ABSTRACT: The symptoms of burning sensation affecting the feet, thought to be due to a distal small-fiber neuropathy (DSFN) affecting somatic unmyelinated fibers, are usually accompanied by vasomotor or sudomotor changes suggestive of involvement of autonomic fibers. We therefore examined the relationship between pattern of anhidrosis and DSFN and its etiology, comparing patients with "pure" DSFN (with normal nerve conduction) to those with clinical DSFN (minor conduction abnormalities). We reviewed 125 cases with a clinical phenotype of DSFN. These patients had distal burning discomfort, variable sensory deficits, and intact motor function. All had undergone assessment with thermoregulatory sweat test (TST), autonomic reflex screen (ARS), and nerve conduction studies and electromyography (NCS/EMG). TST showed a distal pattern of anhidrosis in 74%. The quantitative sudomotor axon reflex test (QSART) was abnormal in 74%, with 80% of those having a length-dependent pattern of anhidrosis/hypohidrosis. In total, 93% of patients had a distal pattern of abnormality on QSART or TST. The Composite Autonomic Severity Score (CASS) was used to quantify the severity and distribution of autonomic deficits: 98% had CASS abnormality (sudomotor, 98%; adrenergic, 43%; cardiovagal, 35%). EMG was normal or showed unrelated abnormalities in 75%. The most common etiologies of DSFN were idiopathic (73%), presumed hereditary (18%), and diabetes (10%). Sudomotor examination is thus a highly sensitive detection tool in DSFN. Autonomic involvement is mainly distal, and additionally may involve adrenergic and the long cardiovagal fibers.
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DETECTION OF SMALL-FIBER NEUROPATHY BY SUDOMOTOR TESTING

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The "burning feet" syndrome is perhaps the most common presentation of small-fiber neuropathy (DSFN) in clinical practice. These patients have distal involvement with burning, prickling, and some stabbing discomfort, with variable allodynia. They have completely normal motor function, intact tendon reflexes, and normal nerve conduction studies. This pattern of neuropathy has been assumed to be a length-dependent, distal, small-fiber neuropathy demonstrable on skin biopsy.[8] Autonomic fibers are usually involved as well, since these patients commonly have vasomotor symptoms, manifest as excessive coldness, discoloration, or sometimes erythromelalgia.[9,11] Hyper- and hypohidrosis can also be present. On sudomotor testing, approximately 80% of patients have abnormal quantitative sudomotor axon reflex test (QSART) responses.[11] There is good general agreement between loss of intraepidermal fibers (somatic C-fiber involvement) and QSART loss (autonomic C-fiber involvement).[7,10] However, many patients with clinical DSFN have mild or minor nerve conduction abnormalities or minor distal sensory changes. It is not known whether "pure" and relative DSFN are similar or different.

We undertook this study to focus on several key issues that had not been addressed previously, in particular: (1) to compare pure (DSFN with completely normal nerve conduction indices) and clinical DSFN (with mild conduction abnormalities); (2)

Abbreviations: ARS, autonomic reflex screen; BP, blood pressure; CASS, Composite Autonomic Severity Score; DSFN, distal small-fiber neuropathy; EMG, electromyography; HRDB, heart-rate response to deep breathing; IENF, intraepidermal nerve fiber; NCS, nerve conduction studies; NCS/EMG, nerve conduction studies and electromyography; QSART, quantitative sudomotor axon reflex test; TST, thermoregulatory sweat test

Key words: anhidrosis; Composite Autonomic Severity Score (CASS); distal small-fiber neuropathy (DSFN); quantitative sudomotor axon reflex test (QSART); thermoregulatory sweat test (TST).

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to determine the sensitivity of sudomotor examination to detect DSFN; (3) to determine the severity and distribution of autonomic involvement; and (4) to evaluate the cause of DSFN. To undertake this study, we included only patients who clinically had DSFN and had undergone both autonomic reflex screen and thermoregulatory sweat test (TST) and electromyography and nerve conduction studies (EMG/NCS).

METHODS

We retrospectively reviewed 1063 patients that had been seen at the autonomic laboratory with possible indications of a DSFN. Inclusion criteria were that they had clinical features of DSFN. Patients' records were evaluated to determine whether they complained of painful feet. Patients typically described these symptoms as painful, burning, prickling, or tingling feet, often reporting that the symptoms are worse at the end of the day and that bed sheets bother their feet at night. For inclusion in this study, the patient was required to have: (1) full neurological history and examination; (2) bilateral involvement, with deficits not extending beyond the ankles; (3) age of $\geq$18 years and of either gender; (4) autonomic reflex screen to study QSART, cardiovagal function, and adrenergic function; (5) TST; and (6) EMG and NCS of both motor and sensory fibers.

Exclusion criteria were: (1) significant weakness; (2) significant large-fiber sensory loss; (3) generalized autonomic failure; and (4) motor response amplitude or conduction velocity reduction $\geq$20%. Patients with large-fiber dysfunction in whom small-fiber involvement was mostly an ancillary finding not dominating the clinical picture were excluded. Thus, subjects with loss of tendon reflexes beyond the changes expected for age, and significant weakness, defined on neurological examination as weakness $\geq$1 on the Mayo scale (equivalent to >25% loss of strength), except in toe flexors or extensors, were not included in this study. Similarly, patients with significant vibration or proprioception deficit above the ankle, or temperature or superficial pain deficit above the knee were excluded. Finally, subjects were excluded if they presented with orthostatic hypotension or symptoms of neurogenic bladder or bowel, suggesting a more widespread autonomic disorder.

Thermoregulatory Sweat Test. The TST was performed as previously described,[1] in a cabinet with a moderately hot and humid environment (45–50°C air temperature, 35%–40% relative humidity). Mean skin temperature was kept at 39°C. Oral temperature increased at least 1°C or to 38°C (whichever was higher). Maximal sweating was achieved in 30–65 minutes. Sweating was demonstrated by an indicator powder, and the percentage of anhidrosis on the anterior body surface was calculated from images created from digital photographs of sweat distribution.

Autonomic Reflex Screen and Quantitative Sudomotor Axon Reflex Test. Autonomic tests involved an evaluation of postganglionic sudomotor, cardiovagal, and adrenergic functions.[2] QSART to evaluate the postganglionic sympathetic sudomotor axon[5] was recorded routinely from four sites (forearm, proximal lateral leg, medial distal leg, and proximal foot) with acetylcholine stimulus iontophoresed and responses recorded in one compartment of a multicompartmental sweat cell that was separate from the stimulus compartment. The "axon reflex" is mediated by postganglionic sympathetic sudomotor fibers.[5] Control values were derived from studies on 223 healthy subjects aged 10–83 years.[6] Heart-rate responses to deep breathing (HRDB) and Valsalva ratio were used to evaluate cardiovagal function.[6] HRDB was the heart-rate range with the subject supine and breathing at six breaths per minute. For the Valsalva maneuver, the subject was rested and recumbent and was asked to maintain a column of mercury at 40 mm Hg for 15 seconds. The Valsalva ratio is the ratio of maximal to minimal heart rate. Control values were based on 157 healthy subjects aged 10–83 years.[6] Adrenergic function was evaluated by the blood pressure (BP) and heart-rate responses to the Valsalva maneuver and head-up tilt. Beat-to-beat BP was monitored continuously (Finapres monitor; Ohmeda, Englewood, Colorado).

The results of the autonomic battery of tests were corrected for confounding effects of age and gender and graded semiquantitatively from 0 (no deficit) to 10 (maximal deficit). The Composite Autonomic Severity Score (CASS) consists of three subscores: sudomotor (CASS-sudo; 0–3); cardiovagal (CASS-vag; 0–3); and adrenergic (CASS-adr; 0–4).[3] The total score and subset scores provide an evaluation of the severity and distribution of autonomic failure.

Statistics. Descriptive statistics were used. To determine the differences between groups, we ascertained that the data were normally distributed and used the unpaired Student's *t*-test. Data were described as mean $\pm$ standard deviation and significance was accepted at $P < 0.05$.

RESULTS

We screened 1063 potential cases referred to the Autonomic Laboratory; 125 met all of our inclusion criteria, resulting in a clinical phenotype of DSFN. The female:male ratio was 1.8:1 (81 women, 44 men). The age range was 19–84 years, with a mean age of 54 years and standard deviation of 14.3 years. The duration of symptoms ranged from 2 to 480 months (mean, 48 ± 72.8 months).

We reviewed the possible causes of the neuropathies and were unable to identify a specific cause in 73%, which were labeled as idiopathic by the treating neurologist. Among our cases, 18% were thought to be hereditary (on the basis of positive family history with or without pes cavus) and 10% of the patients had diabetes. The remaining 11 patients had a variety of other possible causes for the neuropathy: inflammatory/autoimmune (3); postviral (2); alcohol-related; inflammatory bowel disease or its treatment (metronidazole); Sjögren's syndrome; amyloidosis; Crohn's disease; and connective tissue disorder.

Thermoregulatory Sweat Test. Overall, 91% of the patients had abnormal sweating on the TST. We compared the patterns of anhidrosis and found that 74% of patients showed distal patterns. This number includes 43 patients who had a distal pattern combined with another area of the body that also demonstrated anhidrosis. The percentages of patients with other patterns in isolation were: regional, 6%; focal, 6%; global, 3%; segmental, 1%; and multifocal, 1%.

We also compared the percentage of the body area that exhibited anhidrosis and how that related to the patterns. Not surprisingly, those with only a distal pattern of anhidrosis had a relatively small area that lacked sweating (average 4.6% of body area).

Quantitative Sudomotor Axon Reflex Test. The most common site of reduced sweat output was the foot (35% of patients), followed by the distal leg (29%), proximal leg (26%), and forearm (15%). Of the patients, 62% met the criteria for a length-dependent pattern (LDP), defined as sweat output at the distal sites (foot and distal leg) less than one-third that at the proximal sites (forearm and proximal leg). There was a reduction in either foot or distal leg in 49%, and in both foot and distal leg in 16%. An absolute reduction in QSART, defined as less than 5th percentile when corrected for age and gender, occurred in 58% of the patients.

Table 1. Severity and distribution of CASS abnormalities.

CASS	Cardiovagal	Adrenergic	Sudomotor	Total
0	69 (65%)	70 (57%)	3 (2%)	2 (2%)
1	26 (21%)	39 (32%)	59 (47%)	26 (21%)
2	17 (14%)	13 (11%)	39 (31%)	32 (26%)
3		1 (1%)	24 (19%)	30 (24%)
4				19 (15%)
5				12 (10%)
6				3 (2%)
7				1 (1%)

Table 2. Nerve conduction studies and electromyogram (NCS/EMG).

Description	*N*	%
Normal	78	62
Abnormal, unrelated	16	13
Polyneuropathy, sensorimotor, axonal	15	12
Polyneuropathy, sensorimotor, mixed	5	4
Polyneuropathy, motor, axonal	2	2
Polyneuropathy, sensory, axonal	2	2
Polyneuropathy, sensorimotor, demyelinating	1	1
Polyneuropathy, sensory, mixed	1	1
Mild* neuropathy	3	3
Distal sensory axonal	1	1

**Borderline nerve conduction slowing or motor unit changes.*

Autonomic Reflex Screen and CASS Scores. Most patients had normal or mildly abnormal cardiovagal and adrenergic results on the autonomic reflex screen (ARS), receiving CASS subscores of 0–1 in those areas. For the sudomotor subscore, however, 50% earned a 2 or 3, indicating a moderate or severe involvement of postganglionic sudomotor fibers (Table 1). Overall, 98% of subjects showed a sweating abnormality.

By comparing and combining the results of the QSART and TST, we found that 123 of the 125 patients (98%) showed some level of sweating abnormality. Additionally, 93% of those in the study exhibited a distal pattern in either QSART or TST. More specifically, there was a length-dependent QSART or distal TST pattern in 93%; distal TST pattern plus length-dependent QSART pattern in 43%; length-dependent QSART pattern plus any TST abnormality in 56%; any QSART abnormality plus any TST abnormality in 70%; and either a QSART or TST abnormality in 98%.

Nerve Conduction Studies and Electromyogram. As shown in Table 2, the majority of patients had normal NCS/EMG tests, or showed unrelated abnormalities such as a radiculopathy or carpal tunnel syn-

Table 3. Comparison of current study with earlier studies.

	Stewart et al.[11]	Tobin et al.[12]	Novak et al.[7]	Current study			
				Total	Abnormal NCS	Normal NCS	*P*-value†
Number of patients	40	15	92	125	47	78	
QSART abnormalities	32/40 (80%)	12/15 (80%)	67/92 (73%)	96/125 (77%)	35/47 (74%)	61/78 (78%)	0.79
TST distal patterns of anhidrosis	18/25 (72%)	NA	NA	93/125 (74%)	35/47 (74%)	58/78 (74%)	0.84
TST any abnormality	24/25 (96%)	NA	NA	114/125 (91%)	44/47 (94%)	70/78 (90%)	0.53
Either TST or QSART abnormality	36/40 (90%)	NA	NA	123/125 (98%)	46/47 (98%)	77/78 (99%)	>0.99
Cardiovagal abnormality	11/40 (28%)	9/12 (75%)	59/92 (64%)	43/125 (35%)	15/46 (33%)	28/76 (37%)	0.78
Adrenergic abnormality	0/40* (0%)	2/12* (17%)	0/92* (0%)	53/125 (43%)	21/46 (46%)	32/77 (42%)	0.80

We used Pearson's chi-square test with Yates continuity correction, except for "TST any abnormality" and "Either TST or QSART abnormality," which are based on Fisher's exact test due to small numbers in some cells of the 2 × 2 table. NA, not available.
**Adrenergic abnormality or orthostatic hypotension.*
†Comparing current study with previous studies.

drome. Of note, 15 (12%) had a sensorimotor axonal polyneuropathy and another 4% had mixed polyneuropathies. The abnormalities on NCS/EMG were generally very mild (see exclusion criteria), suggesting mainly subclinical involvement. Medial plantar recordings were performed on 44 of 65 (68%) patients who were <55 years of age, and were normal in 33 patients (75%). Recordings can be absent in normal subjects ≥55 years and are usually not performed in patients >55 years.

Comparison of Clinical With Pure Distal Small-Fiber Neuropathy. When patients with DSFN with completely normal nerve conduction indices (pure DSFN) were compared to those with minor/mild conduction abnormalities (clinical DSFN; Table 3), the findings were essentially identical without any parameter being statistically different.

DISCUSSION

The main findings of this study are that patients with DSFN without and with mild conduction abnormalities have similar results on autonomic function tests, supporting the clinical concept that these patients have the same disorder. Additionally, we demonstrated a high frequency of distal sudomotor abnormalities in DSFN and the frequent, albeit modest impairment of distal adrenergic and cardiovagal fibers.

There are three previous studies (Table 3) of note that examined the relationship between anhidrosis and DSFN.[7,11,12] Our study included a larger group of patients (125 vs. 40, 15, and 92, respectively) and was the only one to incorporate the complete neurophysiological spectrum of tests for all patients (full ARS, TST, and NCS/EMG). With regard to sudomotor testing, our numbers correlate well with the results of the other studies, yielding numbers that were within 8% of their findings. Unlike most previous studies, we included four sites in the QSART as opposed to two sites, allowing us to gain a better understanding of the pattern of abnormal sweating.

The primary difference in our results occurred in the ARS, likely due to a more detailed evaluation of the adrenergic function. We included an examination of the baroreflex-mediated blood pressure responses to the Valsalva maneuver, which provide indices of baroreflex-mediated vagal and systemic control of the circulation,[4,13] whereas the other studies focused solely on presentation of orthostatic hypotension.

The main finding of this study is that neurophysiological testing was able to detect small-fiber abnormalities in up to 98% of cases. Specifically, sudomotor testing was abnormal in 98% of subjects, indicating an excellent correlation between the clinical and laboratory data. Furthermore, a length-dependent pattern was the most common pattern found, being present in 93% of cases. The findings on QSART and TST should be viewed as complementary. For instance, some cases might have anhidrosis on TST distal to the foot QSART recording site (over proximal foot) and normal QSART. Other cases might show a length-dependent pattern on QSART and intact TST. When both tests are available, the optimal criterion of either length-dependent pattern in QSART or distal pattern on TST provides a test of high sensitivity with 93% yield.

Although most of these patients are paucisymptomatic, the extent of nerve dysfunction may be more extensive than clinically apparent. Indeed, up to 60% of our subjects had evidence of cardiovagal or adrenergic dysfunction on autonomic testing, albeit of mild severity. Furthermore, 24% also had evidence of large-fiber involvement as documented by NCS/EMG.

These results are in keeping with prior studies and, while confirming our clinical impression that most of these patients have only minimal distal abnormalities, some may have more widespread involvement. Recognizing this may aid the clinician in requesting other investigations in order to identify a specific cause for the patient's neuropathy as well as allowing for adequate monitoring of the patient's clinical course.

Clinical DSFN is a common presentation, with pain as the main complaint. Two sophisticated tests are skin biopsy with determination of intraepidermal nerve fiber (IENF) density and QSART. There is discordance in the literature on the agreement between QSART and skin biopsy results. Separate publications from the same group reported poor agreement[8] and robust agreement.[7] Novak et al.[7] reported a coefficient of determination (R^2) of 0.86 between QSART abnormalities and IENF density. The study by Singer et al.[10] provides some insights on this discrepancy. Their study evaluated IENF, QSART, and skin norepinephrine content from the skin biopsy site. The studies were done on highly selective phenotypes of DSFN, nonspecific neuropathy, pandysautonomia (without somatic neuropathy), neuropathic postural tachycardia syndrome, and diabetic neuropathy. They found a significant relationship between QSART and IENF, but it was less robust than that of Novak et al.[7] More importantly, they found that in some conditions, such as diabetic neuropathy and DSFN, there was good agreement, whereas in pandysautonomia and postural tachycardia syndrome (POTS) there was no involvement of IENF. The appropriate conclusion is that somatic and autonomic tests evaluate different unmyelinated fiber populations. The reason that autonomic tests are typically useful is because both fiber populations are commonly affected together.

What is the value of autonomic function tests in the clinical setting? Based on this and other studies on DSFN, the following conclusions seem reasonable. For patients with the clinical phenotype of DSFN, the distribution of abnormalities in QSART is a sensitive test. If a full autonomic reflex screen is done, the finding of distal adrenergic impairment (indicative of loss of peripheral baroreflex-mediated vasoconstriction on Valsalva maneuver[13]) or cardiovagal impairment provides supplementary support. If TST is available, the sensitivity of the test is further enhanced. Because this one study was based on a highly selected phenotype, which is culled from a much larger group, it is likely that the yield in patients who do not fulfill the criteria would be lower. Finally, it should be realized that patients with a selective somatic DSFN will have normal QSART.

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