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Performance of Quantitative Sudomotor Axon-Reflex Test (QSART) in Patients with Symptoms of Small Fiber Neuropathy

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Abstract

Objective: We report the performance of the Quantitative Sudomotor Axon Reflex Test (QSART) in consecutive patients with symptoms of Small Fiber Neuropathy (SFN) admitted to our out-patient clinic during the period from the December 2009 to the March 2013.

Methods: Patients with normal Nerve Conduction Study (NCS) and clinical symptoms indicating SFN were included. A total number of 137 patients were screened of whom 84 patients met inclusion criteria with results of both QSART and Quantitative Sensory Testing (QST).

Results: Forty-two percent of the patients suspected for SFN had abnormal QSART results affecting postganglionic sympathetic Sudomotor nerve fiber function among whom 27% had a moderate to severe degree of dysfunction. QST findings were abnormal in 50% of the patients. Cold Detection Thresholds (CDT)/Warm Detection Thresholds (WDT) suggested that hypoesthesia was present in the foot of 14% and 12% the patients, respectively. Heat pain Threshold (HPT) findings suggest thermal hyperalgesia of the foot and the hand in 13% and 21% of the patients, respectively. QSART and QST were both abnormal in 19% of the patients, only. We found no differences of QST measures in patients with substantial Sudomotor dysfunction compared to those without.

Conclusion: In patients with symptoms of SFN, thermal sensory function and Sudomotor function should be considered as separate and potential complementary diagnostic tests.

Keywords: Small fiber neuropathy/physiopathology; Small fiber neuropathy/diagnosis; Pain threshold/physiology; Reflex/physiology; Neural conduction/physiology; Skin/innervation

Abbreviations: SFN: Small Fiber Neuropathy; CDT: Cold Detection Threshold; WDT: Warm Detection Threshold; HPT: Heat Pain Threshold; IENFD: Intra-Epidermal Nerve Fiber Density; QST: Quantitative Sensory Test; QSART: Quantitative Sudomotor Axon Reflex Test; NCS: Nerve Conduction Study

Introduction

Small fiber neuropathy, SFN, is a subgroup of peripheral neuropathies, which involves loss of thin unmyelinated C-fibers and thinly myelinated Aδ-fibers. Patients suffering from SFN describe symptoms of spontaneous or stimulus-evoked neuropathic pain along with burning, shooting or prickling sensations in affected areas. In addition, patients may experience cold/warm perception deficits, autonomic dysfunctions, allodynia and hyperalgesia [1-6]. Patients with pure SFN show neither motor weaknesses, tendon

hyporeflexia nor proprioceptive abnormalities.

The symptoms of SFN have a predominantly symmetric distal distribution with a length-dependent graduation, but asymmetric, multifocal and focal distributions are also frequently reported, with the focal presentations often being at distal parts of the sensory nerve dermatomes. Small fiber neuropathy is associated with a substantial number of diseases. The most frequent associated diseases are metabolic disorders (diabetes mellitus, impaired glucose intolerance), hypovitaminosis, auto-immune mediated diseases (e.g. Sjögren disease, sarcoidosis) and genetic diseases. In a considerable number of patients, the etiology of SFN is unknown and classified as idiopathic [1-3,7,8].

The clinical diagnosis of SFN is supported, when patients with predominantly SFN-symptoms are found to have a disturbance of small fiber sensory function at clinical examination. The finding of hypoesthesia towards temperature and pin-prick is often present in combination, but many patients have combined hyperesthesia.

For research purpose the diagnosis of SFN relies on clinical and Para clinical criteria. In diabetes possible SFN is present in patients reporting SFN-related pain symptoms, without reporting other causes of the pain. The possible diagnosis of SFN is present in patients in whom symptoms are accompanied by clinical signs of SFN with a distribution compatible with the symptoms. Definite SFN is suggested to require additional abnormalities of Quantitative Sensory Testing (QST) of temperature and/or structural abnormalities of the density of small nerve fibers entering the epidermis [9].

The pathology in SFN often involves the autonomic nervous system with loss or dysfunction of postganglionic nerve fibers in the same anatomical distribution as the painful symptoms, the clinical sensory findings or the epidermal nerve fiber loss. Focal skin symptoms with reduced or persistent sweat production, a more general temperature control disturbance, symptoms from unregulated organ blood supply or orthostatic intolerance occur as well. For the establishment of a diagnosis of autonomic dysfunction, autonomic reflex screening is needed [10].

The examination of postganglionic sympathetic control of cutaneous Sudomotor function by the Quantitative Sudomotor Axon Reflex Test [11] addresses dysfunctions in the most distal part of the nervous system. Using the QSART as a diagnostic test in SFN could reveal involvement of the postganglionic sympathetic fibers, and thus add important information about location and severity of the lesion. The introduction of QSART in the diagnostic criteria of SFN has been hampered, however, by reports of the test demonstrating poor reliability [12]. For these reasons the QSART is still not included in the proposed diagnostic work-up for SFN. We wanted to investigate, whether QSART changes did indeed reflect the pathology suspected to result from loss of sensory small fiber function. The study is, on the other hand, not a study of the value of QSART in establishing a definite diagnosis of SFN.

We investigated how QSART performed in a cohort of patients with symptoms of SFN, in whom large fiber neuropathy was excluded with conventional electrophysiological methods, focusing the data analysis on describing the internal consistency between QST for temperature and the QSART. In addition, we aimed at evidence for QSART predictability of temperature thresholds abnormalities that could indicate a diagnosis of SFN.

Methods

Inclusion criteria

From December 2009 to March 2013, data from consecutive referred patients with symptoms of SFN were collected, retrospectively. Patients were subjected to a standardized small fiber investigation. Inclusion criteria were painful symptoms such as burning, itching or shooting sensations in the hands and/or in the feet in patients with normal nerve conduction studies. Patients with verified affections of the central nervous system, major psychiatric diseases or genetic disorders were excluded. We also excluded patients, who received medications which could affect the study of Sudomotor function.

Clinical evaluation

The patients had a standardized neurological examination to test muscle strength, tendon reflexes, plantar response, coordination tests, and sensory function for proprioception, pinprick and vibration (128 Hz non-graded tuning fork) at the toe/fingertip of the index finger. At the end of the study period patient charts were retrospectively evaluated for the proposed etiology of the painful condition.

Nerve conduction study

Nerve conduction studies were performed using standard techniques with surface recording electrodes. Motor conduction studies of the median and ulnar nerves were performed in one arm and of the peroneal and tibial nerves in both legs and sensory conduction studies of the median and ulnar nerve were performed in one arm and of the sural nerve in both legs. The results were compared to normal values and reported as Z-scores. The normal values used are derived from an unpublished Danish multicenter, sex- and age-corrected and temperature-controlled dataset. For this study, an abnormal nerve conduction study was defined as a reduction in motor or sensory nerve action potential amplitudes in more than two nerves involving more than one limb. (https://www.dskn.dk/_doc/normalmateriale/ENG_report.pdf).

Quantitative sensory test: Thermal threshold

Thermal thresholds were examined with a thermal stimulator

(Medoc TSA-2001; Medoc Ltd., Ramat Yishai, Israel). The contact heat stimuli were applied with a Peltier element with an active surface of 9 cm^2 on the thenar eminence and on the dorsum of the foot.

Warm and Cold Detection Thresholds (WDT, CDT) and Heat Pain Threshold (HPT) were recorded, all using the method of limits. For temperature and pain thresholds, an average of five and three trials, respectively, were averaged and compared to normal values from the German Research Network on Neuropathic Pain as Z-values [13]. Both upper and lower limits of the normal range were used to categorize any deviation as hyposensitive/hypoalgesic or hypersensitive/hyperalgesic.

Quantitative sensory test: Vibration threshold

Vibration thresholds were examined with a Vibrameter (Somedic AB, Hörby, Sweden) the probe resting at the dorsum of the metacarpal bone of the index finger and the dorsomedial aspect of the 1st metatarsal bone. Using the method of limits, three values of vibration thresholds were averaged, and compared to normal values and reported as Z-scores [14].

Quantitative Sudomotor Axon Reflex Test (QSART)

The postganglionic sympathetic nerve function was examined by the Quantitative Sudomotor Axon Reflex Test (QSART) (Q-SWEAT™, Model 1, Meridian Sweat Capsules and Iontophor ®II; all WR Medical Electronic Co, Stillwater, MN, USA) at standard positions on the medial forearm, proximal lateral leg, medial distal leg and on the proximal dorsum of the foot. Sweat capsules were filled with 10% (w/vol) acetylcholine in sterile water. After securing a stable recording, drug electrophoresis with 2mA for 5 minutes was performed, the humidity being recorded at least 15 minutes after the start of iontophoresis. Sweat output was calculated as the area under the curve until 10 minutes after start of the iontophoresis subtracting the basal sweat output. The sweat output was compared to normal values [15]. Results were reported as a percentage of the lower limit of normal values for the age group. The distribution of results from the individual patient was summarized as a Sudomotor score. The QSART Sudomotor index score was graded from 1 to 3, indicating mild, moderate or severe dysfunction of the postganglionic sympathetic Sudomotor fibers, respectively [16].

All examinations mentioned above were performed unilaterally on the side with the most severe symptoms. The patients were lying in a supine position in a quiet room at a comfortable temperature, the skin temperature ensured being ≥32°C at the stimulation sites. Data from healthy subjects was included as a quality control.

Statistical analysis

Biometric data, QST data (temperature and vibration) and QSART volume data were described using means and standard deviations for most parameters. Gender, autonomic symptoms and Sudomotor indices were reported using frequencies. We analyzed all non-categorical data for skewness, kurtosis and analyzed for normality using the Shapiro-Wilks test Age, QST data and QSART volumes were found not to be distributed significantly different from a normal distribution and were compared using an independent samples t-test.

Frequency tables were compared using Pearson two-sided Chi-Square-Test. A 5% level of significance was applied for all statistical testing using an IBM SPSS 24 Statistics program.

Data protection

The recovery of data from the patient files was done according to national data protection regulations. (The Danish Data Protection Agency RH-2015-291; The Danish Patient Safety Authority 3-3013-1374/1/). The investigation was further approved by the regional ethics committee (H-2-2009-114).

Results

Among the 137 consecutive patients, 15 patients with either verified affections of CNS, major psychiatric disorder or genetic disorder did not fulfil the inclusion criteria. Further 38 patients were lacking either QST and/or QSART data leading to exclusion. Eighty-four patients (30 men and 54 women) were included, having a mean age of 49.9 [SD ±14.1, range 20-82]. Medical records showed 82% reported symptoms dominated by dysesthesia while 18% of the patients had unspecific paresthesia in feet and/or in hands (Table 1).

Descriptive overview of patients	
Number of patients	84
Male/Female	30 (36%)/54 (64%)
Age; mean ± S.D.	49.9 years ±14.1
Age; range	[20-82 years]
Symptoms	
Dysesthesia	69 (82%)
Paresthesia	15 (18%)

Table 1: Patient characteristics and symptoms.

The etiology of SFN was identified in 28 patients (33.3%) while in 56 patients (66.7%) it was defined as idiopathic. Nine patients had multiple associated diseases identified as possible etiologies. Etiologies were most frequently metabolic disorders as diabetes mellitus, (7 patients, 8.3%), impaired glucose tolerance (2 patients 2.4%), vitamin B12 deficiency (2 patients, 2.4%) and hypothyroidism (2 patients, 2.4%). Another significant group were

patients with activated immune system as Sjögren's syndrome (6 patients, 7.1%), sarcoidosis (2 patients, 2.4%), celiac disease (1 patient, 1.2%), systemic lupus erythematosus (2 patients, 2.4%), unspecified vasculitis (4 patients, 4.8%) and other rheumatological diseases (rheumatoid arthritis, psoriasic arthropathy, mixed connective tissue disorder, polymyalgia rheumatica) (7 patients, 8.3%). The remaining cases had Monoclonal Gammopathy of Undetermined Significance (MGUS) (1 patient, 1.2%) and infection with Human Immunodeficiency Virus (HIV) (1 patient, 1.2%).

QST-vibration data were available from 76 of the 84 patients included. Sixteen patients (21.1%) had an abnormal vibration threshold in the foot in spite of no vibration abnormality found on clinical investigation at recruitment, while 21 (27.6%) patients had an abnormal vibration threshold in the hand.

QST-temperature data revealed that three of the 84 (3.6%) patients had hypoesthesia towards heat and nine (10.7%) patients towards cold in the hand. Additionally, two (2.4%) and three (3.6%) patients had thresholds suggesting hyperesthesia towards heat and cold, respectively. Heat pain thresholds suggested hypoalgesia at the hand in three (3.6%) patients, but hyperalgesia in 18 (21.4%) patients.

Ten of the 84 (11.9%) had foot hypoesthesia towards heat and 12 (14.3%) towards cold. Hyperesthesia towards heat and cold in the feet were found in only four (4.8%) and one (1.2%) patients, respectively. Heat pain thresholds revealed hypoalgesia to heat in five (6.0%) patients whereas 11 patients had hyperalgesia (13.1%) in the feet.

Hypoesthesia towards vibration in the hands and feet were found in 20 (26.7%) and 16 (21.1%) patients, respectively. Only one (1.3%) patient had hyperesthesia towards vibration in the hands. In all, we found QST abnormalities for temperature in 42 of out 84 patients (50%) (Table 2).

	QST Hypoesthesia	QST Hyperesthesia	QST abnormality
Hand			
WDT	3 (3.6%)	2 (2.4%)	5 (6.0%)
HPT	3 (3.6%)	18 (21.4%)	21 (25.0%)
CDT	9 (10.7%)	3 (3.6%)	12 (14.3%)
VPT	20/75 (26.7%)	1/75 (1.3%)	21/75 (28.0%)
Foot			
WDT	10 (11.9%)	4 (4.8%)	14 (16.7%)
HPT	5 (6.0%)	11 (13.1%)	16 (19.0%)
CDT	12 (14.3%)	1 (1.2%)	13 (15.5%)
VPT	16/76 (21.1%)	0/76 (0%)	16/76 (21.1%)

CDT: Cold Detection Threshold; HPT: Heat Pain Threshold; VPT: Vibration Perception Threshold; WDT: Warm Detection Threshold.

Table 2: The distribution of sensory disturbances on QST to temperature in the 84 patients. The number of patients is displayed together with their frequencies. Abnormalities are reported separately for hypoesthesia and hyperesthesia.

Sudomotor results

Using the QSART Index Score, 35 out of 84 patients (41.7 %) had abnormal results, and 23 (27.4%) had a significant degree of Sudomotor dysfunction with a Sudomotor Score of 2 or 3, suggesting moderate to severe involvement of the postganglionic sympathetic Sudomotor fibers (Table 3).

QSART Index Score	Normal QST results	Abnormal QST results	
0	26	23	49 (58.3%)
1	5	7	12 (14.3%)
2	5	8	13 (15.5%)
3	6	4	10 (11.9%)
Total	42	42	84 (100%)

Table 3: Distribution of QSART Index Score and their frequencies in patients with or without QST abnormalities for temperature (CDT, HPT, WDT). (QSART Index Score 1 = mild dysfunction, Index Score 2 = moderate dysfunction, Index Score 3 = severe dysfunction of postganglionic sympathetic Sudomotor fibers.) Pearson Chi-Square 1.609; df3; p=0.657.

Sixteen (19.0%) patients had both abnormal QSART Index Score and abnormal CDT and/or WDT at the feet. Those patients did not score higher on the QSART Index Score than patients without abnormal QST (Chi-square test; p=0.11). As a result, we did not find the QSART Index Score to be higher in patients with symptoms of SFN including both symptoms and abnormal QST results.

To address the importance of the temperature thresholds on the Sudomotor results further, 2x2-analysis was performed for each recording site (QST) and each sensory quality.

We did not find any significant relation between the presence of an abnormal WDT, CDT or HPT and the QSART Index Score. Only patients with a normal CDT at the hand tended to have predominantly lower QSART Index Scores of 0 (p=0.06). The overall test results comparing frequencies of abnormal QST and QSART are summarized in Table 4.

Hand										
QSART	**Normal WDT**	**Abnormal WDT**	**Total**		**Normal HPT**	**Abnormal HPT**	**Total**		**Normal CDT**	**Abnormal CDT**	**Total**
Normal	47	2	49		37	12	49		45	4	49
Abnormal	32	3	35		26	9	35		27	8	35
Total	79	5	84		63	21	84		72	12	84
	Chi-square 0.74; df1; p=0.39				Chi-square 0.02; df1; p=0.90				Chi-square 3.60; df1, p=0.06		
Foot										
QSART	**Normal WDT**	**Abnormal WDT**	**Total**		**Normal HPT**	**Abnormal HPT**	**Total**		**Normal CDT**	**Abnormal CDT**	**Total**
Normal	43	6	49		40	9	49		43	6	49
Abnormal	27	8	35		28	7	35		28	7	35
Total	70	14	84		68	16	84		71	13	84
	Chi-square 1.66; df1; p=0.20				Chi-square 0.035; df1; p=0.85				Chi-square 0.94; df1; p=0.33		

QSART	**Normal VPT-H**	**Abnormal VPT-H**	**Total**	**QSART Index Score**	**Normal VPT-F**	**Abnormal VPT-F**	**Total**
Normal	31	11	42	Normal	35	8	43
Abnormal	24	9	33	Abnormal	24	9	33
Total	55	20	75	Total	59	17	76
	Chi-square 0.11; df1; p=0.92				Chi-square 0.81; df1; p=0.37		

Table 4: 2x2 table for all three sensory qualities of QST in 84 patients and vibration pressure threshold for 76 patients. Patients are divided according to the presence of QST abnormalities, at hands and feet, and QSART Index Score. Both patients with hypoesthesia and hyperesthesia are considered abnormal. Pearson two-sided Chi-squared Test.

Subgroup analysis

To examine the influence of a dysfunction of the autonomic nerve fibers further, the individual data points were divided into subgroups according to the presence of an abnormal QSART Index Score of 1-3. Thirty-five out of 84 patients had an autonomic dysfunction. They had similar age and gender distribution without differences of autonomic symptoms or signs of large fibers dysfunction compared to patients without autonomic nerve dysfunction. Thermal thresholds at the hand and feet did not differ significantly between groups (Table 5).

		Subgroup analysis: Sudomotor abnormalities			Subgroup analysis: Abnormal QST Vibration		
		Sudomotor index 0	**Sudomotor index 1-3**	**p**	**Normal QST-vib.**	**Abnormal QST-vib.**	**p**
Number		49	35		59	17	
Age (Years)		47.9 (1.9)	52.8 (2.5)	0.12	48.7 (1.8)	47.5 (3.4)	0.77
Sex (F/M)		32/17	22/13	0.82	39/10	20-jul	0.58
Autonomic symptoms		1.8 (0.3)	2.2 (0.4)	0.41	2.0 (0.3)	1.9 (0.6)	0.92
Suralis amplitude		0.28 (1.21)	0.44 (1.10)	0.52	0.51 (1.18)	-0.16 (1.13)	**0.04**
Vibration threshold	Hand	1.28 (1.39)	1.25 (1.37)	0.94			
	Foot	1.02 (1.47)	1.11 (1.68)	0.85			
WDT	Hand	-0.20 (1.02)	0.20 (1.21)	0.11	-0.09 (1.11)	0.33 (1.15)	0.17
CDT		0.23 (1.1)	0.58 (1.29)	0.19	0.37 (1.11)	0.76 (1.32)	0.22
HPT		0.62 (1.74)	0.96 (1.58)	0.36	0.60 (1.50)	1.00 (1.93)	0.37
WDT	Foot	0.58 (1.09)	0.74 (1.30)	0.55	0.64 (1.11)	0.70 (1.35)	0.86
CDT		0.52 (1.25)	0.70 (1.40)	0.54	0.38 (1.22)	1.35 (1.53)	**0.008**
WDT		0.16 (1.43)	0.30 (1.49)	0.66	0.17 (1.31)	1.13 (1.68)	0.93
QSART sweat output (µl)	Hand				594 (536)	594 (443)	1
	Proximal				230 (179)	184 (180)	0.35
	Distal				292 (253)	330 (257)	0.59
	Foot				724 (560)	634 (358)	0.53
Sudomotor Index					0.83 (0.15)	0.94 (0.26)	0.72

Table 5: Subgroup analysis of patients divided according to their test result from the autonomic Sudomotor function (QSART) test or their sensory large-fiber QST vibration test (QST-vib.). Amplitudes of sural sensory nerve action potentials and quantitative sensory thresholds were reported as z-scores. Sudomotor sweat outputs were reported as actual volumes. Age, gender and autonomic symptom load and QST-temperature threshold results were compared across subgroups. Vibration thresholds and QSART Sudomotor outputs and Sudomotor index were compared when appropriate. All non-categorical values were compared using an Independent Sample T-Test and sex distribution was compared using a Pearson Chi-Square test.

To examine the influence of a slight large-fiber dysfunction, the dataset was divided into subgroups according to the presence of normal or abnormal vibration thresholds in the foot. Seventeen out of 76 (22.4%) patients had abnormal vibration thresholds at the feet despite having normal nerve conduction studies on inclusion. Patients with abnormal vibration thresholds did have significantly lower CDT at the feet compared to patients with normal vibration thresholds (0.38±1.22 vs. 1.35±1.53, p=0.008), but they did not differ for other thermal thresholds at the foot or hand. In addition, they did not differ in autonomic nerve function (absolute sweat output at the four recordings sites, Sudomotor Index Score) or in their autonomic symptoms, age or gender compared to patients without vibration abnormalities.

Discussion

The optimal tools for diagnosing small fiber neuropathy are under investigation and several diagnostic methods have been introduced with the aim to make early diagnosis possible and to monitor disease progression and treatment responses. There is evolving agreement on a diagnostic standard for clinical and research purposes [1,17-19] with criteria involving clinical findings of neuropathic pain, abnormal thermal thresholds and low Intraepidermal Nerve Fiber Density (IENFD).

Using those criteria, SFN is found to be present at an increased frequency in patients with several disorders in which pain is a more or less consistent part of the clinical picture [20]. Studies of definite SFN are important to define whether a peripheral small fiber neuropathy is actually present. Still not adequate knowledge exists about patients whose symptoms do not meet SFN criteria but still exhibit symptoms of SFN, and still less is known about the performance of QST and QSART among them.

Before including the Sudomotor axon-reflex test in the diagnostic work-up of SFN, we need to ascertain, that the test reflects a primary peripheral dysfunction of autonomic nerve fibers caused by similar injuries to small diameter nerve fibers as those causing loss or dysfunction of small sensory nerve fibers. In our cohort of patients with symptoms of SFN, we did not find any internal consistency between QST and the Sudomotor test. As a result, we ask whether the two tests reflect a common clinical entity.

Differences in performance between the two tests could be a result of a difference in susceptibility to injury from the same toxic factors in the microenvironment of the nerve fibers. Or the difference could be a result of different pathophysiology with sensory fiber injury in the peripheral nerve and autonomic fiber injury at another more proximal level with a dying-forward injury to the postganglionic sympathetic nerve.

In 122 patients with sensory symptoms and no nerve conduction abnormalities Thaisetthawatkulit, et al. also found no correlation between QSART volume and QST (CDT, HPT) or IENFD in patients with definite SFN. They concluded QSART to be an independent measure of autonomic dysfunctional in distal SFN, which could be seen as a complementary measure of SFN while IENFD is an anatomic measure which does not convey information of small fiber function [21]. In accordance with this observation we corroborate the lack of concordance between QSART and QST in our group of patients with symptoms of SFN. Only twenty percent of our patients had concurring abnormal results from the somatic and autonomic nervous system. This finding, in our selected and homogenous group of patients, might well indicate the necessity of using multiple test modalities for identification of unrecognized cases of SFN.

In the larger group of patients with possible SFN, Schley, et al. found reduced IENFD was correlated to abnormal cold/warm detection thresholds, whereas reduced dermal innervation was best correlated to abnormal cold/heat pain thresholds, without a relationship between loss of fibers and neuropathic pain [22]. Similar results were found by another group of researchers who could not establish a correlation between IENF density at the lower limb and intensity of pain [17]. With this discrepancy between epidermal nerve fibers count and somatic dysfunctions in a broader group of patients with symptoms SFN, a more complex mechanism of pain-generation should be suspected. Using QST abnormality as a prerequisite for diagnosing SFN is in line with clinical dogma that the clinical examination of sensory deficits differentiates neuropathic pain from other causes of pain [23-26]. In our cohort of patients referred predominantly on the basis of neuropathic symptoms, we found abnormalities in QST of temperature in 50% of the patients. As a result, we were able to secure a clinical diagnosis of probable SFN in this group.

This low incidence could be a result of referral bias, as we receive predominantly patients based on painful symptoms and findings suggesting SFN but without convincing etiology. As a result, we have few patients with diabetes but more patients who have concomitant inflammatory or cardiovascular diseases. Another bias is the use of near-nerve conduction technique to diagnose a mixed large and small fiber neuropathy. We usually find the near-nerve technique more sensitive in detecting minor large fiber neuropathy abnormalities and would not refer the patient diagnosed with those established abnormalities for further small fiber studies.

This referral bias might also result in the high proportion of abnormal QSART results. As 41.7% of the patients had abnormal QSART results and 27.4% had a substantial abnormality, we suggest that those patients with predominantly autonomic neuropathy would not meet the criteria of definite SFN but might belong to another clinical entity. With the low overall prevalence of QST abnormalities we are in risk of a type 2 error to detect the correlation between QST and QSART. We have a fairly balanced QSART dataset, but we did not find even borderline results in the legs.

Somewhat surprisingly, a fourth of the patients showed affected thermal thresholds at the hands with gain of function for warm threshold and loss of function for heat pain threshold as well. Since abnormalities in SFN are distally distributed, it is unexpected that QST results at the hands in our study run in parallel with QST results at the feet. However, these results are compatible with the symptomatic complaints of allodynia and hyperalgesia expressed by the patients.

Furthermore, our results are in line with previous studies investigating Sudomotor function in small fiber neuropathy

patients [27,28]. Studies have shown that QSART is effective in documenting dysfunction of the postganglionic Sudomotor fibers with high sensitivity and should be considered an appropriate tool for investigating SFN [19], if not appropriate for diagnosis of definite SFN.

We did not find any difference in Sudomotor Index Score between patients with or without abnormal QST. This lack of prognostic power goes both ways, as we did not find any difference of the QST abnormalities in patients with a significant Sudomotor Index Score abnormality, either.

The strength of this study is focusing on patients with symptoms of SFN and we suggest that such a cohort of patients could add to the knowledge in the literature of real-world patients. The description of test performance in patients with Definite SFN addresses diagnostic issues within this stringently separate group of neuropathy patients.

Our results need confirmation in a prospective study where improved focus on both the clinical pain description, a more detailed clinical examination and the use of additional examination of central pain pathways might improve the understanding of the diagnostic process in patients experiencing painful symptoms suggesting SFN. Those studies should also include IENFD to better differentiate the group of patients with Definite SFN from patients with other causes of painful peripheral nerve conditions.

The weakness of this study is primarily its retrospective nature, and because of this, the use of SFN evaluation used at that point in time. We did not perform skin biopsy then and future studies will require inclusion of IENFD to compare the performance of other tests in that context.

Conclusion

In conclusion, our study showed that 27.4% of the patients suspected for SFN did have substantial abnormal Sudomotor abnormalities suggesting a pathology affecting postganglionic nerve fiber function. Furthermore, 50% of our patients had abnormal thermal thresholds indicating a probable SFN. Further research is needed to unravel the complex origin of pain in patients suspected to have SFN. Emphasis should focus on the need for application of various test modalities to include evaluation of autonomic and somatic nerve fibers as well as central mechanisms underlying the pain. Increased awareness of SFN and the use of the diagnostic tools QSART and QST might well contribute to improved diagnostics in patients suffering from SFN.

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