecting the lower extremities, in three cases. (50%) Needle EMG was performed in one patient, uncovering myopathic findings (Table 3).

In contrast, when looking at the group diagnosed with the nDNA variant, 12 (63.2%) patients exhibited muscle weakness. Examination of DTRs revealed hyperactive reflexes in 6 cases, while one patient had no DTRs. In the remaining patients, DTRs were normal. Elevated CK levels were detected in one patient. NCS revealed neuropathy in seven (46.6%) cases with axonal polyneuropathy predominantly affecting the lower extremities in five cases. Additionally, two cases with Surfeit 1 (*SURF1*) gene variants were identified as having demyelinating neuropathy. Needle EMG was performed in three cases, uncovering myopathic findings (Table 4).

DISCUSSION

Peripheral nervous system involvement is thought to be underdiagnosed in patients with MD, while central nervous system involvement is more predominant[10]. Previous studies indicated that peripheral neuropathy has been detected in approximately 30% of patients with MD[15,20]. In our study, this rate was significantly elevated, potentially due to the routine assessment of patients-including asymptomatic cases-through NCS. This high rate of neuropathy supports the recommendation of NCS as part of the diagnostic evaluation and an ongoing surveillance tool.

Mitochondrial neuropathy, has been found to be more frequently diagnosed in patients with nDNA variants compared to those with mtDNA variants[14]. In our study, neuropathic findings were documented at a higher rate compared to those reported in the literature. As is known axonal neuropathy is detected in cases of MD caused by mtDNA variants[14]. Similarly, our study supports this finding, as two of our cases carrying the more common *MT-ATP6* variant, which leads to the Leigh phenotype, also exhibited axonal neuropathy[21]. Among the other three variants, the *MT-CYB* variant, affecting cytochrome b, was associated with axonal neuropathy, consistent with mtDNA variants. In contrast, the *MT-ND4* variant, affecting complex I, was not associated with neuropathy but exhibited myopathic findings.

Table 2. Comparison of signs and symptoms of neuropathic patients and patients with normal electrophysiologic findings

	Neuropathy (n=10)	Normal (n=15)	p-value
Age (median, range)	8.50 (2-13)	10.0 (1-17)	0.290
Muscle weakness, n (%)	7 (70)	9 (60)	0.691
Dysmorphologic features, n (%)	6 (60)	8 (53.3)	1.000
Ophthalmoparesis, n (%)	5 (50)	7 (46.6)	1.000
Seizures, n (%)	4 (40)	7 (46.6)	1.000
Abnormal DTRs, n (%)	5 (50)	5 (33.3)	0.442
Skeletal deformities, n (%)	2 (20)	5 (33.3)	0.659
Muscle atrophy, n (%)	3 (30)	3 (20)	0.653
Visual problems,n (%)	2 (20)	4 (26)	1.000
Hearing loss, n (%)	3 (33)	1 (6.6)	0.267
Endocrine dysfunction,n (%)	1 (10)	3 (20)	0.626
Cardiomyopathy, n (%)	2 (20)	1 (6.6)	0.560

DTRs: Deep tendon reflexes

Table 3. The physical examination and electrophysiological findings, creatine kinase levels of the patients with a mitochondrial variant

Patient	Age (year)	Variants	Muscle strength/ DTRs	CK (U/L)	Median motor CMAP Amp (mV)/NCV (m/s)	Tibial motor CMAP Amp (mV)/ NCV (m/s)	Median sensory SNAP Amp (µV)/ NCV (m/s)	Sural sensory SNAP Amp (µV)/NCV (m/s)	EMG	Electrophysiological diagnosis
1	4	NC_012920.1(*MT-CO3*):m.9804G>A	Normal/ normoactive	211	5.52/34.80	4.02/38.60	16.20/40.10	18.00/34.20	-	Normal
2	12	NC_012920.1(*MT-ATP6*):m.8993T>G	Decreased/ hypoactive	107	5.00/43.60	4.17/32.30	7.00/41.40	NR	-	Axonal polyneuropathy
3	8	NC_012920.1(*MT-CYB*): m.73A>G	Normal/ hyperactive	161	7.07/56.80	2.59/36.60	52.20/39.90	NR	-	Axonal polyneuropathy
4	8	NC_012920.1(*MT-ND4*):m.11696G>A	Decreased/ normoactive	210	6.29/47.50	5.33/45.00	32.30/58.50	7.20/45.00	Reduced normal MUPs Polyphasic MUPs	Myopathy
5	1	NC_012920.1(*MT-ATP6*):m.*9077T>C*	Decreased/ hypoactive	36	5.69/38.00	4.87/39.80	5.40/35.50	7.30/35.00	-	Normal
6	3	NC_012920.1(*MT-ATP6*):m.8993T>G	Decreased/ normoactive	64	2.08/42.40	1.32/66.70	NR	20.10/32.00	-	Axonal polyneuropathy

Patients are presented according to the time of their initial presentations. Pathological findings are shown in bold letters.

Amp: Amplitude, CK: Creatine kinase, CMAP: Compound muscle action potential, DTRs: Deep tendon reflexes, NCV: Nerve conduction velocity, SNAP: Sensory nerve action potential, EMG: Electromyography, NR: No response, MUPs: Motor unit potentials

Table 4. The physical examination, electrophysiological findings and creatine kinase levels of the patients with a nuclear variant										
Patient	**Age (year)**	**Variants**	**Muscle strength/ DTRs**	**CK (U/L)**	**Median motor CMAP Amp (mV)/NCV (m/s)**	**Tibial motor CMAP Amp (mV) /NCV (m/s)**	**Median sensory SNAP Amp (μV) /NCV (m/s)**	**Sural sensory SNAP Amp (μV) /NCV (m/s)**	**EMG**	**Electrophysiological diagnosis**
7	6	NM_001195518.2 (*MICU1*):c.553C>T (p.Arg185Ter) Homozygous	Decreased/ normoactive	15076	5.43/44.50	5.33/53.20	24.40/52.00	12.10/43.00	Reduced normal MUPs Polyphasic MUPs	Myopathy
8	16	NM_018838.5 (*NDUFA12*): c.121dupG, p.Glu41GlyfsTer10 Homozygous	Decreased/ normoactive	176	5.17/60.60	5.00/49.30	48.20/55.60	13.00/50.80	Reduced normal MUPs Polyphasic MUPs	Myopathy
9	14	NM_002693.3(*POLG*): 1808T>G (p.Met603Arg) Homozygous	Decreased/ hyperactive	121	6.49/52.60	10.10/45.50	72.10/94.50	9.60/53.70	-	Normal
10	12	NM_003172.4 (*SURF1*): c.484G>A (p.Val162Met) Homozygous	Decreased / hyperactive	225	6.20/43.80	3.24/23.00	8.60/21.30	11.90/30.80	Normal	Demyelinating polyneuropathy
11	10	NM_020247.5 (*COQ8A*): c.1009G>A (p.Ala337Thr) Homozygous	Normal/ hyperactive	179	7.32/66.30	10.65/55.70	25.80/55.30	8.40/64.00	-	Normal
12	6	NM_020247.5 (*COQ8A*): c.1009G>A (p.Ala337Thr) Homozygous	Normal/ normoactive	95	3.54/45.40	4.86/43.40	22.00/55.00	5.30/48.50	-	Normal
13	1	NM_016035.5 (*CoQ4*): c.437T>G (p.Phe146Cys) Homozygous	Normal/ normoactive	63	3.37/31.00	10.93/36.10	23.20/37.60	11.30/33.50	-	Normal
14	2	NM_003172.4 *(SURF1)* c.845_846del (p.Ser282Cysfs*9) Homozygous	Decreased/ normoactive	61	2.71/29.70	1.69/20.80	15.20/31.30	NR	-	Demyelinating polyneuropathy
15	16	NM_032317.3 (*DNAJC30)*:c.352G>T (p.Glu118Ter) Homozygous	Normal/ Normoactive	120	6.24/61.00	9.52/45.70	68.40/69.60	25.80/55.60	-	Normal
16	16	NM_018838.5 (*NDUFA12*): c.121dupG, p.Glu41GlyfsTer10 Homozygous	Decreased/ normoactive	196	6.90/67.40	5.43/50.00	51.50/72.00	9.10/45.00	-	Normal

Table 4. Continued

Patient	Age (year)	Variants	Muscle strength/ DTRs	CK (U/L)	Median motor CMAP Amp (mV)/NCV (m/s)	Tibial motor CMAP Amp (mV) /NCV (m/s)	Median sensory SNAP Amp (μV) /NCV (m/s)	Sural sensory SNAP Amp (μV) /NCV (m/s)	EMG	Electrophysiological diagnosis
17	11	NM_001303 (*COX10*):c.674C>T(p. Pro225Leu) Homozygous	Decreased/ absent	29	NR	NR	0.95/25.00	6.40/46.30	-	Demyelinating polyneuropathy
18	9	NM_017909.4 (*RMND1*) c.203A>G (p.Asn238Ser) Homozygous	Decreased/ normoactive	110	12.33/51.00	2.50/44.80	27.30/54.10	3.50/36.70	Reduced normal MUPs Polyphasic MUPs	Axonal polyneuropathy, myopathy
19	8	NM_033109.4 (*PNPT1*) c.1576_1578dupGAT (p.Asp526dup) Homozygous	Decreased/ hyperactive	98	9.14/50.40	11.20/44.20	11.90/37.30	5.10/33.60	-	Axonal polyneuropathy
20	16	NM_003730.6 (*RNASET2*):c.194A>C (p.His65Arg) Homozygous	Decreased/ hyperactive	70	10.01/57.10	6.57/51.50	54.40/56.50	13.50/50.90	-	Normal
21	17	NM_000116.5 (*TAZ*) :c.718G>A (p.Gly240Arg) Homozygous	Normal/ normoactive	118	5.82/48.5	7.41/46.4	24.4/54.6	17.4/54.8	-	Normal
22	13	NM_004553.6 (*NDUFS6*):c.309+5G>A Homozygous	Decreased/ normoactive	88	7.82/38.50	NR	8.50/34.50	NR	-	Axonal polyneuropathy
23	10	NM_002693.3 (*POLG*) c.3151G>C (p.Gly1051Arg) Homozygous	Normal/ normoactive	166	5.49/49.60	4.23/43.90	20.00/60.20	10.80/44.30	-	Normal
24	5	NM_002693.3 (*POLG*) c.752C>T (p.Thr251Ile), c.1760C>T (p. Pro587Leu) Compound Heterozygous	Normal/ normoactive	52	2.80/41.3	1.8/59.5	59/56.8	15/50	-	Axonal polyneuropathy
25	15	NM_0144772.3 (*NAXE*) c.641T>G (p. Ile214Ser) Homozygous	Normal/ normoactive	155	5.41/48.9	9.53/43.2	47.6/61.20	14.9/55.6	-	Normal

Patients are presented according to the time of their initial presentations. Pathological findings are shown in bold letters.

Amp: Amplitude, CK: Creatine kinase, CMAP: Compound muscle action potential, DTRs: Deep tendon reflexes, NCV: Nerve conduction velocity, SNAP: Sensory nerve action potential, EMG: Electromyography, NR: No response, MUPs: Motor unit potentials

On the other hand, the rate of neuropathy findings in patients with nDNA variants aligns with findings reported in several other studies[8-10]. The frequency of neuropathy in patients with mtDNA variants in our study was higher than that observed in cases with nDNA variants, which may be related to the limited number of our cases. Among patients with nDNA variants, we found axonal neuropathy in five and demyelinating neuropathy in two cases. Our patients with variants in the *SURF1* gene exhibited findings of demyelinating neuropathy, consistent with previous reports[14,21]. In two cases with *POLG* variants, NCS results were normal. Since *POLG* variants have been associated with axonal neuropathy in the literature, this finding may be due to NCS being performed at an early stage[14]. In accordance with the literature data the third patient with a *POLG* variant showed electrophysiological findings consistent with axonal neuropathy despite the absence of relevant clinical signs. In this cohort axonal neuropathy was detected in cases with nDNA variants associated with the Leigh phenotype (*NDUFA12*, *NDUFS6*). This finding, which supports axonal loss, was consistent with the pathophysiology of Leigh syndrome[22].

In the case with a pathogenic *COX10* variant, severe demyelinating neuropathy was observed. Given its late onset (11- year delay), it was hypothesized that axonal loss occurred first, followed by demyelination. This assumption was further supported by previously reported biopsy findings of an adult case, which demonstrated both axonal and myelin involvement[23]. Contrary to the expected myelin loss, axonal neuropathy was observed in our case with *PNPT1* mutation[24].

Given the difficulty of performing EMG in pediatric case series, needle EMG was not performed on every patient; instead it was reserved for cases presenting with muscle weakness or where significant muscle involvement was suspected. One of these cases (Patient 7) showed elevated CK levels. In that case with a variant in the *MICU1* gene, which is associated with calcium transport, myopathy was present, consistent with the literatüre[25]. Although the absence of elevated CK levels in the other three patients suggested that EMG could be primarily reserved to diagnose myopathy, we could not ascertain its definitive diagnostic value, as it was not applied in asymptomatic cases.

We evaluated the physical examination and clinical findings of the cases with neuropathy and those with normal NCS findings, and could not find any statistically significant difference between the two groups regarding musle weakness, abnormal DTR, skeletal deformities, and muscle atrophy. This fact indicates that, although physical examination and clinical findings are important diagnostic tools, there remains a significant need for electrophysiological testing. Moreover, the absence of differences in physical findings highlights the need for repeated NCS assessments during follow-up to detect neuropathy that may develop over time.

Study Limitations

The present study is valuable as it aims to identify neuropathy and myopathy in MD, which are rare genetic disorders. However, its limitations include a small sample size, single-center design, and retrospective nature. Additionally, failure to perform needle EMG in every patient and inability to repeat NCS for patients with initially normal results represent further study limitations.

CONCLUSIONS

In this study, we observed a higher incidence of neuropathy in patients with mtDNA mutations, which contrasts with findings reported in the literature. Furthermore, an increased prevalence of neuropathy was also noted in cases with nDNA mutation. However, we were unable to demonstrate a correlation between these electrophysiological and neurological examination findings or symptoms. Additionally, a large proportion of patients with myopathy did not exhibit elevated CK levels. Therefore, NCS and needle EMG can be utilized as screening tools in cases with a clinical suspicion of MD.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Dokuz Eylül University Non-Interventional Studies Ethics Committee (approval number: 2024/17-21, dated: 15.05.2024).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Surgical and Medical Practices: P.T.K., A.İ.P., A.S.H., N.A., U.Y., Concept: H.B.Ş., P.T.K., A.İ.P., A.A., A.S.H., N.A., U.Y., Design: H.B.Ş., P.T.K., A.İ.P., A.A., A.S.H., N.A., U.Y., Data Collection or Processing: H.B.Ş., M.B., Ç.G., Analysis or Interpretation: H.B.Ş., M.B., Ç.G., A.A., Literature Search: H.B.Ş., M.B., Ç.G., A.S.H., Writing: H.B.Ş., P.T.K., A.İ.P., N.A., U.Y.

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