Research Article

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Electrophysiological study of patients with spinocerebellar and Friedreich's ataxia

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Abstract

Objective: Spinocerebellar (SCA) and Friedreich's ataxia (FRDA) patients were selected in order to undergo standardized protocol for the evaluation of bioelectrical activity of their nerves and muscles. We aimed to gather information on the severity and distribution of their peripheral nerve involvement.

Methods: Eighteen genetically proven SCA and FRDA patients were examined during this study and a control group of 31 age-matched healthy individuals was formed. Both groups underwent conduction studies of sensory and motor nerves, F waves, needle EMG of proximal and distal muscles, and motor unit number estimations (MUNE) of selected muscles on upper and lower extremities.

Results: Amplitudes of all sensory nerves, as well median and peroneal motor amplitudes were low. Median, ulnar, tibial, and peroneal motor conduction velocities were significantly slowed. MUNE in abductor pollicis brevis and tibialis anterior muscles were significantly lower. Needle EMG testing of respective muscles showed neurogenic involvement in the third of the patients.

Conclusion: Polyneuropathy is frequently detected in SCA and FRDA patients. The sensory nerves in lower extremities were predominantly involved; however motor dysfunction was also noted. MUNE can offer quantitative information on motor nerve fiber and motor neuron involvement. Nerve conduction studies and needle EMG demonstrate clinical or subclinical polyneuropathy in patients with SCA and FRDA ataxia. MUNE might present another parameter for peripheral involvement.

Keywords: Spinocerebellar ataxia, Friedreich's ataxia, polyneuropathy, motor unit number estimation, peripheral nervous system

INTRODUCTION

Spinocerebellar ataxias (SCA) are autosomal dominant neurodegenerative disorders characterized by cerebellar ataxia and variety of associated neurological symptoms, like oculomotor abnormalities, pyramidal and extrapyramidal symptoms, peripheral neuropathy, and cognitive disturbances (1, 2). Based on the classification put forward by Anita Harding, the autosomal dominant spinocerebellar ataxias (ADCA) were divided into three groups (3):

1) ADCA type I, which alongside cerebellar degenerations have variable involvement of other parts of the nervous system (1, 3);
2) ADCA type II, which are characterized by retinal degeneration in association with cerebellar disease;
3) ADCA type III, which consist of "pure" cerebellar ataxia (4).

There is also large group of recessive spinocerebellar ataxias, which are variable in genetic and clinic feature, and are not part of current study (5).

Friedriech's ataxia (FRDA) is a progressive autosomal recessive neurodegenerative disorder and the most common type of the inherited ataxias (6). Among important clinical FRDA symptoms, progressive gait-limb ataxia, speech disturbances, muscle weakness, scoliosis, pes cavus, reduced vibration sense and hypertrophic cardiomyopathy can be detected (7-9). Age of onset of symptoms can determine heterogeneity of clinical manifestation, mean-

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ing that delayed-onset FRDA cases can have less pronounced symptoms, longer disease duration before wheelchair confinement (10).

In the majority of cases, FRDA is caused by a GAA trinucleotide expansion. It is localized in the first intron of the FXN gene on chromosomes 9q13. Pathogenesis consists of interference to the frataxin transcription and this condition leads to reduced level of the protein which is named frataxin (7). Severely reduced frataxin level impairs transport and homeostasis of mitochondrial iron, and this altogether results in respiratory chain dysfunction and oxidative stress (11).

Peripheral nerve involvement in SCAs and FRDA ataxia has been described in several previous studies. They have demonstrated that the pathology is not localized only to the central nervous system (7, 12-17). However, most of these studies used only a limited number of peripheral nerves for conduction studies, moreover they did not possess the variety of electrophysiological parameters that we used, and they did not use motor unit number estimation (MUNE) as an additional quantitative tool for the analysis of peripheral motor nerves.

This study was performed to study and compare the extent of peripheral nerve involvement in SCAs and FRDA patients. One of its aims is to test the feasibility of application of MUNE in patients with peripheral motor nerve involvement.

METHODS

Cases

Electrophysiological tests were performed in 18 subjects (8 females and 10 males). Ten of the patients had a confirmed diagnosis for genetically Friedreich's ataxia, while 8 other had been genetically diagnosed with spinocerebellar ataxia. Among patients with spinocerebellar ataxia, 1 was diagnosed with SCA1, 4 were diagnosed with SCA2, and 3 were diagnosed with SCA3.

The control values were obtained from 31 healthy individuals (11 females and 20 males) who volunteered for the study and whose age ranged between 22 and 58 years (mean 36.7±9.5). None of the control group individuals suffered from any chronic illnesses.

A written informed consent was obtained from each patient and control group member, and the ethics committee of the University of İstanbul, İstanbul Medical Faculty approved the study.

Electrophysiological Methods

Both patient and control groups underwent identical, same-order protocol of electrophysiological study which was composed of sensory and motor nerve conduction studies, F responses, and needle EMG of proximal and distal muscles to upper and lower extremities. In addition to this, MUNE of related hand and leg muscle was performed. Four-channel electromyography system (Keypoint, vs 5.03) was used for registration and analysis of neurophysiologic studies.

Surface electrodes were used for the evaluation of sensory and motor nerve conduction studies. While the stimulating electrode was placed above nerve which would be recorded, the recording electrode was placed above nerve or muscle, in dependence whether we were studying sensory or motor nerve. Nerve conduction studies were performed prior to needle EMG and MUNE calculations.

Sensory nerve conduction studies were performed for right median, ulnar, sural and superficial peroneal nerves. Median and ulnar response were recorded in orthodromic fashion, whereas sural and superficial peroneal responses were recorded in antidromic way. Distal latency, the amplitude of the sensory nerve action potential (SNAP), and the nerve conduction velocity were the parameters recorded.

Right median, ulnar, peroneal and tibial nerves were selected for motor nerve conduction evaluation. The peak latency, the amplitude of compound muscle action potential (CMAP), and the nerve conduction velocity were tested parameters. The minimum F wave latency (at least 20 F waves analyzed) and the percentage of persistency were among the parameters that were analyzed for F wave responses using median, ulnar and tibial nerves.

Needle EMG study was performed extensively in order to cover muscles of upper and lower extremities with proper distribution to proximal and distal ones. The right deltoid, biceps, triceps, extensor digitorum communis, first interosseus dorsalis and abductor pollicis brevis muscles were chosen for the neurophysiologic examination of the upper extremity. The muscles of lower extremity that were used for this aim were right anterior tibialis, gastrocnemius and lateral vastus muscles. A needle electrode (37 mm, Medelec) was used for this study, and the bioelectrical activity during rest and contraction of the abovementioned muscles was recorded. The pathologic spontaneous activities, together with duration, amplitude and phase count of motor units were evaluated, where the prolonged, high amplitude, normal or polyphasic motor unit potentials were described to be neurogenic motor unit potentials. Progressive participation of motor units to the progressively increasing contraction and their firing frequency were also qualitatively evaluated. Gaps in participation to contraction, high frequency (>30 Hz) motor unit firing and reduced interference pattern during the maximal contraction were considered to be in favour of neurogenic involvement and were commented as to show electrophysiological findings of a developed reinnervation.

The motor unit number estimation analysis was performed based on the original method that was developed by Alan McComas and is known as "incremental method". First, the maximal muscle response or so-called the M-wave was evoked through the use of supramaximal stimulation. After the recording of the M-wave, the stimulation potential had been lowered to a minimal possible level yielding this way a motor action potential similar to M-wave in shape and which left no doubts that it is in fact the motor potential that originates from the minimally stimulated motor unit number. Furthermore, the use of graded electrical stimuli was applied, which were delivered to a nerve in order to successively evoke incrementally increasing muscle potentials. After ten such responses had been evoked, the average motor unit action potential amplitude was calculated assuming that the incremental increase in the CMAPs corresponded to the activity of single motor unit. MUNE was then calculated by dividing the average motor unit action potential amplitude by the amplitude of the M-wave.

We estimated the motor unit number of abductor pollicis brevis muscle by placing the recording electrode on thenar, and stimulating the median nerve in the wrist. Estimation of the motor unit number of anterior tibialis muscle was made by stimulating the peroneal nerve immediately laterally to the neck of fibula and placing the recording electrode on anterior tibial muscle in the localization that yielded maximal M-wave.

Statistical Analysis

Descriptive statistics were made for each of the examined parameters in both groups. The mean value, standard deviation, and the minimal and maximal values were calculated, and then the mean-based group comparisons were performed. Comparative parametric and non-parametric test (T-test and Mann-Whitney) were used for this purpose. The selection of tests to be used was done based on the distribution of parameters for which comparison was made. Statistical Package for the Social Sciences (SPSS version 15, Inc.; Chicago, IL, USA) was used for statistical analysis. Statistically significance threshold was set to be $p<0.05$.

RESULTS

Patients were selected from the Movement Disorders Unit at Department of Neurology of İstanbul Faculty of Medicine. Examined patients had mean age of 34.3±12.1 (19-62) years and the mean duration of the disease was 9.3±4.3 (1-20) years. Neurological evaluation of the patients included the age at the onset of symptoms, the disease duration, and the pres-

Table 1. Demographic, clinical, and radiological characteristics of patients

					Neurologic examination					Cerebellar atrophy in MRI
Cases	Sex	Age	Duration	Type of ataxia	Dysarthria	Deep tendon reflexes	Muscle weakness	Atrophy	Cerebellar findings	
1	M	26	7	FRDA	+	+	-	-	moderate	+
2	M	26	11	FRDA	+	-	-	+	severe	+
3	M	34	14	FRDA	+	-	-	+	severe	+
4	M	20	9	FRDA	+	-	-	+	severe	+
5	M	24	5	FRDA	+	-	+	+	severe	+
6	M	25	7	FRDA	+	-	-	+	severe	+
7	F	30	20	FRDA	+	-	+	+	severe	+
8	M	19	8	FRDA	+	-	+	-	severe	+
9	M	34	10	FRDA	+	-	-	-	moderate	+
10	F	28	5	FRDA	+	-	-	-	mild	+
11	F	55	10	SCA3	+	+	-	-	severe	+
12	F	50	13	SCA2	+	-	-	-	moderate	+
13	F	39	11	SCA2	+	+	-	-	severe	+
14	F	36	11	SCA2	+	+	-	-	severe	+
15	M	62	13	SCA2	+	+	-	-	moderate	+
16	F	28	9	SCA1	+	-	-	-	severe	+
17	F	46	4	SCA3	+	+	-	-	mild	+
18	M	35	1	SCA3	+	-	-	-	severe	+

FRDA: Friedreich's ataxia; SCA: Spinocerebellar; F: female: M: male

ence of symptoms that might have suggested the involvement of the peripheral nervous system (pain, muscle cramps, weakness, paresthesias). The Medical Research Council scale (0-5) was used to measure the muscle strength. Ataxia was classified as mild, moderate and severe based on our own classification that was used for the purposes of this study. All of the patients during their neurologic examination showed different degrees of dysarthria. Though none of the patients suffered from muscle weakness, patients with Friedreich's ataxia had mainly a more prominent atrophy in their lower extremities (Table 1).

The sensory median responses were not recorded in 6 patients out of the 18 examined patients, while the ulnar and sural responses were not recorded in 8 patients, and the superficial peroneal responses were not recorded in 13 out of these 18 patients. The sensory nerve action potentials of all four sensory nerves were significantly lower ($p<0.01$) in patients group in comparison to healthy control group. The conduction velocity of the sensory ulnar nerve was found to be significantly slower ($p<0.05$) than that of the control group (Table 2).

The compound motor action potentials of the median and peroneal nerves were found to be significantly lower ($p<0.01$). The conduction velocities of all four motor nerves examined were also slower compared to the healthy individuals (Table 3).

No statistically significant difference between both groups in relation to the F wave responses was noticed. Six of 18 examined patients had motor unit potential patterns that indicated chronic neurogenic changes in examined muscles – prolonged, high amplitude motor unit potentials together with reduced interference pattern during voluntary contractions.

The estimated motor unit number was found to be lower in both abductor pollicis brevis ($p<0.05$) and anterior tibialis ($p<0.01$) muscles. Maximal M-wave voltages that these two muscles were able to produce were also significantly lower in comparison to the healthy group. Mean step interval between two consecutive stimulations of the abductor pollicis brevis muscle was significantly higher ($p<0.01$). No difference was found for tibialis anterior in relation to this last parameter (Table 4).

Table 2. Sensory conduction study

Nerve	Parameter	Normal (n=31) Mean±2SD (min-max)	Patient (n=18) Mean±2SD (min-max)	Significance
Median nerve	Velocity (m/s)	63.0±8.5 (41.2-81.3) n=31	59.9±8.9 (43.1-72.3) n=12	
	Amplitude (mikroV)	22.6±9.0 (13.0-56.0) n=31	7.3±5.9 (1.4-19.0) n=12	p<0.01
Ulnar nerve	Velocity (m/s)	61.0±8.5 (42.9-77.5) n=31	54.0±5.7 (47.6-68.0) n=10	p<0.01
	Amplitude (mikroV)	12.6±4.2 (8.1-30.0) n=31	5.6±3.8 (1.0-13.0) n=10	p<0.01
Sural nerve	Velocity (m/s)	54.7±7.0 (42.4-66.7) n=31	52.1 ± 8.9 (40.0-66.7) n=10	
	Amplitude (mikroV)	17.6±5.4 (9.4-28.0) n=31	7.1±4.8 (1.0-15.0) n=10	p<0.01
Superficial peroneal nerve	Velocity (m/s)	52.4±5.8 (41.9-61.2) n=31	51.9±8.1 (41.4-63.2) n=5	
	Amplitude (mikroV)	11.7±4.0 (6.3-25.0) n=31	4.7±1.9 (1.5-6.3) n=5	p<0.01

SD: standard deviation; min: minimum; max: maximum

Table 3. Motor conduction study

Nerve	Parameter	Normal (n=31) Mean±2SD (min-max)	Patient (n=18) Mean±2SD (min-max)	Significance
Median nerve	Distal latency 1 (ms)	2.9±0.5 (2.3-4.5)	3.2±0.6 (2.2-4.5)	
	Velocity (m/s)	60.0±5.5 (51.1-71.9)	54.4±4.9 (43.8-63.6)	p<0.01
	Amplitude 1 (mV)	8.5±1.8 (6.0-12.8)	7.0±1.6 (4.0-9.7)	p<0.01
Ulnar nerve	Distal latency 1 (ms)	2.3±0.5 (1.3-4.0)	2.4±0.4 (1.8-3.5)	
	Velocity 1 (m/s)	65.7±6.4 (53.9-84.0)	60.1±8.7 (38.0-76.9)	p<0.05
	Velocity 2 (m/s)	62.1±6.4 (50.0-77.3)	58.9±10.7 (33.9-80.0)	
	Amplitude 1 (mV)	7.9±1.5 (4.9-11.2)	8.1±1.5 (5.6-10.4)	
Tibial nerve	Distal latency 1 (ms)	4.4±0.9 (3.3-6.5)	5.1±1.4 (3.2-9.2)	p<0.05
	Velocity (m/s)	47.7±4.4 (40.0-58.7)	43.5±5.6 (33.1-58.9)	p<0.01
	Amplitude 1 (mV)	9.0±2.9 (2.0-16.6)	9.3±3.5 (4.3-16.3)	
Peroneal nerve	Distal latency 1 (ms)	3.4±0.7 (2.3-5.0)	4.1±0.9 (3.0-6.3)	p<0.05
	Velocity (m/s)	50.7±4.2 (42.5-58.9)	45.6±6.1 (30.7-62.0)	p<0.01
	Amplitude 1 (mV)	5.2±1.7 (2.4-9.2)	3.8±1.4 (2.0-7.6)	p<0.01

SD: standard deviation; min: minimum; max: maximum

Table 4. Motor unit number estimation

Muscle	Parameter	Normal (n=31) Mean±2SD (min-max)	Patient (n=18) Mean±2SD (min-max)	Significance
Abductor pollicis brevis (APB)	Maximal M area (mVms)	59.8±17.7 (37.8-123.7) n=31	49.6±14.1 (18.6-72.4) n=18	p<0.05
	Mean step distance (mVms)	0.6±0.1 (0.4-0.9) n=31	0.8±0.3 (0.4-1.7) n=18	p<0.01
	Estimated motor unit number	123.1±25.3 (71-176) n=31	98.3±45.6 (13-184) n=18	p<0.05
Tibialis anterior (TA)	Maximal M area (mVms)	56.2±15.3 (26.0-89.4) n=31	40.8±10.8 (23.9-59.9) n=18	p<0.01
	Mean step distance (mVms)	0.7±0.2 (0.4-1.1) n=31	0.7±0.3 (0.4-1.6) n=18	
	Estimated motor unit number	114.4±41.4 (54-204) n=31	80.1±40.9 (35-203) n=18	p<0.01

SD: standard deviation; min: minimum; max: maximum

DISCUSSION

Spinocerebellar and Friedreich's ataxia are heterogeneous group of hereditary ataxias with variety of neurological symptoms and signs. Number of SCAs, which is in direct correlation with genetic loci identified, is increasing gradually over the years, and clinical findings are as much variable (16). As for FRDA, clinical findings are in inverse correlation with trinucleotide repeats. As low is trinucleotide repeats number, as delayed is onset of symptoms, age of death, as mild are clinical signs and cardiomyopathic findings (18, 19). Previous studies have demonstrated also inverse correlation between trinucleotide repeats and neurophysiological findings (19). All of our patients showed different levels of cerebellar findings, with dysarthria affecting all patients and being the most pronounced sign. Correlation of clinical and electrophysiological findings with trinucleotide repeat number was beyond the scope of our investigation.

During the study, the sensory median responses were not recorded in 6 patients, and ulnar and sural responses were not recorded in 8 patients, while the superficial peroneal responses were not recorded in 13 out of 18 patients. The sensory nerve action potentials of all four sensory nerves were significantly lower in the patients group. These findings indicated for the existence of axonal degeneration in the sensory fibers of these nerves. They were in correlation with previously reported sensory axonal degeneration in half of the patients, 80% and 75% of SCA1, SCA2 and SCA3 patients, respectively (16). Another concomitant study which was reporting that nearly half of SCA2 and SCA3 patients had lower SNAPs was further supporting our findings (20). Schöls et al. reported that SCA1 subgroup was the most heavily affected, however the existence of only one SCA1 patient in our cohort provided insufficient grounds for such a comparison, moreover we were not able to register her sensory conduction responses (16). Another finding of current study indicated that 42% of SCA1, 80% of SCA2 and 54% of SCA3 patients had axonal polyneuropathy with the heavier involvement of sensory nerves (21, 22).

The most serious pathologic involvement was found among patients with Friedreich's ataxia. The sensory median responses were not recorded in 6 patients, and the ulnar and sural responses were not recorded in 7 patients, and the superficial peroneal responses were not recorded in 8 patients out of the total ten FRDA patients examined in this study. These findings were in line with the previously reported findings of the studies on peripheral nervous system involvement in FRDA patients (12, 17). Pathologic studies have demonstrated that dorsal root ganglia of FRDA patients are smaller than normal, sometimes making difficult to identify them during macroscopic evaluation (23). Magnetic resonance imaging has been also helpful in documenting that spinal cords of these patients are thinner. This change is expressed mostly in thoracic region. The abovementioned changes in dorsal root ganglia are explanatory as to why sensory conduction studies cannot be recorded in almost all FRDA patients.

The median and peroneal motor nerve amplitudes were found to be significantly lower in patient cohort, which were evaluated together with the needle EMG findings, which showed that intrinsic hand and extensor ankle muscles were passing through the denervation – reinnervation process. Lower motor unit number estimates of abductor pollicis brevis and anterior tibialis muscles only further supported the abovementioned conclusion.

Even though slower conduction velocities of the median, ulnar, tibial and peroneal motor nerves were also reported earlier before, this slowing was more secondary to the axonal degeneration rather than suggestive of a primary demyelinating neuropathy (20, 24). Despite decrease in CMAPs, absence of significant prolongation in distal latencies was another fact that led to primarily axonal involvement of peripheral nerves. In addition, no significant statistical difference between the two groups as regards the median, ulnar and tibial F responses' minimal latency values was supportive of the absence of serious myelin sheath damage through the length of nerves that would slow conduction. The normal persistency of F responses ruled out the possibility of a conduction block at the radicular level.

The estimated motor unit number was found to be lower in both abductor pollicis brevis and anterior tibialis muscles. The maximal M-wave voltages that these two muscles were able to produce were also significantly lower in comparison to the healthy group. The mean step interval between two consecutive stimulations of the abductor pollicis brevis muscle was significantly higher ($p<0.01$), however no difference was found for tibialis anterior muscle with regard to this last parameter. These findings were suggestive of the difference in bioelectrical activity between those affected from SCA and FRDA as compared to the healthy individuals. In other words, the total bioelectrical activity produced by abductor pollicis brevis (APB) and tibialis anterior (TA) muscles in SCA and FRDA patients was lower than that produced by the same muscles of the healthy people. The lower number of motor units in these two muscles was in correlation with lower values of CMAPs of median and peroneal muscles, which are the nerves responsible for the motor innervation of APB and TA, respectively. Higher degree of reinnervation in APB muscle yielded a higher mean step interval between consecutive stimulations of motor units. However, this was not the case with the TA muscle; instead it was indicative of lost effectiveness of the reinnervation process. This difference between these two muscles was strong evidence that the pathology hidden under the roof was indeed the distal axonal denervation.

The qualitative analysis of needle EMG findings showed that 33% of patients showed different levels of neurogenic changes that can be translated as prolonged, high amplitude, normal or polyphasic motor unit potentials with reduced interference pattern, more emphasized in APB and TA muscles. Qualitatively evaluated needle EMG findings are prone to subjective interpretation, and consequently there is a need for quantitative data in order to follow peripheral motor nerve involvement. Besides CMAPs, motor unit number estimation can be used for translation of motor function into the numbers. In addition to needle EMG and MUNE, peripheral nerve ultrasound can give further details in determining whether neuropathic process in SCA patients is limited only to neuropathy, or neuronopathy is another fuel to peripheral nerve damage (25).

We were not able to establish any link between the severity of motor functions and electrophysiological findings. The severity of axon loss and myelinated fibre reduction seems not to be related with disease severity and duration (19). Electrophysiological studies performed consecutively within year did not show any change, despite clinical worsening of the patients (19). Since our investigation involved single stop evaluation, it is difficult to conclude the evolution of symptoms and electrophysiological state within years.

As a result, this study supported the existence of the polyneuropathy with the dominance of sensory involvement in SCA and FRDA patients. Whereas, the predominance of involvement in the lower extremities with amplitudes being more severely affected than the conduction velocity and distal latencies, are supportive for primarily axonal type of polyneuropathy. CMAP levels, needle EMG findings and motor unit number estimates emphasize that motor fibers of peripheral nerves are also affected. The lower motor unit number estimates can be interpreted as a motor axonal or a lower motor neuron degeneration finding, and could present a parameter for follow-up of motor functionality.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Medical Faculty of İstanbul, on 17.12.2010 (decision number 1086).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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