Electroneuromyographic Features in Fabry Disease: A Retrospective Review

Çetin Kürşad AKPINAR¹, Hande TÜRKER², Oytun BAYRAK², Nilgün CENGİZ²

¹Clinic of Neurology, Vezirköprü State Hospital, Samsun, Turkey

²Department of Neurology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey

ABSTRACT

Introduction: Fabry disease (FD) is an X-linked recessive inherited disorder characterized by lysosomal alpha-galactosidase deficiency. The purpose of our study was to assess and compare the electroneuromyographic (ENMG) findings of 15 patients with Fabry disease and the electroneurographic (ENG) findings of 15 healthy controls. We have not encountered any similar study in the medical literature of our country. Therefore, we believe that our study will contribute to national literature.

Methods: Fifteen patients with Fabry disease, 13 females and 2 males and 15 healthy controls, 13 females and 2 males, were included in the study. The definite diagnosis of patients with Fabry disease was made based on the enzyme level and genetic mutation. The patients with Fabry disease were examined with ENMG, while the healthy control group was examined with ENG. In the patients with a normal ENMG examination, neuropathic pain was attributed to the small fiber involvement.

Results: Patients with Fabry disease had neuropathic pain (LANSS score ≥ 12). While neurological examination was normal in eight patients, glove- and stocking-type hypoesthesia and decreased deep tendon reflexes were observed in five and two patients, respectively. Axonal

polyneuropathy was detected in one patient. The ENMG examinations of the other patients were normal. Enzyme replacement therapy could not be initiated in one patient because of pregnancy. The neurological examination of the healthy control group was normal. There was no statistically significant difference between the ENMG features of both groups ($p > .05$). As in other studies, a routine ENMG examination was normal in our patients with early-stage Fabry disease. Neuropathic pain, seen in patients with Fabry disease in literature, is thought to be due to small fiber involvement.

Conclusion: Fabry disease should be considered in the differential diagnosis of patients with neuropathic pain at young ages. It should be kept in mind that ENMG examination can be normal at the early stages. Quantitative sensory test, autonomic tests (R-R interval and sympathetic skin response) and skin biopsy should be performed in such cases. In our country, pediatric physicians work on Fabry disease more than physicians dealing with Fabry disease in adults. Therefore, in this retrospective study, we aimed to draw adult and pediatric neurologists' attention to Fabry disease.

Keywords: Electroneuromyography, Fabry disease, small fiber neuropathy

INTRODUCTION

Fabry disease (FD) is a disease characterized by the pathological accumulation of glycosphingolipid Gb3 in some cells; it progresses with a lack of lysosomal alpha-galactosidase and is inherited in an X-linked recessive manner (1). The GLA gene that encodes the lysosomal alpha-galactosidase at chromosome Xq22.1 has a mutation (2). In most of the diseases inherited in an X-linked manner, women are asymptomatic. However, typical symptoms are seen in women who are affected and the disease may take a serious course (3). As a result of pathological accumulation in tissues, fibrosis develops with inflammation and the organs stop functioning. Thus, renal-, cardiac-, neurological- and skin-related symptoms arise (4). FD is the second most common lysosomal storage disease after Gaucher disease. Different studies show its prevalence in men to be varies between 1/7000 and 1/17000 (4,5,6).

During the early period of FD, axons with large myelins are not generally affected, whereas small-sized myelin and myelin-free nerve fiber involvement are frequent. Thus, the electroneuromyographic (ENMG) examinations during the early periods may seem normal (7,8). The purpose of this study was to assess and compare the ENMG findings of 15 patients with FD and electroneurographic (ENG) findings of 15 healthy controls. No similar studies were found in the literature of our country. In this sense, we believe that this study will contribute to national literature.

METHODS

Ethics Committee Approval with the number 2014/602 was granted from Ondokuz Mayıs University Faculty of Medicine Medical Research Ethics Committee.

Patients

The ENMG results of the 15 patients who were diagnosed as having FD and who were recorded in the Neuromuscular Diseases Polyclinic of Ondokuz Mayıs University Faculty of Medicine, Department of Neurology between January 2013 and February 2013 and

Correspondence Address: Dr. Çetin Kürşad Akpınar; Clinic of Neurology, Vezirköprü State Hospital, Samsun, Turkey

E-mail: dr_ckakpinar@hotmail.com

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the ENG results of 15 age-matched healthy controls were retrospectively examined. The healthy control group was formed from the patients who were sent to our electrophysiology laboratory with a pre-diagnosis of polyneuropathy and whose ENG examinations were normal.

A total of 30 people, 15 patients with FD (13 females, 2 males) who were diagnosed as having FD and 15 (12 females, 3 males) healthy controls were included in the study. The patients included in the control group had normal ENG results and they did not have a disease. The diagnosis of FD was made based on the enzyme level and genetic mutation. Neuropathic involvement was thought to have developed in patients with a normal routine ENMG examination because of small fiber involvement.

ENMG

All electrophysiological examinations were conducted in a quiet environment with a normal room temperature with the patient lying on his back and with a skin temperature of 32°C and over a superficial stimulator, recording electrodes and a concentric needle. ENMG recordings were made by conventional methods using 2010 make 4-channel Medelec Synergy (VIASYS Healthcare, Madison, USA, 2010) device. In nerve conduction analysis, the median and ulnar nerves from the upper extremity and tibial, peroneal and sural nerves from the lower extremity were analyzed (Table 1). In the myographic examination, the deltoid and abductor digiti minimi muscles from the upper extremity and vastus lateralis and gastrocnemius muscles from the lower extremity were examined.

In the ENG examination of both groups that was performed by polyneuropathy, at least two motor and two sensory nerve conduction tests from both the two lower extremities and one upper extremity and F responses were studied. In the group of patients with FD, the EMG examination was conducted on at least two muscles, one proximal and one distal, from both extremities. Nerve conduction speeds and distal motor and sensory latency are the values obtained by our laboratory from normal individuals. Table 1 shows the normal values of nerve conduction test. In needle EMG, the input activity of muscles, evaluation of motor unit potentials and maximum recruitment in muscles were checked.

Sensory conduction analysis was performed with 20 μ V sensitivity and a sweep rate of 10 ms at an interval of 20 Hz–2 kHz filtration, whereas mo-

tor conduction analysis was performed with 5 μ V sensitivity and a sweep rate of 50 ms at an interval of 3 Hz–5 kHz filtration. The peak latency, sensory action potential amplitude, conduction speed of sensory responses, initial latency, compound muscle action potential amplitude and motor conduction speeds of motor responses were evaluated.

Needle EMG examinations were studied at an interval of 3 Hz–10 kHz filtration and a sweep rate of 100 ms. Denervation potentials at 100 μ V sensitivity during rest, the characteristics of motor unit potentials at 200 μ V sensitivity during mild contraction and the characteristics of interference at 500 μ V sensitivity during full contraction were assessed.

In the analysis of the upper extremity sensory nerves, the median nerve recording was antidromically made at the finger–wrist segment by putting the ring electrodes on the third finger and the ulnar nerve recording was made by putting the ring electrodes on the fifth finger. In the analysis of the upper extremity motor nerves, the median nerve recording was made by recording the stimulus at the abductor pollicis brevis sent from the wrist and cubital area and the ulnar nerve recording was made by recording the stimulus at the abductor digiti minimi muscle given from the wrist, elbow and upper elbow.

Lower extremity sural nerve sensory analysis was performed by recording orthodromic stimulation on the leg and outer malleolus recording. In the analysis of lower extremity motor nerves, the tibial nerve recording was made by recording the stimulus at the abductor hallucis muscle sent from the wrist and hollow of the knee and the peroneal nerve recording was made by recording the stimulus at the extensor digitorum brevis muscle given from the head of the fibula and side of the knee.

Statistical Analysis

The data obtained from the research were coded in the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) 15.0 program and SPSS 15.0 was used in all statistical calculations. The continuous variables that showed normal distribution were expressed as mean $\pm$ standard deviation and the numerical variables were expressed as median (minimum–maximum). Student's t-test was used for comparison of the significance between the means of the two groups. A significance level of $p < .05$ was considered as significant for all tests.

Table 1. Normal values of nerve conduction tests

	Warning points	Recording point	Amplitude Motor (mV). Sensory (μ V)	Latency (ms)	V (m/s)	F wave (ms)
Median	Wrist	Third finger	>20	<3.4	>50	
Ulnar	Wrist	Fifth finger	>18	<3.0	>50	
Sural	Calf	Wrist	>5	<4.5	>40	
Median	Wrist	APB	>5	<4.1	>50	<31
	Elbow	APB				
Ulnar	Wrist	ADM	>7	<3.1	>50	<32
	Below Elbow	ADM				
Peroneal	Ankle	EDB	>3	<5.1	>40	<50
	Below Knee	EDB				
Tibial	Ankle	AH	>6	<5.5	>40	<51
	Knee	AH				

APB: abductor pollicis brevis; ADM: abductor digiti minimi; EDB: extensor digitorum brevis; AH: abductor hallucis; V: velocity

Table 2. Demographic characteristics of the patients with Fabry disease

Patients no	Sex	Age	Additional disease	NE	Genetic Analysis	EMG	LANSS
1	F	51	Hypothyroidism	GSH	+	Axonal PNP	24
2	F	26	Hypothyroidism	GSH	+	N	24
3	F	17	Migraine	GSH	+	N	18
4	F	40	PHT	-	+	N	24
5	F	34	HT	DTR↓	+	N	26
6	F	46	RA	DTR↓	+	N	14
7	F	12	-	-	+	N	12
8	F	19	-	-	+	N	19
9	F	50	RLS	GSH	+	N	16
10	F	29	Hypothyroidism	-	+	N	12
11	M	59	-	-	+	N	16
12	F	23	-	-	+	N	14
13	M	49	-	-	+	N	16
14	F	45	-	-	+	N	26
15	F	29	-	GSH	+	N	24

F: female; M: male; PHT: pulmonary hypertension; HT: hypertension; DTR: deep tendon reflexes; RA: rheumatoid arthritis; RLS: restless leg syndrome; GSH: glove-sock hypoesthesia; PNP: polyneuropathy; N: normal; NE: neurological examination

RESULTS

The ages of the patients with FD were between 12 and 59 years, with a mean of 35.3 ± 14.4 years. The ages of the healthy control group were between 18 and 60 years, with a mean of 39.2 ± 10.1 years. Thirteen patients with FD were female and two were male. Twelve patients of the control group were female and three were male. In the neurological examination of patients with FD, eight patients had normal results, two had decreased deep tendon reflexes and five had glove- and stocking-type hypoesthesia. The neurological examinations of the control group were normal. All the patients were found to have neuropathic pain (LANSS scoring 12 and over). One patient was found to have axonal polyneuropathy, whereas the ENMG examinations of the other patients were normal. One of the patients had pulmonary hypertension, one had cornea verticillata, two had angiokeratoma and five had proteinuria (Tables 2, 3). One of the patients could not undergo enzyme replacement therapy (ERT) because of pregnancy. No statistically significant difference was found between the ENMG features of the groups.

DISCUSSION

During the late period of FD, after the large fiber involvement, the decrease in compound muscle action potential amplitude is more frequent than slowing in the speed of conduction (5,9). Initial symptoms (neuropathic pain, angiokeratoma, cornea verticillata, sensitivity to heat and sweating dysfunction) are seen during childhood and adolescence. Renal failure and cardiac and cerebrovascular complications are seen during adulthood. Eighty percent of the patients have neurological symptoms. Because autonomic functions are realized through small fibers, findings such as decreased sweating and cardiac rhythm disorder, which are seen in FD, develop as a result of autonomic dysfunction (10). Peripheral neuropathy in FD generally depends on the involvement of small myelin and myelin-free nerve fibers and the leading symptom is deterioration in the feeling of heat (11,12). Early diagnosis and ERT stabilize the disease and prevent progression (13). Early deaths can be seen in patients who are not

There are two groups of small nerve fibers: the first group is the small myelin A delta fibers and the second is the myelin-free C fibers. Based on the involvement of the A delta and C fibers in FD, only small fibers can be affected or only small fibers can be affected initially. Thus, routine ENMG examination is normal in the onset of the disease. Neuropathic pain, which is a comorbidity of FD, is generally based on small fiber neuropathy (14). Studies have reported that it is possible to know about small nerve fiber involvement by measuring the decrease in the intraepidermal nerve fiber density (15). There are two methods that can show small fiber involvement. The first one is the non-invasive quantitative sensory test and the second is invasive skin biopsy (16).

Although the pain mechanism of FD is not still fully understood, the possible mechanism is the accumulation of glycolipids in the dorsal root ganglion and Schwann cells (16). Moller et al. (3) reported that peripheral nerve damage can be due to sensory axonal hyperexcitability and central sensitization. The most frequent onset symptom of FD is neuropathic pain. It is seen in 60–80% of men and 40–60% of women. The average age of onset is 9 years in men and 15 years in women. Symptoms can be seen in women more frequently; however, the course of symptoms is more severe in men (5). The first and most characteristic finding of peripheral neuropathy is loss in the feeling of heat that develops as a result of length. This situation is more obvious in the cold (17). In parallel with literature, the complaints of pain in the patients in our study started during early age.

Large nerve fibers can be assessed by routine ENMG examination. Because FD frequently causes small fiber involvement during the early period, ENMG examination is normal during this period. Studies in different years have reported that nerve conduction tests are normal in FD (9,18,19,20). In other studies by Fukuhara et al. (21), Kaye et al. (22) and Onishi et al. (19), which assessed large myelin fibers, patients with FD who had a normal ENMG examination were shown to have histopathological changes limited to small fibers. In our study, one of the patients was found to have large fiber involvement and patients were thought to have small

Table 3. Nerve conduction test findings of the patients with Fabry disease

Investigation of nerves	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Median (Left)															
DSAP PL (ms)	3.5	3.1	3.4	3.2	3.3	3.3	3.0	3.1	3.4	3.3	3.1	3.0	3.4	3.3	2.9
Amplitude (μV)	15	30	22	25	24	25	40	24	27	29	25	28	22	20	41
Velocity (m/s)	48	55	51	52	50	57	62	51	54	55	53	61	52	50	60
Ulnar (Left)															
DSAP PL (ms)	3.1	2.3	2.5	2.1	2.4	2.5	2.7	2.6	2.6	2.3	2.2	2.6	2.5	2.8	2.7
Amplitude (μV)	16	25	20	28	26	29	23	21	28	26	25	22	29	21	22
Velocity (m/s)	49	52	55	56	53	58	51	50	54	52	56	57	58	51	50
Median (Left)															
BKAP DML (ms)	4.3	3.6	3.4	3.7	3.2	3.3	3.3	3.1	3.8	3.7	3.5	3.6	3.4	3.3	3.5
Amplitude (mV) W/E	4/4.1	10/8	9/8	11/9	12/8	8/8	9/7.9	11/9	10/8	8/6.2	7/7	8.1/7	8.5/8	14/9.8	13/9
Velocity (m/s)	44	57	51	56	52	55	53	59	50	58	54	55	57	52	56
Ulnar (Left)															
BKAP DML (ms)	3.2	2.0	2.6	2.5	2.1	2.4	2.2	2.7	2.1	2.8	2.4	2.5	2.2	2.3	2.4
Amplitude (mV) W/BE	5/4.8	9/7.5	9/8	10/7	9/8.5	8/7	9.1/9	7/7	8/8.1	7.7/7	6.7/6	10/8	8.9/8	7.3/7	8.2/8
Velocity (m/s) DS	49	56	50	59	57	52	54	57	54	53	55	56	56	52	58
Peroneal (Left)															
BKAP DML (ms)	5.1	4.6	4.1	3.6	3.9	4.4	4	4.1	3.8	4.5	4.2	4.2	4.5	4.4	3.8
Amplitude (mV) A/FH	2/1.9	6/5.2	7/4.1	6.1/5	6/4	7/6	8/8	7.5/5	7/5.7	6/6.1	9/8.4	8/7.1	6/6	10/9.3	8/7.7
Velocity (m/s) DS	38	44	49	41	47	44	42	43	46	47	45	49	48	48	43
Peroneal (Right)															
BKAP DML (ms)	5.0	4.5	4.1	4.2	4.6	4.2	3.8	4.4	4.5	4.5	4.2	3.7	3.8	4	4.5
Amplitude (mV) A/FH	2.1/2	7.1/5	9/8.4	7/7.1	7/6	9/9	8/7.5	6.1/6	4.2/3	6/5.2	7/4.4	6.5/5	6/4.4	5/4.9	6.2/5
Velocity (m/s) DS	37	49	45	49	48	48	43	48	49	44	49	41	47	49	49
Tibial (Left)															
BKAP DML (ms)	5.6	5.1	4.3	4.0	4.5	4.5	4.8	4.4	4.4	4.0	4.1	4.0	4.1	4.4	4.0
Amplitude (mV) A/PO	4/3.7	9/8.1	7.7/7	4.1	8/6	9/6	10/9	10/7	9.1/7	9/9	8/6	8/8	7/5	10/7	7/7.1
Velocity (m/s) DS	39	43	11/9	43	45	47	42	48	47	48	43	46	41	48	45
Tibial (Right)															
BKAP DML (ms)	5.3	4.8	4.4	4.0	4.1	4.4	4.0	4	4	4.7	4.3	4.1	4.5	4.1	4.4
Amplitude (mV) A/PO	3.1/2	10/9	10/7	9/9.1	8/6	10/7	9/9	7.5/7	6/6.1	8/8	6.7/7	11/9	9/6	9.7/8	12/9
Velocity (m/s) DS	37.5	41	49	47	42	49	47	45	45	48	41	44	46	48	44
Sural (Left)															
DSAP PL (ms)	YY	4.1	3.5	3.1	3.4	3.3	2.5	3.7	3.2	3.5	4.1	3	3.8	3.6	2.9
Amplitude (μV)	YY	10	8	7	6	8.1	9.3	6.6	7	5	8	9	10	6.9	5.5
Velocity (m/s)	YY	49	44	47	45	44	50	45	43	49	51	47	43	41	40
Sural (Right)															
DSAP PL (ms)	6.5	3	3.8	3.5	4.1	3	3.8	3.6	3.5	3.1	3.4	3.3	2.5	3.7	3.4
Amplitude (μV)	1.1	9	9	5	8	9	10	6.9	8	7	6	8.1	9.3	6.6	6
Velocity (m/s)	34	47	51	49	51	47	43	41	44	47	45	44	50	45	45

*Pathological values are in bold. BKAP: Compound muscle action potential, DSAP: Sensory nerve action potential, PL: Peak latency, DML: Distal motor latency, W: Wrist, E: Elbow, BE: below elbow, DS: Distal, P: Proximal, PO: Poplitea, FH: Fibular head, mV: Millivolt, μV: Microvolt, ms: Milliseconds

Table 4. Causes of small fiber neuropathy

Hereditary	Acquired	
Fabry disease	Diabetes mellitus	Vasculitis
Tangier disease	Impaired glucose tolerance	Sjögren's syndrome
Friedrich disease	Alcoholism	Sarcoidosis
HIV	Guillain-Barre syndrome	Systemic lupus erythematosus
Familial amyloidosis	Systemic amyloidosis	Hyperlipidemia
Ross syndrome	AR Hereditary of neuropathy	Paraneoplastic syndrome
AR: autosomal recessive; HIV: human immunodeficiency virus		

fiber involvement. In the definitive diagnosis of FD, other diseases that can cause small fiber involvement should be excluded (Table 4).

In our country, ERT (0.2 mg/kg agalsidase alpha or 1 mg/kg agalsidase beta, through intravenous infusion, once every two weeks) can be applied to patients who do not respond to neuropathic pain treatment and to those who have organ involvement. ERT was not applied to one of our patients because of pregnancy. Studies have shown that ERT causes improvement in organ functions and life quality (7). In patients who developed Fabry neuropathy, ERT was shown to cause improvement in small fibers with a quantitative sensory test after 18–24 months follow-up (14). In their prospective study, Uceyler et al. (23) showed that sensory damage based on small fiber activation is associated with gender, renal functions and progression despite ERT. Most of the patients were found to have small fiber activation, whereas 12% of the patients were found to have large fiber activation. Of the 120 patients in the study, 89 did not have neurological symptoms and 106 had normal ENMG examinations. They also showed that the intraepidermal nerve fiber density was 46% less in FD when compared with that in the control group. While ERT cannot protect small fiber functions in male patients with renal function disorder, it can protect small fiber functions in patients with good renal functions (23).

The ENMG findings in our study were in parallel with those in literature; however, not every study had detailed documentation of the findings. It can be said that the findings were detailed in this study; however, the limitations of the study were the retrospective design of the study, less number of patients and the absence of quantitative sensory test, autonomic tests and skin biopsy. In our country, only physicians of pediatric metabolism deal with FD and the disease is not sufficiently known by adult and pediatric neurologists. The purpose of this study was to attract the attention of adult and pediatric neurologists to FD and to contribute to literature.

In conclusion, FD should be considered as a definitive diagnosis in patients who are found to have neuropathic pain during early age. It should be kept in mind that neuropathic pain is seen very frequently during the early period of patients with FD as a result of small fiber involvement and routine ENMG examination can be normal.

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