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Sympathetic skin response, cutaneous silent period and nociceptive flexion reflex in Fabry disease

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Abstract

Background & Objective: Fabry disease is one of the well-known causes of the small fiber neuropathy. This study aims to explore small and large nerve fiber functions in patients with Fabry disease without using any extra equipment in a standard neurophysiology laboratory. *Methods:* Patients with Fabry disease at our tertiary center were invited to the electrophysiology laboratory. Routine nerve conduction studies (NCS), sympathetic skin response (SSR), cutaneous silent period (CSP) and nociceptive flexion reflex (NFR) tests were performed. The same protocol was applied to matched healthy subjects. *Results:* Nineteen patients and 19 healthy controls were included. Carpal tunnel syndrome was diagnosed in 3 patients (15.9%). Palmar and plantar SSRs could not be obtained in 4 and 9 patients, respectively. Abnormal CSP responses in the upper and lower extremities were recorded in 2 and 7 patients, respectively. The NFR response was abnormal in 8 patients. In total, at least one of the SSR, CSP or NFR was abnormal in 73.7% of patients.
Conclusions: The study showed that combining SSR, CSP and NFR tests along with NCS could help to determine any abnormality in small and large fiber functions in most patients. The overall sensitivity of all tests was approximately 70% compared with the clinical diagnosis of small fiber neuropathy. This study is unique in that it explored a combination of NCS, SSR, CSP and NFR tests in Fabry disease.

Keywords: Fabry disease; electrophysiology; sympathetic skin response; cutaneous silent period; nociceptive flexion reflex, small fiber neuropathy

INTRODUCTION

Fabry disease is a treatable disease caused by a deficiency of alpha-galactosidase A. Despite being one of the most common lysosomal storage diseases, it is very rare with an incidence of 1/5,000 per year.[1] This enzyme defect leads to the accumulation of a glycolipid called globotriaosylceramide in the endothelium, multiple tissues and organs leading to heart diseases, kidney failure, stroke, osteoporosis, autonomic nervous system impairment or disorders of the peripheral nervous system.[2,3]

One of the most characteristic, disabling and earliest involvements in Fabry disease is small fiber neuropathy that causes excruciating, burning and stabbing pain, paresthesia, anhidrosis and intestinal dysmotility.[4-6] Cold and exercise intolerance are also well-known.[7,8] A reduction in the number of small fibers (unmyelinated and small myelinated) has been reported in addition to the accumulation of glycolipids in the autonomic ganglia and dorsal root in many histological studies.[9-11] However, due to methodological difficulties, electrophysiological small fiber testing has rarely been studied in patients with Fabry disease.[12,13] It is difficult to accurately detect small fiber neuropathy in all patients. One study reported that small fiber neuropathy can only be detected in 20% of Fabry patients with quantitative sensory testing (QST).[6] Another report showed that sweat gland dysfunction can be diagnosed with Sudoscan® in 44.5% of patients.[14]

The diagnosis of small-fiber neuropathy of any cause using neurophysiological tests is challenging. Many different methods have been proposed for this purpose. But most of them could

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not be a part of routine clinical practice because of requiring extra pieces of equipment such as QST, thermal sensory analyzer, Sudoscan® or carbon dioxide laser.[15] On the other hand, sympathetic skin response (SSR), cutaneous silent period (CSP) and nociceptive flexion reflex (NFR) tests can be applied in standard neurophysiology laboratories without any extra equipment and all three tests have been reported to help showing small fiber functions.[16-18]

In this study, we aimed to analyze the clinical features of peripheral nervous system dysfunction and SSR, CSP and NFR tests along with standard nerve conduction studies (NCS) in patients with Fabry disease.

METHODS

All patients with Fabry disease who were followed up at our tertiary center were invited to the neurophysiology laboratory to study SSR, CSP and NFR along with standard NCS. Patients with skin abnormalities that could hamper recordings, diabetes mellitus, chronic kidney failure, malignancy, or other comorbidities that may cause neuropathy were excluded from the study. All participants who agreed to participate in the study were included.

Healthy subjects were voluntary hospital workers whose age (±2 years), sex and height (±2 cm) matched one to one with a Fabry patient. The strobe guidelines were followed during the course of the research.[19]

Written consent was obtained from all the participants. The local ethics committee approved this study. The approval number was 83045809-604.01.02.

Clinical evaluation

A detailed neurological examination was performed by a neurologist for all patients. The clinical assessment of small fiber neuropathy was based on positive and negative sensory and autonomic symptoms.[17,20] Enzyme replacement therapy status and visual analog scale (VAS) pain scores were recorded for each patient.

Electrophysiological evaluation

The same four-channel computerized modular electromyography machine (Neuropack, Nihon Kohden, Japan) was used to study all tests described. We performed NCS, SSR and CSP tests in the upper and lower extremities, and NFR test in the right lower extremity. Skin temperature was maintained above 32 °C before each test.

Nerve conduction studies

Standard nerve conduction tests were performed on the two upper and right lower extremities. We specifically performed the following studies: antidromic sensory nerve action potentials (SNAPs) of the median (recorded from 2nd finger), ulnar (recorded from 5th finger), and sural nerves (recorded from lateral malleolus) as well as compound muscle action potentials (CMAPs) of the median (recorded from abductor pollicis brevis (APB)), ulnar (recorded from abductor digiti minimi (ADM)), peroneal (recorded from extensor digitorum brevis (EDB)), and tibial (recorded from flexor hallucis brevis (FHB)) nerves. The F-responses of the median and tibial nerves were also recorded.

Sympathetic skin response

SSRs were recorded in the right upper and lower extremities. Active electrodes were placed on the palm and sole, the reference electrodes were placed on the dorsum of the hand and foot for the upper and lower extremity recordings, respectively. The contralateral median and tibial nerves were stimulated with an electrical stimulus at 40 mA current intensity and 0.2 ms duration. The latencies and amplitudes of the responses were recorded and compared as described elsewhere.[21] Filters were set between 1 Hz for the low-frequency filter and 500 Hz for the high-frequency filter. The sensitivity was 500 μV/division and the sweep speed was 500-1000 ms/division.

Cutaneous silent period

The CSPs were studied using the common methodology in the right upper and right lower extremity.[16] For the upper extremity, while patients doing isometric contraction, the stimulus was given on the second finger and the recording was obtained from the APB muscle. For the lower extremity, the stimulus was applied to the sural nerve below the lateral malleolus and recordings were obtained from the tibialis anterior and EDB muscles. The stimulus intensity was set to 20 times the perception threshold with a duration of 0.2 ms. The filter settings were the same as those for a motor conduction study (10 Hz-10 kHz). The sweep speed was 20-50 ms/div for both upper and lower limbs. Ten CSP responses were averaged and rectified and the duration and latencies were analyzed offline. The CSP onset latency was defined as a decrease in the EMG trace below 80% of the baseline preceding the stimulus and the duration of CSP was calculated

from the onset latency to the return of the EMG signal above 80% of the baseline.

Nociceptive flexion reflex

The NFR tests were performed in the right lower extremity. The surface electrodes were placed on tibialis anterior (TA) and gastrocnemius (GK) muscles as described by Kugelberg *et al*.[22] A train consisting of four stimuli at an intensity of 20 mA was given using a hand-held pad stimulating electrodes on the plantar surface of the foot.

Data and statistical analysis

We measured the following parameters in each participant:

- CMAPs: amplitude, distal latency (DML), and conduction velocity (CV);
- SNAPs: amplitudes, and peak latencies;
- F-waves: latencies, and persistency;
- SSRs: amplitude, and distal latency**;**
- CSPs: onset latency, end latency, duration and suppression index of the entire CSP; onset latency, end latency, duration and suppression index of I1; onset and end latency, duration, and amplitudes of E2; onset latency, end latency, duration and suppression index of I2; mean EMG amplitude of the E3 component during the 100 ms following CSP end latency; E3%; and
- RIII components of NFRs: amplitude, distal latency, and probability.

First the normality of the data was determined. Independent samples t-test was used to compare parameters between patients with Fabry disease and healthy subjects when the data were normally distributed. The Mann-Whitney U test was used otherwise. We also assessed the presence of an abnormal response in each patient. An abnormal response was defined as a ±2SD deviation from the mean value of healthy subjects or absence of a response. In the second step, we investigated the association between clinical and abnormal electrophysiological findings using the chi-square test.

SPSS 20.0 (IBM SPSS Statistics for Windows) was used for statistical analysis. Data are expressed as mean and standard deviation. Statistical significance was set at $p < 0.05$.

RESULTS

We invited 27 patients with Fabry disease; five patients did not undergo electrophysiological studies and three patients were excluded because of comorbidities. A total of 19 patients and 19 matched healthy subjects were included in the study. There were 13 females and 6 males in each group. The mean age of the patients was 37.3±16.0 years and the mean age of the controls was 37.3±15.3 years (p=0.992). The mean height of the patients and controls were 165.3±8.5 cm and 165.2±9.5 cm respectively (p=0.917).

Clinical findings

The mean age of the patients at the time of diagnosis was 32.4±18.6 years and the mean duration of the disease was 5.9±3.3 years. All patients were treated with enzyme replacement therapy. Three patients did not exhibit any symptoms. Burning was the most frequently reported symptom (n=11), followed by pain (n=4), hyperhidrosis (n=4), numbness (n=4), and warm intolerance (n=3). The mean VAS score was 4.1±3.4 (range: 0-10). All patients with symptoms reported glove and stocking-type distribution except two patients, who had numbness or pain only in their hands.

Electrophysiological findings

Nerve conduction studies: Three patients with Fabry disease had carpal tunnel syndrome (CTS) while none of the healthy controls had CTS. The prevalence of CTS in our cohort was 15.9%. Other than CTS, distal latencies, amplitudes and CVs of CMAPs (Table 1) and peak latencies and amplitudes of SNAPs (Table 2) were similar between patients and healthy subjects.

Sympathetic skin response: Palmar and plantar SSRs were obtained in all of the healthy controls, however, palmar SSR was absent in 4 patients (21.5%) and plantar SSR were absent in 9 patients (47.4%). The mean latency of plantar SSR was 2.1±0.5 ms in the patient group and 1.8±0.7 among healthy subjects (p=0.027). The mean amplitude of plantar SSR was 75.5***±55.0*** μV in the patient group while it was 169.6±98.7 μV among healthy subjects (p=0.034). The mean latency and amplitude of the palmar SSRs did not differ between the two groups. There were no associations between the clinical findings and abnormal SSRs. The two patients who did not report any symptoms had abnormal SSRs (patients 4 and 9).

Cutaneous silent period (upper extremity): CSP latencies, suppression of the EMG area and CSP duration (except I1 duration) were not different

Table 1: Summary of motor nerve conduction studies in patients and healthy subjects

Nerve, Parameter	Patients	Healthy subjects	p
R, Median CMAP amp, mV	10.7±3.1	11.5±3.6	0.426
R, Ulnar CAMP amp, mV	11.2±2.8	10.9±2.0	0.243
L, Median CMAP amp, mV	10.0±2.9	10.9±2.9	0.336
L, Ulnar CAMP amp, mV	11.2±2.5	10.4±1.8	0.192
R, Median CMAP dLat, ms	3.1±0.5	2.9±0.4	0.178
R, Ulnar CMAP dLat, ms	2.3±0.2	2.3±0.3	0.462
L, Median CMAP dLat, ms	3.1±0.5	2.9±0.4	0.423
L, Ulnar CMAP dLat, ms	2.2±0.3	2.3±0.3	0.197
R, Median CMAP CV, m/s	57.4±3.2	59.7±4.3	0.077
R, Ulnar CMAP CV, m/s	60.5±5.4	60.2±3.4	0.837
L, Median CMAP CV, m/s	58.4±3.1	60.4±3.8	0.084
L, Ulnar CMAP CV, m/s	61.1±0.9	61.2±3.9	0.927
R, Median F lat, ms	27.2±2.5	26.0±1.6	0.162
L, Median F lat, ms	26.1±3.2	25.3±2.2	0.529
R, Peroneal CMAP amp, mV	5.4±1.4	5.0±1.3	0.283
R, Tibial CMAP amp, mV	10.3±4.1	10.8±2.7	0.641
R, Peroneal CMAP dLat, ms	3.6±0.6	3.6±0.8	0.945
R, Tibial CMAP dLat, ms	4.3±0.9	4.0±0.7	0.119
R, Peroneal CMAP CV, m/s	48.7±4.0	48.1±2.9	0.656
R, Tibial CMAP CV, m/s	44.8±3.6	45.7±3.7	0.173
R Tibial F lat, ms	47.8±4.7	42.2±4.4	0.062

R: right, L: left, amp: amplitude, dLat: distal latency, CMAP: compound muscle action potential, CV: conduction velocity,

between patients and healthy subjects. Only the duration of I1 was statistically shorter in patients than the healthy subjects (13.4±6.9 vs. 20.1±9.0, p=0.016). Other CSP parameters of the upper extremities are summarized in Table 3. The onset latency was abnormally long and the I1 duration was abnormally short in two patients (Patients 9 and 19). There was no specific relationship between the clinical findings and abnormal upper-extremity CSP.

Table 2: Summary of sensory nerve conduction studies in patients and healthy subjects

Nerve, Parameter	Patients	Healthy subjects	p
R, Median amp, μV	65.2±25.4	67.1±19.8	0.702
R, Ulnar amp, μV	58.6±25.8	63.1±21.8	0.415
R, Median pLat, ms	3.2±0.3	3.0±0.3	0.106
R, Ulnar pLat, ms	2.6±0.2	2.6±0.2	0.883
L, Median amp, μV	67.0±27.5	71.3±23.8	0.535
L, Ulnar amp, μV	59.5±25.9	63.6±22.7	0.448
L, Median pLat, ms	3.2±0.6	3.0±0.3	0.163
L, Ulnar pLat, ms	2.6±0.3	2.5±0.2	0.662
R, Sural amp, μV	24.5±10.5	30.7±10.4	0.084
R, Sural pLat, ms	3.1±0.8	3.0±0.5	0.504

R: right, L: left, amp: amplitude, pLat: peak latency.

Table 3: The CSP parameters of upper extremity in patients and healthy subjects

	Patients	Healthy subjects	p
Onset latency, ms	40.0±7.9	36.9±10.2	0.391
I1 end latency, ms	53.4±8.7	57.1±11.4	0.286
LLR end latency, ms	68.2±10.6	69.4±8.9	0.930
CSP end latency, ms	123.5±12.9	120.3±9.1	0.478
I1 duration, ms	13.4±6.9	20.1±9.0	**0.016**
LLR duration, ms	68.2±10.6	69.4±8.9	0.930
I2 duration, ms	55.3±14.8	50.9±9.8	0.329
I1, %	41.7±29.3	48.4±14.9	0.274
LLR, %	23.2±23.6	34.3±16.2	**0.024**
I2, %	45.8±23.1	56.8±24.3	0.301
Post CSP, %	135.5±67.8	143.7±16.5	0.460

CSP: cutaneous silent period, I1: first inhibitory phase, I2: second inhibitory phase, LLR: long-loop reflex

Cutaneous silent period (lower extremity): CSP latencies and CSP durations did not differ between patients and healthy subjects. However, the LLR and post-CSP indices were significantly lower in the patient group than in the healthy subjects. The mean LLR index recorded from tibialis anterior muscle was 10.8±7.4% in patients and 22.7±6.8% in controls ($p<0.001$) and the mean LLR index recorded from EDB muscle was 11.1±10.7% in the patient groups and 20.0±8.3% in controls ($p=0.003$). We could not obtain response EDB recordings in five patients (26.3%) and the onset latency was delayed in 2 more patients compared to the presence of a response in all healthy subjects ($p=0.046$). The patients with no response had abnormal sweating or burning except for one, who had no symptoms. Patients with a delayed response experienced aching pain or cold intolerance. All the CSP parameters of the lower extremities are summarized in Table 4.

Nociceptive flexion reflex: The latency and amplitudes of early and late responses were similar between patients and healthy subjects whereas the probability of response over the TA and GK muscles was lower in the patient group than in the healthy subjects ($p=0.030$ and $p=0.022$, respectively). Most patients with numbness (75%) had abnormal NFR; however, there was no specific association with other symptoms.

In total, at least one response in the SSR, CSP or NFR tests could not be obtained normally in 73.7% (14/19) of patients. When we excluded 3 patients with no symptoms, 68.7% (11/16) of patients had at least one abnormal test finding. It is demonstrated in Table 5 along with the clinical and demographic characteristics of the patients.

DISCUSSION

The major findings of this study were i. abnormal SSRs and NFR in more than half of the patients in the presence of normal routine NCS; ii. reduced amplitudes and longer latencies of the plantar SSRs, and iii. reduced probability of NFR. The upper-extremity CSP was normal in most patients; however, we were able to dichotomize patients using lower-extremity CSPs: patients with a response or no response. The patients with no response had abnormal sweating or burning except for one who had no symptoms.

SSR provides an evaluation of the sudomotor function of the skin. The effector organs and reflex generators that cause this response are cholinergic eccrine sweat glands. The efferent fibers of SSR are myelinated sympathetic fibers originating from the spinal intermediolateral nucleus and synapse with postganglionic unmyelinated C fibers in the paravertebral sympathetic ganglion extending from the 1st thoracic segment to the 2nd lumbar segment. These C fibers generate the response by stimulating the eccrine sweat glands.[23] The present study demonstrated that palmar and plantar SSRs could not be obtained in 21.5% and 47.4% of patients with Fabry disease, respectively. In addition, despite being similar for palmar SSRs, the latencies were significantly longer and the amplitudes were significantly lower in plantar SSRs in patients than in healthy subjects. Similarly, Dütsch *et al*. reported that the amplitudes of SSRs were significantly lower in their Fabry cohort than controls.[24] In another study, Gomez *et al*.

Table 4: The CSP parameters of lower extremity in patients and healthy subjects

	Patients	Healthy subjects	p
Rec. from TA			
Onset latency, ms	70.8±14.3	64.9±11.7	0.336
I1 end latency, ms	86.8±12.9	82.2±9.5	0.230
LLR end latency, ms	100.9±12.6	98.5±9.5	0.860
CSP end latency, ms	152.6±12.8	148.9±11.4	0.377
I1 duration, ms	16.0±10.4	17.4±8.5	0.597
LLR duration, ms	100.9±12.6	98.5±9.5	0.860
I2 duration, ms	51.7±13.7	50.5±16.4	0.922
I1, %	47.9±28.0	56.8±18.7	0.353
LLR, %	10.8±7.4	22.7±6.8	**<0.001**
I2, %	40.3±18.3	55.7±21.8	0.114
Post CSP, %	101.5±41.2	141.8±36.9	**0.009**
Rec. from EDB			
Onset latency, ms	63.6±17.6	65.8±15.1	0.525
I1 end latency, ms	87.5±15.5	87.2±12.8	0.683
LLR end latency, ms	104.2±15.8	101.8±11.8	0.474
CSP end latency, ms	160.3±15.7	155.2±15.2	0.205
I1 duration, ms	22.6±13.2	21.4±11.9	0.838
LLR duration, ms	80.8±16.2	82.8±11.8	0.474
I2 duration, ms	57.3±14.7	53.4±19.7	0.563
I1, %	71.0±53.2	80.6±53.6	0.411
LLR, %	11.1±10.7	20.0±8.3	0.003
I2, %	47.3±35.9	65.4±28.6	0.294
Post CSP, %	102.2±32.9	116.6±24.9	0.336

CSP: cutaneous silent period, I1: first inhibitory phase, I2: second inhibitory phase, LLR: long-loop reflex, TA: tibialis anterior, EDB: extensor digitorum brevis

postulated significant abnormalities of SSRs in patients with Fabry disease.[13] However, they only studied the upper extremity and reported a much higher absence of palmar SSRs than ours (66.7%). All these findings suggest abnormalities in the C fibers. In contrast, two other studies reported that palmar or plantar SSRs were absent in only 4.5% and 8.3% of their cohorts, respectively.[25,26] The difference between different studies may arise not only from the electrophysiological methodology but also from the characteristics of patients: use of enzyme replacement therapy or the duration of the disease before initiation of treatment. It has also been shown that enzyme replacement therapy may influence SSRs.[27] In our cohort, some elderly patients used the specific treatment for a relatively short period.

Previously, only one study has analyzed CSPs from both the upper and lower extremities. Although there were certain methodological differences, the authors described that 8.3% of patients with Fabry disease lacked a CSP response in the lower extremities. They also reported incomplete suppression of EMG activity during CSP in the remaining patients in the same study.[12] Similarly, we could not obtain a CSP response in the lower extremity; however, the percentage of patients with no response was higher. We also determined longer latencies in the upper extremities in two patients by individual analysis and shorter I1 durations by group analysis compared to healthy subjects. There is evidence that the afferent fibers of the CSP are small fibers since the velocity calculated by the stimulation of the afferent cutaneous nerve from two different points is in the range of 9-18 m/s and the fibers

Table 5: Clinical and demographic characteristics of patients

Patients	Age, sex, duration of tx	Normal Sweating	Burning	Pain	Numbness	Palmar SSR	Plantar SSR	UE-CSP	LE-CSP	NFR
Patient 1	24, F, 2	N	Present	Absent	Absent	N	N	N	N	N
Patient 2	27, F, 1	Abn	Present	Absent	Absent	N	Abn	N	N	Abn
Patient 3	36, F, 2	Abn	Present	Absent	Absent	Abn	Abn	N	Abn	N
Patient 4	44, M, 2	N	Absent	Absent	Absent	Abn	Abn	N	N	N
Patient 5	22, M, 4	Abn	Present	Absent	Absent	Abn	Abn	N	Abn	Abn
Patient 6	30, M, 3	Abn	Absent	Absent	Present	Abn	Abn	N	N	Abn
Patient 7	77, F, 3	Abn	Absent	Present	Absent	N	Abn	N	N	N
Patient 8	44, M, 3	N	Absent	Absent	Absent	N	Abn	N	N	Abn
Patient 9	60, F, 2	N	Absent	Absent	Absent	Abn	Abn	Abn	Abn	N
Patient 10	28, M, 2	Abn	Present	Present	Absent	N	N	N	N	N
Patient 11	43, F, 11	N	Present	Absent	Absent	N	N	N	N	N
Patient 12	21, F, 11	Abn	Absent	Present	Absent	N	N	N	N	N
Patient 13	20, F, 2	Abn	Absent	Present	Absent	N	N	N	N	N
Patient 14	25, F, 10	N	Present	Absent	Present	N	Abn	N	N	N
Patient 15	51, F, 4	N	Present	Present	Absent	N	Abn	N	Abn	Abn
Patient 16	63, F, 2	Abn	Absent	Absent	Present	N	Abn	N	Abn	Abn
Patient 17	37, F, 3	Abn	Present	Absent	Present	N	N	N	N	Abn
Patient 18	30, M, 9	N	Present	Absent	Absent	N	Abn	N	N	N
Patient 19	26, F, 2	N	Present	Absent	Absent	N	Abn	Abn	N	Abn

Tx: treatment, UE: upper extremity, LE: lower extremity, SSR: sympathetic skin response, CSP: cutaneous silent period, NFR: nociceptive flexor reflex, N: normal, Abn: abnormal

are high-threshold indicating the presence of A-delta fibers in the afferent arm.[23] The presence of abnormal CSP recorded on EDB muscle was related to a symptom suggesting small fiber involvement. The type of involvement is different in Fabry disease. The reduced probability in the presence of normal conduction studies (normal motor pathway) suggests that the probability may be a good indicator of A-delta function.

Our study is the first to analyze the effect of small-fiber neuropathy on NFR in Fabry disease. The late (RIII) response occurs in the range of 85-120 ms as a result of stimulation of high-threshold nociceptive A-delta fibers. Movement activity was observed in the extremities where the stimulus was given. There are also studies that have suggested that C fibers may contribute to the late (RIII) response.[28,29] When the afferent stimulus reaches the spinal level, excitatory and inhibitory responses are generated through a series of complex interneuronal connections. We have previously reported alterations in NFR in restless legs syndrome and akathisia.[30]

Overall, if we consider the clinical symptoms in these patients as the gold standard criteria to diagnose small fiber neuropathy, the overall sensitivity of all three tests was relatively low (around 70%). However, they are clearly higher than some previous methods.[6,14] Lefaucheur *et al*. described laser-evoked potentials as the most sensitive test (altered in 79% of patients), followed by electrochemical skin conductance (61%), warm detection threshold (55%), SSR (41%), and cold detection threshold (32%). The authors recommended the use of a combination of laser evoked potentials, assessing A-delta sensory fibers, warm detection threshold, assessing sensory C fibers, and electrochemical skin conductance, assessing autonomic C fibers, to approach for the diagnosis of small fiber neuropathy in Fabry disease along with other etiologies.[15] We did not compare our findings with laser evoked potentials or QST, which we acknowledge as the limitation of our study. The same authors also diagnosed small-fiber neuropathy based on clinical findings.

Our study also showed that the prevalence of clinically and electrophysiologically confirmed CTS was 15.9% in the cohort of patients with Fabry disease. This was quite high when compared to that in the general population. In one of the most comprehensive studies with 2,466 subjects, the prevalence of clinically and electrophysiologically confirmed CTS was 2.7% in the general population.[31] The other two electrophysiological studies also showed an increased incidence of CTS in patients with Fabry disease with similar rates of 25% and 27% in their cohorts respectively.[25,26] The possible accumulation of glycolipids in the carpal tunnel and tendons is one of the mechanisms that have been speculated. Unlike these three studies, another prospective study did not postulate any abnormalities in median nerve conduction studies in patients with Fabry.[13] However, that study had a small sample size (n=9) and only one of them was female.

The main limitation is the lack of skin biopsy which can be considered as the gold standard diagnostic test for small fiber neuropathy. Comparing our electrophysiological study results with those of skin biopsies could be more informative. Another limitation is that the NFR test could not be obtained in some healthy individuals despite it being unexpected to have no response in SSR and CSP test in healthy subjects. Patients who did not agree to participate in the study could be considered another limitation.

In conclusion, by this study, we conclude that, in addition to clinical findings, performing SSR, CSP and NFR tests along with routine NCS could help diagnosing small fiber neuropathy in patients with Fabry disease when objective findings are needed. These tests can be performed in standard electrophysiology laboratories without requiring any additional equipment.

DISCLOSURE

Financial support: None

Conflict of interest: None

Data availability: The data that supports the findings of this study is available on request from the corresponding author.

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