ORIGINAL ARTICLE

Associated conditions in small fiber neuropathy – a large cohort study and review of the literature

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Background and purpose: Small fiber neuropathy (SFN) is a common disorder leading to neuropathic pain and autonomic symptoms. The objective of this study was to investigate associated conditions in a large cohort of SFN patients and compare the prevalence to healthy individuals.

Methods: A total of 921 patients with pure SFN were screened according to a standardized comprehensive diagnostic algorithm and compared with literature findings.

Results: No associated condition could be found in 53% of the patients. Autoimmune diseases, sodium channel gene mutations, diabetes mellitus including glucose intolerance, and vitamin B12 deficiencies were more prevalent than reported literature findings, followed by alcohol abuse, chemotherapy, monoclonal gammopathy of undetermined significance, and haemochromatosis. In patients who were already known with a possible underlying condition at screening, additional underlying conditions were still found in another 26.7% of patients.

Conclusions: Based on these results, it is recommended that patients with pure SFN are screened at least for autoimmune diseases, sodium channel gene mutations, diabetes mellitus including glucose intolerance, and vitamin B12 deficiency, even when they already have a potential underlying condition at referral.

Introduction

Small fiber neuropathy (SFN) affects the thinly myelinated Aδ-fibers and the unmyelinated C-fibers and leads to excruciating neuropathic pain and autonomic symptoms [1] with a negative impact on quality of life expectations [2]. The diagnosis of pure SFN is based on typical complaints, combined with abnormal intraepidermal nerve fiber density in skin biopsy and/or abnormal temperature threshold testing levels, without signs of large nerve fiber involvement [1,3]. SFN has been described in several conditions, such as diabetes mellitus and sodium channel gene mutations [1,4]. Management is mostly based on symptomatic treatment. Knowing which conditions are associated with SFN is important, since some conditions are potentially treatable. Most patients diagnosed with SFN undergo many diagnostic tests to find an underlying cause, leading to high burden for patients and high health-related costs [5]. Illustratively, it was shown that Fabry disease was not found in 725 patients with isolated SFN, even though it has been mentioned in the literature as a potential underlying illness [6]. This may also apply to other conditions. A better selection of associated conditions may result in a more targeted diagnostic workup with lower costs.

The aims of this study were to investigate associated conditions in a large cohort of patients with pure SFN and to compare the prevalence with literature reports on these conditions in healthy persons. Finally, recommendations are provided for a more targeted diagnostic workup in patients with pure SFN.

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Methods

Patients

From January 2010 to December 2015, all consecutive patients fulfilling the diagnosis criteria for SFN at our SFN Center, Maastricht University Medical Center+ (MUMC+), were included in this study. MUMC+ serves as a tertiary referral center for SFN in the Netherlands. Records on complaints and medical history were collected in a standardized fashion as described earlier [7]. To confirm the diagnosis of SFN, patients needed to have the typical complaints of SFN combined with a reduced intraepidermal nerve fiber density in skin biopsy [8] and/or abnormal temperature threshold testing [9] without large nerve fiber involvement based on neurological examination (normal muscle strength, vibration sense, and tendon reflexes) and nerve conduction studies.

To find possible underlying conditions, blood and urine analyses, and a chest X-ray were performed (Table 1). The selection of these additional investigations was based on a literature review [1,10–12] and on corresponding diagnostic guidelines (see below).

Underlying conditions

The following underlying conditions were screened for: alcohol abuse, diabetes mellitus including glucose intolerance, haemochromatosis, autoimmune diseases, monoclonal gammopathy of undetermined significance, sodium channel gene mutations, and vitamin B12

Table 1 Diagnostic tests performed in patients referred to the SFN Center

Kind of test		Disease investigated	Abnormal values
X-ray	Chest X-ray	Sarcoidosis	
Blood samples	Glucose	Diabetes mellitus	Two sober plasma levels of ≥ 7.0 mmol/l or the combination of a sober plasma glucose level of ≥ 7.0 mmol/l, a random plasma glucose level of ≥ 11.1 mmol/l with complaints of hyperglycemia, or a level of ≥ 11.1 mmol/l after 120 min
	Glucose tolerance test	Impaired glucose tolerance	Sober level of < 7.0 mmol/l and a level of ≥ 7.8 and < 11.1 mmol/l after 120 min
	Cholesterol	Hypercholesterolemia	Low density lipoprotein value above 3.1 mmol/l, high density lipoprotein value lower than 0.9 mmol/l and triglyceride value above 2.1 mmol/l
	Liver function	Hepatic impairment	Increased liver functions
	Kidney function	Renal insufficiency	Glomerular filtration rate < 30
	Thyroid function	Hypothyroid or hyperthyroid function	Increased or decreased thyroid stimulating hormone/thyroxin
	Vitamin B1	Vitamin B1 deficiency	<100 nmol/l
	Vitamin B6	Vitamin B6 toxicity	>200 nmol/l
	Vitamin B12	Vitamin B12 deficiency	<148 pmol/l
	Anti-tissue transglutaminase	Coeliac disease	Present
	Anti-extractable nuclear antigen antibodies	Sjogren's disease	Present
	Antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, and soluble Interleukin-2 receptor	Other autoimmune diseases	Present or soluble IL-2 receptor above 700 U/l
	Monoclonal gammopathy	Monoclonal gammopathy of undetermined significance	Present
	Borrelia burgdorferi (immunoglobulin I and M)	Lyme's disease	Present
	Anti-human immunodeficiency virus 1 and 2	Human immunodeficiency virus	Present
	Alpha-galactosidase A activity and alpha-galactosidase A gene	Fabry disease	< 30 mmo/l and variants class 3, 4 or 5.
	SCN9A, SCN10A and SCN11A gene	Sodium channel gene mutations	Variants with uncertain clinical significance, possibly pathogenic, probably pathogenic or pathogenic variants
Urine sample	Lysosomal globotriaosylceramide	Fabry disease	>0 nmol/mmol creatinine

SCN, sodium voltage-gated channels.

deficiency. The definitions of these underlying conditions are summarized in Appendix S1.

Literature comparison

Literature research on potential conditions related to SFN was performed in the PubMed database using the keywords 'small fiber neuropathy', 'small fibre neuropathy', 'neuropathy', 'painful neuropathy', 'etiology', in combination with the different known conditions. Also Dutch guidelines were searched for prevalence of the conditions in healthy controls.

Statistics

Patients' characteristics were expressed as mean with standard deviation when data were normally distributed. When not normally distributed, the median and interquartile range were calculated. Frequencies between two groups were compared by using the chi-squared test. A stepwise approach was conducted: the prevalence of conditions potentially related to SFN was measured and subsequently compared with reported prevalence in healthy controls. Analyses were performed using SPSS (Version 23.0, SPSS Inc., Chicago, IL, USA).

Standard protocol approvals, registrations and patient consents

The MUMC+'s Medical Ethics Committee and Board of Directors approved this study. According to the Code of Conduct for the Use of Data in Health Research [13], for this type of retrospective study informed consent does not need to be obtained if the data are used anonymously and patients are given the opportunity to object to the use of their medical and personal data for research (which is the case in the MUMC+).

Results

Of 1275 patients screened, the diagnosis of pure SFN could be established in 72% (n = 921; Fig. 1). The characteristics of SFN patients included in the study are shown in Table 2. After the diagnostic workup, no underlying condition was found in 488 patients (53%).

Results of the total cohort of patients with pure SFN

In the total cohort, 696 patients (75.6%) did not have known SFN-related comorbidities before the diagnostic workup.

The diagnostic workup (n = 921) showed immunological conditions in 175 patients (19%), including sarcoidosis (3.0%), Sjogren's disease (1.3%), coeliac disease (0.5%), other autoimmune diseases (8.8%) and non-specific abnormal immunological laboratory findings (6.1%). Eight patients had two or more of these conditions. The other most frequently found associated conditions with available prevalence numbers in the general population were variants in *SCN9A* (8.5%), *SCN10A* (4.8%) and *SCN11A* (3.4%), diabetes mellitus (7.7%), vitamin B12 deficiency (4.7%), alcohol abuse (3.0%), chemotherapy (2.2%), monoclonal gammopathy of undetermined significance (MGUS) (1.4%) and haemochromatosis (0.3%) (Fig. 2). The MGUS subtypes included IgG-MGUS (62%), IgM-MGUS (15%), IgA-MGUS (15%) and a biclonal-MGUS (8%, IgG and IgA). The glucose intolerance test was performed in 493 of these patients. In total, 48 patients were found with glucose intolerance (9.7%). The prevalences of the other conditions screened for are shown in Appendix S2. In 488 patients (53%), no underlying conditions were found despite extensive laboratory testing (idiopathic SFN). Of the above-mentioned conditions, only variants in the SCN9A-gene were found significantly more often in patients with a non-length-dependent pattern of SFN compared to patients with length-dependent complaints (12.4% vs. 6.9%, P value 0.014), whereas all other conditions showed no differences.

Results for the group of SFN patients without known associated conditions at presentation

Of the patients without comorbidity at presentation (n = 696), abnormal immunological laboratory findings were present in 5.9%, variants in *SCN9A* in 9.6%, *SCN10A* in 4.5%, *SCN11A* in 3.4%, diabetes mellitus in 3%, vitamin B12 deficiency in 0.75% and MGUS in 0.6%. In 379 of these patients, glucose intolerance was tested and this was diagnosed in 35 patients (9.2%). In total, associated conditions were found in 208 of these patients (29.9%) with additional diagnostic tests.

Results for the group with known comorbidities at presentation

In the group of patients who were already known to have one or more comorbidities (n = 225) at presentation, new abnormalities were found: abnormal immunological laboratory findings (5.8%), variants in *SCN9A* (4.9%), *SCN10A* (5.8%) and *SCN11A* (3.1%), and diabetes mellitus (2.7%). In 114 of these patients, glucose intolerance was tested and was

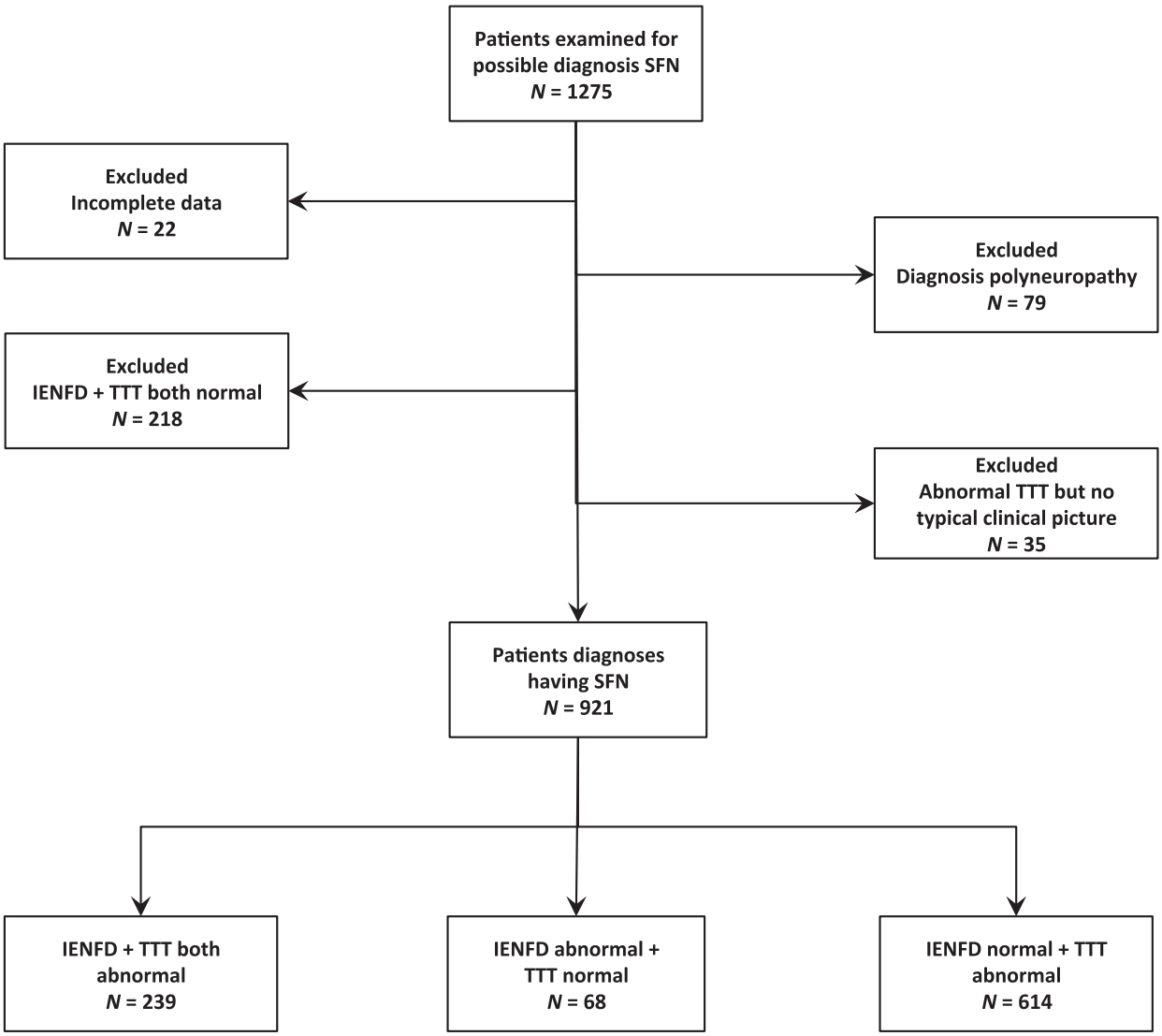

Figure 1 Flowchart of inclusion/exclusion. IENFD, intraepidermal nerve fiber density; SFN, small fiber neuropathy; TTT, temperature threshold testing.

Table 2 Characteristics of patients with confirmed diagnosis of SFN

	Total, n = 921
Female (%)	532 (57.8)
Age at visit, median (IQR)	53 (44–61.5)
Age at onset, median (IQR)	47 (38–57)
Duration of complaints, median (IQR)	3 (2–7)
Diagnosis SFN	
Abnormal TTT (%)	614 (66.7)
Abnormal skin biopsy (%)	68 (7.4)
Abnormal TTT and skin biopsy (%)	239 (26)

IQR, interquartile range; SFN, small fiber neuropathy; TTT, temperature threshold testing.

diagnosed in 13 patients (11.4%). In total, additional associated conditions were found in 60 patients (26.7%) with our diagnostic panel.

Discussion

In our cohort of 921 patients with pure SFN, an underlying condition was found in 433 patients (47%). The most prevalent conditions were immunological conditions, sodium channel gene mutations, diabetes mellitus including glucose intolerance, and vitamin B12 deficiency, and at least these entities are suggested to be tested in the diagnostic workup of potential SFN. Even if comorbidity was present at presentation, still other associated conditions were found in 26.7% after diagnostic testing. After thorough workup, 53% of patients had no underlying cause (idiopathic pure SFN), which is in conformity with the literature [11,14]. A recent study also described a high prevalence of immunological

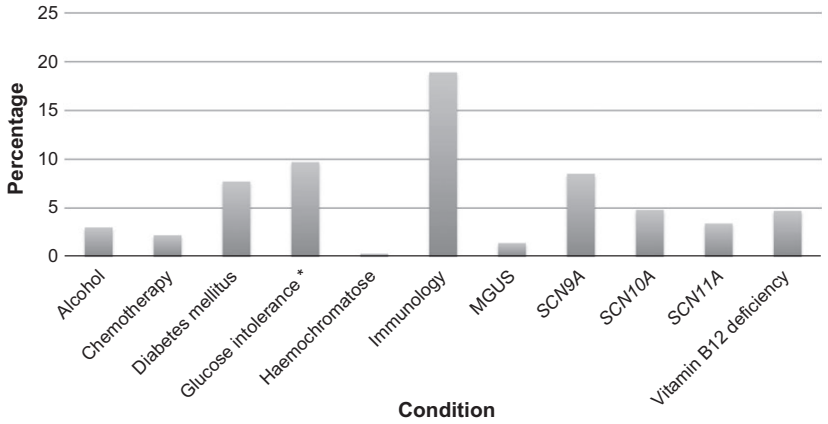

Figure 2 Prevalence of possible underlying causes in patients with SFN (n = 921). *Glucose intolerance was only tested in 493 patients instead of 921. Immunology: sarcoidosis, Sjogren's disease, coeliac disease, other autoimmune diseases and abnormal immunological laboratory findings (antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, monoclonal gammopathy, soluble interleukin-2 receptor, anti-tissue transglutaminase and anti-extractable nuclear antigen antibodies). MGUS, monoclonal gammopathy of undetermined significance; SCN, sodium voltage-gated channels.

abnormalities, but no association with diabetes mellitus or vitamin B12 deficiency, possibly due to a smaller sample size and different criteria for the diagnosis of SFN [15].

Immunological abnormalities

Immunological conditions may affect nerve fibers [16] and were found in 12.9% (n = 119) of patients, whereas another 6.1% of patients had one or more abnormal immunological laboratory findings. The overall prevalence of autoimmune diseases in the Netherlands is around 3%−6% [17], which is much lower than in our cohort.

Also the prevalence of sarcoidosis is higher in our cohort than in the general European population (3.0% vs. 0.005%−0.03%) [18]. However, the prevalence of sarcoidosis in our cohort might be an overestimation, because until 5 years ago MUMC+ was a tertiary referral center for patients with sarcoidosis.

Sjogren's disease was present in 1.3% of our SFN patients compared to a prevalence in the general population of 0.1%−4.8%, and thus within the reported limits in the general population [19]. Of our patients, 0.5% had coeliac disease, with a prevalence of recognized coeliac disease of 0.016% and non-recognized coeliac disease around 0.35% in the Netherlands [20].

Sodium channel gene mutations

In 16.7% of SFN patients a sodium channel gene variant was found. The sodium channels $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$, coded by *SCN9A, SCN10A* and *SCN11A* respectively, are all preferentially expressed in peripheral nerves [21]. Mutations in the SCN9A-, SCN10A-, and SCN11A-gene, showing electrophysiological changes in the corresponding channel, have been described by others and us in patients with SFN [7,22,23]. Although the exact mechanism for axonal degeneration is not completely clear, it is plausible that DRG neuron hyperexcitability results in neuropathic pain [24]. The results in this cohort are comparable with the results that were published earlier in a smaller cohort (n = 393) [4], although prevalence is lower than the results for *SCN9A*-variants in a small cohort of patients with biopsy-confirmed idiopathic SFN [7]. *SCN9A*-variants were more frequently found in the patients with a non-length-dependent pattern, which is in line with the description of different clinical patterns in patients with *SCN9A*-mutations and SFN [25].

Diabetes mellitus

Diabetes mellitus was found in 7.7%, of which most (90.1%) were type 2 diabetes. Peripheral neuropathy is the most common complication of diabetes mellitus with lifetime prevalence up to 50% [26]. The prevalence of diabetes is around 6% in the Netherlands [27]. Our proportion found in SFN (7.7%) is higher than the prevalence of patients in the Netherlands. The prevalence in our cohort probably is an underestimation, as most patients with painful diabetic neuropathy will not be referred to our center because painful neuropathy is a well-known complication of diabetes mellitus.

In addition, as has been suggested in the literature, the glucose tolerance test was also abnormal in 9.7%

of the patients, adding to the underlying conditions of SFN [28,29].

Vitamin B12 deficiency

Vitamin B12 deficiency was present in 4.7% of SFN patients. The prevalence of vitamin B12 deficiency is less than 3% in the general population aged between 20 and 39 years, and increases gradually up to 10% or higher in people of 70 years or older. The prevalence of vitamin B12 deficiency in our SFN population was higher than in the general population. According to general guidelines, vitamin B12 deficiency was diagnosed when serum vitamin B12 was below 148 pmol/l or when there was a history of vitamin B12 deficiency for which patients were treated. Homocysteine or methylmalonic acid was not assessed, which may have led to underestimation of functional vitamin B12 in patients with serum vitamin B12 of 148−258 pmol/l.

Alcohol abuse

In our cohort 3.0% of the patients (n = 28) reported an alcohol consumption of >5 IU/day. As people tend to underreport their alcohol intake, this may be an underestimation as well [30]. The typical presentation of alcohol-related peripheral neuropathy is a painful, burning neuropathy and autonomic instability [31]. In the Netherlands, the estimated prevalence of alcohol abuse is 0.75% of adults between 18 and 65 years old [30]. The prevalence of alcohol abuse is higher in our cohort of patients with pure SFN suggesting an association.

Chemotherapy

Chemotherapy-induced peripheral neuropathy is a well-known adverse event of several chemotherapeutic agents, and was present in 2.2% (n = 20) of our patients with pure SFN. Different prevalences are mentioned, between 17% and 88%, for different ages, different grades of neuropathies and different agents [32]. The prevalence of chemotherapy found in our cohort is probably underestimated, as these patients are usually not referred because the neuropathy is considered an expected adverse event of the treatment.

Monoclonal gammopathy of undetermined significance

In our cohort, 1.4% of patients were known with MGUS. The etiology of MGUS in peripheral neuropathy is not very well understood [33]. In healthy subjects (above 45−50 years old) MGUS is found in 3.2%−3.5% [34,35]. The prevalence of monoclonal gammopathy increases with age [36]. The prevalence of MGUS in our population is lower than the prevalence found in the general population. However, the overall prevalence is based on subjects between 45 and 50 years old, and in our population there were patients ranging from 11 to 85 years.

Haemochromatosis

Three patients (0.3%) had haemochromatosis. In northern European countries, 0.4% of the people are homozygotes for the C282Y allele [37]. This means that the prevalence in the whole population is equal to the prevalence in patients with SFN, which makes the association between SFN and haemochromatosis less likely.

Patients with associated conditions at presentation

Despite having an associated condition at presentation, additional associated conditions were found in 26.7% of our SFN cohort. Finding other diseases might lead to new treatment possibilities for these patients, and possibly relieve complaints or prevent disease progression.

Pathophysiology

This study shows that some of the associated conditions are more prevalent in patients with pure SFN compared to healthy persons. However, the underlying pathophysiology is still unclear in most of these conditions. It would be of interest to investigate these specific conditions in detail in animal models, to search for underlying mechanisms. This knowledge would also stimulate the development of targeted therapy. Better treatments would lead to reduction of pain, and therefore to lower health costs [5].

Conclusion

Autoimmune diseases, sodium channel gene mutations, diabetes mellitus including glucose intolerance, and vitamin B12 deficiency are the most common underlying conditions in patients with pure SFN; despite a thorough workup no underlying condition could be found in 53% of the SFN patients. The prevalence of alcohol abuse, autoimmune diseases, diabetes mellitus including glucose intolerance, and vitamin B12 deficiencies seems higher in our population of patients with pure SFN than found in the general population. Moreover, the prevalence of SFN is much higher in patients who received chemotherapy compared to the prevalence of SFN in the Netherlands. For these conditions a causal relationship with small nerve fiber damage is suspected. Further research is needed to explore the exact pathophysiological mechanisms. Although some patients are

already known with an underlying condition at presentation, it is still recommended that all patients with pure SFN are tested for diabetes mellitus including glucose intolerance, autoimmune diseases, sodium channel gene mutations, and vitamin B12 deficiency. Testing for rarer underlying conditions can be considered in SFN, based on specific signs or symptoms.

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Disclosure of conflicts of interest

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Definitions of underlying conditions.
Appendix S2. Prevalence of other conditions.

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