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Small fiber neuropathy: Swiss cohort characterization

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Abstract

Introduction/Aim: There is currently insufficient clinical and epidemiological data concerning small fiber neuropathy (SFN). This research analyzes data from medical records to determine epidemiology, demographics, clinical characteristics and etiology of SFN.

Methods: This is a retrospective, observational study of sequential patients diagnosed with definite SFN (typical clinical features, normal nerve conduction studies, abnormal epidermal nerve fiber density) from the end of November 2016 to the middle of July 2019 at the Cantonal Hospital Lucerne, central Switzerland.

Results: A total of 84 patients (64.3% female) with a mean age of 54.7 y were analyzed. Symptoms had been present in patients for an average of 4.8 y when entering the study. A length dependent clinical pattern was seen in 79.8%. All patients had sensory discomfort. Etiology could not be determined in 35.7% of patients, who were diagnosed with idiopathic SFN; 34.5% of patients had an apparently autoimmune SFN, followed by14.3% of patients with metabolic causes. The estimated incidence was at least 4.4 cases/100.000 inhabitants/y. The minimum prevalence was 131.5 cases/100.000 inhabitants.

Discussion: This study indicates significant incidence and prevalence rates of SFN in Switzerland. SFN can vary greatly in its symptoms and severity. Extensive work-up resulted in two thirds of the patients being assigned an etiological association. The largest group of patients could not be etiologically defined, underlining the importance of further research on etiologic identification. We expect increased awareness of the developing field of SFN.

KEYWORDS
autoimmune neuropathy, incidence prevalence, neuropathic pain, sensory and autonomic neuropathies, small fiber neuropathy

Abbreviations: aaSFN, apparently autoimmune small fiber neuropathy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCP, cyclic citrullinated peptide; EMLA, eutectic mixture of local anesthetic; ENFD, epidermal nerve fiber density; GBS, Guillain-Barré syndrome; HbA1C, hemoglobin A1C; HIV, human immunodeficiency virus; Ig, immunoglboulin; IVIG, intravenous immunoglobulin; NRS, numerical rating scale; POTS, postural tachycardia syndrome; QSART, quantitative sudomotor axon reflex test; SFN, small fiber neuropathy; SNRI, serotonin-noradrenalin reuptake inhibitors; SSW, stimulated skin wrinkling.

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1 | INTRODUCTION

Despite advances in the understanding of small fiber neuropathy (SFN), many questions are still unanswered concerning its epidemiology, demographics, and clinical characteristics.[1] Diagnostic criteria have recently been established, and diagnostic categories of clinically possible, probable, and definite have been proposed.[2] To date, epidemiology and demographics have been examined by only one retrospective study, which found a minimum incidence of SFN of 11.73 cases per 100 000 population per year and a minimum prevalence of 52.95 per 100,000 population.[3]

The clinical presentation of SFN is heterogeneous and characterized by positive or negative sensory phenomena and autonomic dysfunction, such as cardiovascular, gastrointestinal, or cutaneous vasomotor symptoms.[4] Patients often present with sensory disturbance, described as burning pain, tingling/prickling sensation, allodynia,[5] or numbness. Symptoms beginning at the distal extremities are length-dependent.[4] In non–length-dependent SFN, one or more body regions are affected. The pattern is highly variable and distributed irregularly.[6]

Recent studies have identified metabolic, inflammatory, and autoimmune diseases; sodium channel gene mutations; vitamin B12 deficiency; and drug-induced SFN as frequent causes.[7] In about half of the cases, no underlying cause can be found.[8] Finding the underlying cause is important to optimize treatment. If the etiology remains unclear, neuropathic symptoms often require symptomatic treatment. First-line therapies for neuropathic pain are serotonin-norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants, or gabapentin/pregabalin.[9] Pharmacological therapy often fails to achieve a sufficient response or is accompanied by intolerable side effects. In case of a presumed autoimmune cause (also often referred to as apparently autoimmune SFN [aaSFN]) therapy with intravenous immunoglobulin (IVIG) has been advocated, although its efficacy is unknown. In a single, retrospective, unblinded study, 74% of patients administered IVIG experienced improvement of symptoms.[10] In contrast, a recent randomized, double-blind, controlled trial found that IVIG treatment had no significant effect on pain in patients with painful idiopathic SFN.[11]

The aims of this study were to characterize the epidemiology, demographics, clinical characteristics, and etiologic associations of patients with definite SFN in our center and to evaluate differences in patient characteristics, clinical presentations, and epidermal nerve fibre density (ENFD) in the three most common etiological groups (idiopathic, apparently autoimmune, and metabolic).

2 | METHODS

This retrospective, observational study was performed at the neuromuscular clinic at the cantonal hospital of Lucerne, Switzerland. Since 2016, after establishing an SFN laboratory, the center has been serving as a referral center for patients with presumed SFN in central Switzerland. Patients can be referred to the center if they live within the catchment area of the hospital (defined by postal codes) or as a special referral to the center. The hospital catchment area comprises 700,000 inhabitants. However, since we are a reference center, we have defined the central Switzerland population of 813,056 as our catchment area,[12] We obtained this population number as well as population numbers for age categories of 0–20, 20–65, and 65 y or older from the Federal Office of Statistics, an organization responsible for official Swiss statistics.[12] In 2018, 650,115 inhabitants (80%) of the catchment area were 20 y or older. These were considered the reference population at risk for the current study.

The ethics committee approved our project (Project ID 2018–00762).

2.1 | Study participants

Patients sequentially diagnosed as having definite SFN from the end of November 2016 to the middle of July 2019 were included. All patients were required to have a neurologist's clinical diagnosis, a normal sural nerve conduction study plus an abnormal ENFD on skin biopsy from the lower limb. A flowchart of patient disposition is shown in Figure 1.

Clinical histories and data pertaining to the establishment of a diagnosis of definite SFN were extracted from medical records. This included age at diagnosis, age at onset of symptoms, gender, clinical symptoms (length-dependent versus non–length-dependent and leading symptom), a patient-completed validated screening tool for neuropathic pain (painDETECT),[13] etiology (based on a set of standardized routinely performed laboratory tests), results of nerve conduction studies, small nerve fiber function tests (quantitative sudomotor axon reflex test [QSART], and stimulated skin wrinkling [SSW]) and ENFD from skin biopsy. Missing data (painDETECT and QSART) are due to forms not being retrievable and in the case of QSART because of difficulties in the performance of the tests for technical reasons. Response to therapy for control of pain was not recorded in a systematic manner, and so is not included.

In order to be included in the apparently autoimmune group, the criteria for an aaSFN had to be met. We included systemic, organ-specific and nerve-specific aaSFN.[10] Patients with systemic aaSFN had no other apparent cause of neuropathy and either a systemic rheumatologic disorder or autoimmune disease affecting more than one organ system. An organ-specific aaSFN was diagnosed when an organ-related autoimmune disease (such as Hashimoto's thyroiditis or Crohn's disease) was present. The diagnosis of a nerve-specific aaSFN was made when there were otherwise unexplained blood test markers of dysimmunity or inflammation (anti-nuclear antibodies $\geqslant$ 160 dilution, raised erythrocyte sedimentation or C-reactive protein, low complement component 4, low complement component 3, angiotensin converting enzyme, or evidence of Sjögren's autoantibodies [SSA/Ro, SSA/La]).[10] In patients with one first-degree relative with a similar condition, a genetic cause was assumed.

2.2 | Skin biopsy

Skin biopsy is widely accepted as the "gold standard" for diagnosing SFN.[14] Since 2016, we have performed biopsies in a standardized

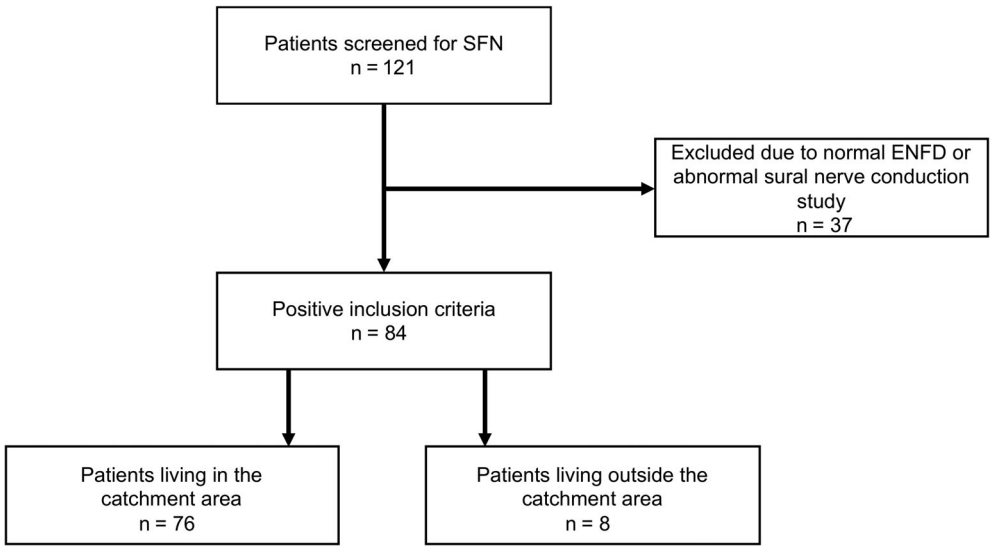

FIGURE 1 Flowchart describing patient disposition

manner at the proximal region of the thigh (20 cm below the anterior iliac spine) and the ankle (10 cm above the lateral malleolus) using a 3 mm disposable punch. The biopsies are processed and incubated with the polyclonal anti-protein-gene product 9.5 antibody (pan-axonal marker). After fluorescence based detection of the antibody, the results are photo documented and evaluated by morphometric cell image analysis.[15] An age- and gender-adjusted normative dataset for ENFD at the lateral distal lower leg was used as reference value for diagnosing SFN. Cutoff values were determined by measuring the ENFD of 528 healthy subjects and using quantile regression analysis to determine the fit of the 5° percentile as the normal cutoff value.[16]

2.3 | Routine blood tests for etiological identification

Hemoglobin A1C (HbA1C), antinuclear antibodies, C3 and C4, Sjögren's (SSA/Ro, SSA/La) and celiac (immunoglobulin [Ig] A TTG) autoantibodies, as well as erythrocyte sedimentation rate, C-reactive protein, angiotensin converting enzyme, rheumatoid factor, anti-cyclic citrullinated peptide (CCP) antibodies, or anti-dsDNA-antibodies were analyzed. Furthermore, liver aspartate aminotransferase (AST)/alanine aminotransferase (ALT), hepatitis C antibodies, folate, Lyme (IgG Western blot), serum protein electrophoresis/immunofixation (monoclonal gammopathy), Fabry disease (activity of α-galactosidase A), and vitamin B12 were reviewed.

The classification of the test results into normal or abnormal was based on the reference values of our laboratory. Diabetes was defined as HbA1C $\geqslant$ 6.5%, Prediabetes was defined as HbA1C $\geqslant$ 5.7% and < 6.5%.[17,18]

2.4 | SNF function tests

QSART determines sweating at standardized sites in the forearm, proximal leg, distal leg, and foot. It assesses postganglionic sympathetic cholinergic function, which can be affected in SFN. A pathologic result was defined by an abnormal value of sweat response in at least one out of four regions.[19] QSART has previously been shown to have a sensitivity of around 50% in the diagnosis of SFN.[20]

SSW occurs 5–30 min after water immersion or contact to vasoconstrictor substances, such as an eutectic mixture of local anesthetic (EMLA) with lidocaine and prilocaine.[21] The pathophysiology behind this phenomena has recently been identified as dependent on digital vasoconstriction mediated via sympathetic nerve fibers and is, therefore, an indicator of limb sympathetic function.[22] To quantify the test result, we used a five-level grading scale.[23] A score under 24 was rated abnormal. The EMLA stimulated wrinkling has a sensitivity of 81.6% in detecting pathologic ENFD.[24]

Although the functional SFN tests described were not used to establish a diagnosis, they provided information about the functionality of SNFs.

2.5 | The painDETECT questionnaire

The painDETECT questionnaire was developed to detect neuropathic pain in patients with chronic low back pain.[13] It consists of questions on pain intensity (at the time of testing, highest pain, and average pain) plus characterization of sensory symptoms.

A numerical rating scale (NRS) from 0 to 10 was used to measure pain intensity. To describe sensory symptoms, a scale from 0 (never) to 5 (very strongly) was used.

2.6 | Statistical analyses

Clinical and treatment data as well as patient characteristics were documented in Medfolio software (NEXUS AG, Villingen-Schwenningen, Germany). The data relevant to our analysis were extracted, and statistical analyses were conducted using STATA´s statistical software package (STATA Version 16.0 or later, StataCorp,

TABLE 1 Demographic characteristics of 84 SFN patients

Characteristic	n (%)
Female n (%)	54 (64.3)
Age at onset (y; mean ± SD)	49.9 ± 14.1
Age at diagnosis (y; mean ± SD)	54.7 ± 12.7
Duration of symptoms (y; mean ± SD)	4.8 ± 6.6

Abbreviation: n, number.

TABLE 2 Patient reported leading symptoms

Presenting symptom	n (%)
Length dependent	67 (79.8)
Sensory discomfort	84 (100)
Burning pain	55 (65.5)
Paresthesia	45 (53.6)
Numbness	22 (26.2)
Allodynia	21 (25.0)
Worsening during rest or at night	26 (31.3)
Autonomic symptoms	36 (42.9)

Abbreviation: n, number.

College Station, Texas, USA). Descriptive statistics for continuous variables were presented as means ± SDs. Comparisons for continuous variables among the three groups were made using the Kruskal-Wallis test. For categorical variables, results were presented as percentages. Comparisons for categorical variables were made using the Fisher exact test.

3 | RESULTS

3.1 | Demographic characteristics of study participants

The main clinical characteristics of our cohort are shown in Table 1. A total of 84 patients diagnosed with definite SFN were included. The youngest patient was 22 y old, the oldest 83 y old. The duration of symptoms at time of first contact varied considerably, from 0.2 to 39 y.

3.2 | Epidemiology

Of the 84 patients, 76 lived in our catchment area in central Switzerland. As a result, the minimum incidence over the period reviewed was at least 4.4 cases/100000 inhabitants/y (95% confidence interval: 3.5–5.5 cases/100000 inhabitants/y). The minimum prevalence using a reference population of 650,115 inhabitants would be 131.5 cases /100000 inhabitants (95% confidence interval: 103.6–164.6 cases/100000 inhabitants), if we assume that the disease is stable over 30 y (the average age of onset is around 50 y and the average life expectancy in Switzerland is around 80 y),[25] as the disease is not usually curable.

TABLE 3 Overview of the different etiologies

Etiology	n (%)
Idiopathic	30 (35.7)
Apparently autoimmune cause	29 (34.5)
Systemic aaSFN	17/29 (58.6)
Nerve-specific aaSFN	10/29 (34.5)
Organ-specific aaSFN	1/29 (3.5)
Other	1/29 (3.5)
Metabolic cause	12 (14.3)
Prediabetes	6/12 (50.0)
Diabetes mellitus type II	4/12 (33.3)
Renal insufficiency	2/12 (16.7)
More than one etiology	3 (3.6)
Other	9 (10.7)
No information	1 (1.2)

Abbreviation: n, number.

3.3 | Clinical presentation

Table 2 lists the clinical presentation of the patients. As expected, sensory discomfort was a presenting symptom in all patients. Autonomic symptoms were reported in less than half of patients.

The painDETECT questionnaire was completed by 56 (66.6%) patients. Mean pain intensity in these patients was NRS 5.1 ± 2.5, highest pain NRS 6.6 ± 2.7. The course of pain was persistent with slight fluctuations in 30.2%, persistent with pain attacks in 30.2%, pain attacks without pain between them in 26.4%, and pain attacks with pain between them in 13.2%. Pain radiated to other regions of the body in 52.3%. Burning pain was the most reported sensory disturbance (reported in 91.1% of cases), followed by tingling or prickling sensation (reported in 78.2%). The screening result was positive for neuropathic origin of pain in 48.2%, unclear in 19.6%,, and negative in 32.1%.

QSART was abnormal in 63.0% (46/73) and SSW in 53.3% (40/75) of patients.

3.4 | Etiology

The distribution of the various etiologies is shown in Table 3. Among patients with a systemic aaSFN were two with sarcoidosis, one with Caplan syndrome, two with Sjögren syndrome, nine with a rheumatologic diagnosis, two with vasculitis, and one with postural orthostatic tachycardia syndrome (POTS). The patient with an organ-specific aaSFN had Cohn's disease. Nerve-specific aaSFN

TABLE 4 Comparison of the three most frequent etiologic groups

	All	Metabolic	Apparently autoimmune	Idiopathic	*P*-value
n	71	12	29	30	
Female sex	45 (63.4)	8 (66.7)	22 (75.9)	15 (50.0)	= .118*
Age at diagnosis (y)	54.0 (46.0, 64,0)	63.5 (52.5, 70.0)	54.0 (45.0, 66.0)	52.5 (45.0, 56.0)	= .038**
Age at onset (y)	51.0 (40.5, 59.0)	59.5 (51.0, 64.0)	51.0 (43.0, 57.0)	45.8 (36.0, 55.5)	= .036**
Length-dependent SFN	55 (77.5)	11 (91.7)	21 (72.4)	23 (76.7)	= .420*
ENFD ankle (fibers/mm)	5.6 ± 2.8	3.6 ± 3.0	5.8 ± 2.7	6.3 ± 2.6	= .043
painDETECT questionnaire					
Now pain	3.5 (0.0, 5.0)	2.0 (0.0, 6.0)	4.0 (3.0, 6.0)	2.0 (0.0, 4.0)	= .293**
Maximum pain	7.0 (5.0,8.0)	7.0 (6.0, 7.0)	8.0 (6.5, 9.0)	6.0 (4.0, 8.0)	= .079**
Average pain	5.0 (3.0,7.0)	6.0 (5.0, 7.0)	5.5 (4.5, 7.0)	3.0 (3.0, 6.0)	= .060**
Course of pain					
Persistant with slight fluctuations	14 (19.7)	2 (16.7)	5 (17.2)	7 (23.3)	
Persistent with pain attacks	12 (16.9)	2 (16.7)	8 (27.6)	2(6.7)	
Pain attacks without pain between	13 (18.3)	1 (8.3)	3 (10.3)	9 (30.0)	
Pain attacks with pain between	6 (8.5)	1 (8.3)	2 (6.9)	3 (10.0)	
Missing information	26 (36.6)	6 (50.0)	11 (37.9)	9 (30.0)	
Pain radiation					
Yes	20 (28.2)	2 (16.7)	9 (31.0)	9 (30.0)	
No	18 (25.4)	4 (33.3)	8 (27.6)	6 (20.0)	
Missing information	33 (46.5)	6 (50.0)	12 (41.4)	15 (50.0)	
Pain characteristics					
Burning sensations	3.0 (2.0, 4.0)	4.0 (3.0, 4.0)	4.0 (2.0, 4.0)	3.0 (2.0, 4.0)	= .538**
Tingling or prickling	3..0 (1.0, 4.0)	2.0 (0.0, 5.0)	3.0 (2.0, 4.0)	2.0 (1.0, 4.0)	= .698**
Allodynia	2.0 (0.0, 3.5)	2.0 (1.0, 5.0)	2.0 (1.0, 4.0)	1.0 (0.0, 3.0)	= .385**
Electric shocks	2.0 (0.0, 4.0)	2.0 (1.0, 4.0)	3.0 (0.0, 4.0)	1.0 (0.0, 3.0)	= .413**
Cold/heat evokes pain	3.0 (0.0, 4.0)	3.0 (1.0, 4.0)	3.0 (1.0, 4.0)	2.0 (0.0, 3.0)	= .308**
Numbness	2.0 (0.5, 3.5)	1.5 (0.0, 4.0)	3.0 (2.0, 4.0)	2.0 (0.0, 3.0)	= .216**
Slight pressure triggering pain	1.0 (0.0, 3.0)	0.5 (0.0, 3.0)	2.0 (0.0, 3.0)	0.0 (0.0, 3.0)	= .267**
Final score	18.0 (11.0, 21.0)	19.0 (11.0, 19.0)	21.0 (13.0, 23.0)	14.0 (11.0, 20.0)	= .155**

Abbreviation: n, number.
Note: Data in n (%), mean ± SD, or median (Q1, Q3).
*Fisher exact test.
**Kruskal-Wallis test.

with elevated blood markers of dysimmunity was identified in six patients with a raised erythrocyte sedimentation rate not otherwise explained (range 17-30 mm/hr), three with elevated anti-nuclear antibodies (1:160–1:320), and one with elevated Sjögren autoantibodies (SSA/Ro 75 U/mL, normal value <7 U/mL)). One patient with aaSFN had Guillain-Barré syndrome (GBS). Other associations were Parkinson disease, human immunodeficiency virus (HIV), chronic hepatitis type C, alcohol abuse, chemotherapy, and presumed genetic causes. More than one-third of patients were diagnosed with idiopathic SFN.

Three of our study participants had more than one possible etiology: One presented with diabetes type II and chemotherapy, one with renal insufficiency and sarcoidosis and one with prediabetes, chemotherapy and elevated blood test markers for dysimmunity.

To evaluate if there were any differences regarding patient characteristics, clinical presentation (symptoms and painDETECT), and ENFD, we analyzed our cohort according to three etiologic groups: metabolic, apparently autoimmune, and idiopathic. The results can be found in Table 4. The highest proportion of women and the largest proportion of non–length-dependent SFN were found in the apparently autoimmune group. Neither the results of the QSART nor those of SSW differed in the groups. A comparison of the average pain intensity, maximum pain intensity, and pain intensity when filling in the painDETECT questionnaire is shown in Figure 2. The highest pain levels were found in the apparently autoimmune group.

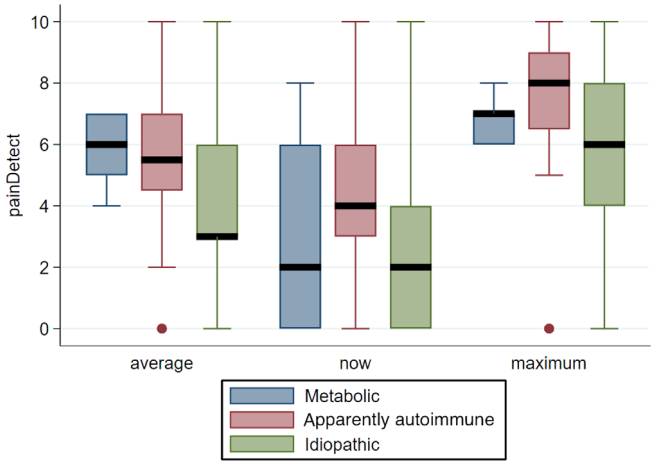

FIGURE 2 Comparison of the intensity of pain in the three groups. Average, average pain intensity in the past 4 wk; now, pain intensity when filling in the questionnaire; max, maximum pain intensity in the past 4 wk [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

The demographic characteristics of the study participants were similar to the literature.[8] The incidence rate in our cohort was lower than that of the Dutch study.[3] This could be caused by several factors, such as differences in the inclusion criteria and in calculation. Only those patients who live in the catchment area were included for analyses. This ensures that our data are not inflated from being a referral center. Another difference is the larger and more rural area of central Switzerland compared to the catchment area of the Small Fibre Neuropathy Centre of the Maastrich University Medical Centre. The calculated minimum prevalence, on the other hand, is higher, due to different calculation approaches. Since our center is the sole institution in central Switzerland that diagnoses definite SFN by a skin biopsy, we presume to cover most of the diagnoses. We are aware of the fact that there must be primary physicians who are confident a patient has an SFN, and so provide their patient with that diagnosis in their medical records without referring them to us. Our data provide the incidence and prevalence of known/diagnosed patients with a definite SFN. For an estimation of the hidden cases ratio, a different, larger study would be needed.

Sensory discomfort was the most frequently mentioned symptom in our patients. Neuropathic pain could be overestimated due to the fact that patients with pain are more likely to seek medical care than patients with negative symptoms, such as numbness.[26]

Since the term SFN was coined in 1992,[27] it has become better defined, but there are still no clear diagnostic criteria available for non–length-dependent SFN. Controversially, it has been suggested that SFN is a non–length-dependent terminal axonopathy with most frequent onset in the distal extremities.[28] Patients with a non–length-dependent SFNs tend to be under-recognized, due to the heterogeneous presentation.[29] Khan et al. showed that non–length-dependent SFN is more likely in women and is more often associated with immune-mediated conditions than the length-dependent pattern.[6] This tendency was also observed in our cohort.

The EMLA stimulated wrinkling was previously found to have a sensitivity of 81.6% and specificity of 74.7% in detecting pathologic ENFD.[24] In our cohort, the SSW was abnormal in only about half of the patients and showed a moderate correlation with the abnormal ENFD of our patients.

Extensive work-up resulted in two thirds of the patients being assigned an etiological association and enabling specific treatment options. Nevertheless, the single largest group of patients could not be etiologically defined. This underlines the importance of further research in etiological identification. According to Oaklander et al., a potential cause can be found through blood screening in 30%–50% of patient with initially idiopathic SFN. She indicates that the tests to be performed will depend on the pre-test probability of an abnormal test result, the availability of the test, and the cost.[30] The study in a Nordic population with very low numbers of Fabry disease in SFN makes this an unlikely diagnosis in our population.[31] In the cohort of Devigili et al., in one quarter of the patients with an initially idiopathic SFN, a possible cause was found at 2-y follow-up.[14] This suggests that patients should be clinically followed up to identify possible causes over time. It is also important to note that intensive glycemic control in patients with diabetes mellitus can in itself lead to therapy-induced neuropathy.[32]

In patients with idiopathic SFN, treatment is symptomatic. A recent randomized, double-blind, controlled trial of patients with painful idiopathic SFN showed that IVIG treatment has no significant effect on pain.[11]

Effective pain control remains a challenge for many patients with SFN, especially if there is no known underlying disease or the underlying disease is not treatable. Further study with more participants and standardized data collection is necessary to evaluate treatment efficacy and long-term outcome. The painDETECT questionnaire is a verified test for pain documentation[13] and has the advantage of providing a form of quantification for treatment response and disease progression in patients with SFN.[33,34]

The limitations of this study are the retrospective study design and lack of systematic collection of specific variables, such as the presence of autonomic symptoms, data concerning drug therapy, and response rate of medications. If autonomic symptoms were not reported spontaneously by the patient, they were not recorded. Considering that such symptoms are often infrequent and mild,[26] it would be helpful to introduce a tool to detect autonomic symptoms in a standardized manner. By restricting our study population to patients with definite SFN with an abnormal ENFD, it is possible that we excluded patients with SFN and normal ENFD, since studies show a sensitivity of 90% and a specificity of 95% for detecting SFN by ENFD.[35] As our center is a referral hospital, a bias toward more complex cases with an above-average number of patients with apparently autoimmune causes is possible. This would explain why our proportion of patients with metabolic causes or toxic neuropathies is lower than one might expect, since these diseases are not infrequent. Another limitation is the lack of genetic testing in our cohort. This

study was neither designed nor powered to detect differences between groups of different etiologies as it does not apply any adjustments for multiplicity. Therefore, the results need to be interpreted with due caution.

Although the incidence and prevalence rates are high for this relatively recently defined disease, we expect this will further rise with increased awareness of SFN.

In conclusion, this study indicates significant incidence and prevalence rates of SFN in Switzerland. SFN is still a relatively unstudied disease that can vary greatly in its symptoms, severity, and etiology. We anticipate increased awareness of this developing field.

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DISCLOSURE OF CONFLICTS OF INTEREST

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data is kept at the research area of the Department of Neurology at the Luzerner Kantonsspital

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Chan AC, Wilder-Smith EP. Small fiber neuropathy: getting bigger! *Muscle Nerve*. 2016;53:671-682.
2. Tesfaye S, Boulton AJ, Dyck PJ, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care*. 2010;33:2285-2293.
3. Peters MJ, Bakkers M, Merkies IS, Hoeijmakers JG, van Raak EP, Faber CG. Incidence and prevalence of small-fiber neuropathy: a survey in The Netherlands. *Neurology*. 2013;81:1356-1360.
4. Terkelsen AJ, Karlsson P, Lauria G, Freeman R, Finnerup NB, Jensen TS. The diagnostic challenge of small fibre neuropathy: clinical presentations, evaluations, and causes. *Lancet Neurol*. 2017;16:934-944.
5. Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. *Lancet Neurol*. 2014;13:924-935.
6. Khan S, Zhou L. Characterization of non-length-dependent small-fiber sensory neuropathy. *Muscle Nerve*. 2012;45:86-91.
7. Haroutounian S, Todorovic MS, Leinders M, et al. Diagnostic criteria for idiopathic small fiber neuropathy: a systematic review. *Muscle Nerve*. 2021;63:170-177.
8. de Greef BTA, Hoeijmakers JGJ, Gorissen-Brouwers CML, Geerts M, Faber CG, Merkies ISJ. Associated conditions in small fiber neuropathy - a large cohort study and review of the literature. *Eur J Neurol*. 2018;25:348-355.
9. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14:162-173.
10. Liu X, Treister R, Lang M, Oaklander AL. IVIg for apparently autoimmune small-fiber polyneuropathy: first analysis of efficacy and safety. *Ther Adv Neurol Disord*. 2018;11:17562856 17744484.
11. Geerts M, de Greef BTA, Sopacua M, et al. Intravenous immunoglobulin therapy in patients with painful idiopathic small fiber neuropathy. *Neurology*. 2021;96:e2534-e2545.
12. Statistik der Bevölkerung und der Haushalte. 2018. Bundesamt für Statistik Web site. https://www.bfs.admin.ch/bfs/de/home/statistiken/kataloge-datenbanken/tabellen.assetdetail.9486012.html. Accessed December 7, 2019.
13. Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin*. 2006;22:1911-1920.
14. Devigili G, Tugnoli V, Penza P, et al. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. *Brain*. 2008;131:1912-1925.
15. Lauria G, Cornblath DR, Johansson O, et al. EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. *Eur J Neurol*. 2005;12:747-758.
16. Provitera V, Gibbons CH, Wendelschafer-Crabb G, et al. A multi-center, multinational age- and gender-adjusted normative dataset for immunofluorescent intraepidermal nerve fiber density at the distal leg. *Eur J Neurol*. 2016;23:333-338.
17. American Diabetes A. Executive summary: standards of medical care in diabetes–2014. *Diabetes Care*. 2014;37(Suppl 1):S5-S13.
18. Diabetes Type 2. Diabetesschweiz. https://www.diabetesschweiz.ch/ueber-diabetes/diabetesformen/diabetes-typ-2.html. Accessed April 2, 2021
19. Thaisetthawatkul P, Fernandes Filho JA, Herrmann DN. Contribution of QSART to the diagnosis of small fiber neuropathy. *Muscle Nerve*. 2013;48:883-888.
20. Blackmore D, Siddiqi ZA. Diagnostic criteria for small fiber neuropathy. *J Clin Neuromuscul Dis*. 2017;18:125-131.
21. Wilder-Smith EP. Water immersion wrinkling–physiology and use as an indicator of sympathetic function. *Clin Auton Res*. 2004;14:125-131.
22. Wilder-Smith EP. Stimulated skin wrinkling as an indicator of limb sympathetic function. *Clin Neurophysiol*. 2015;126:10-16.
23. Teoh HL, Chow A, Wilder-Smith EP. Skin wrinkling for diagnosing small fibre neuropathy: comparison with epidermal nerve density and sympathetic skin response. *J Neurol Neurosurg Psychiatry*. 2008;79:835-837.
24. Wilder-Smith EP, Guo Y, Chow A. Stimulated skin wrinkling for predicting intraepidermal nerve fibre density. *Clin Neurophysiol*. 2009;120:953-958.
25. Lebenserwartung, 1981-2019. Bundesamt für Statistik Web site. https://wwwbfsadminch/bfs/de/home/statistiken/bevoelkerung/geburten-todesfaelle/lebenserwartungassetdetail14387096html
Updated September 29, 2020. Accessed October 31, 2020.
26. MacDonald S, Sharma TL, Li J, Polston D, Li Y. Longitudinal follow-up of biopsy-proven small fiber neuropathy. *Muscle Nerve*. 2019;60:376-381.
27. Stewart JD, Low PA, Fealey RD. Distal small fiber neuropathy: results of tests of sweating and autonomic cardiovascular reflexes. *Muscle Nerve*. 1992;15:661-665.
28. Khoshnoodi MA, Truelove S, Burakgazi A, Hoke A, Mammen AL, Polydefkis M. Longitudinal assessment of small fiber neuropathy: evidence of a non-length-dependent distal Axonopathy. *JAMA Neurol*. 2016;73:684-690.
29. Gemignani F, Giovanelli M, Vitetta F, et al. Non-length dependent small fiber neuropathy. A prospective case series. *J Peripher Nerv Syst*. 2010;15:57-62.

30. Oaklander AL, Nolano M. Scientific advances in and clinical approaches to small-fiber polyneuropathy: a review. *JAMA Neurol*. 2019;76:1240-1251.
31. Samuelsson K, Radovic A, Press R, et al. Screening for Fabry disease and hereditary ATTR amyloidosis in idiopathic small-fiber and mixed neuropathy. *Muscle Nerve*. 2019;59:354-357.
32. Gibbons CH, Freeman R. Treatment-induced diabetic neuropathy: a reversible painful autonomic neuropathy. *Ann Neurol*. 2010;67(4):534-541.
33. Baron R, Treede RD, Birklein F, et al. Treatment of painful radiculopathies with capsaicin 8% cutaneous patch. *Curr Med Res Opin*. 2017;33:1401-1411.
34. Schukro RP, Oehmke MJ, Geroldinger A, Heinze G, Kress HG, Pramhas S. Efficacy of duloxetine in chronic Low Back pain with a neuropathic component: a randomized, double-blind, placebo-controlled crossover trial. *Anesthesiology*. 2016;124:150-158.
35. Themistocleous AC, Ramirez JD, Serra J, Bennett DL. The clinical approach to small fibre neuropathy and painful channelopathy. *Pract Neurol*. 2014;14:368-379.

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