Small fiber neuropathies

REVIEW

Small fiber neuropathies: expanding their etiologies

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Purpose of review
Several conditions have been associated with the development of small fiber neuropathy (SFN). The list of metabolic, immune-mediated, infectious, toxic, drugs-related, and hereditary conditions is still growing and various hypotheses are made about the underlying pathophysiological mechanisms. Understanding these processes is important to provide new targets for treatment. In addition, the specific SFN phenotype can provide direction for the underlying etiology. This review discusses the latest developments concerning the expanding etiologies in SFN.

Recent findings
In the past 18 months, special attention has been paid to immunological etiologies, partly due to the coronavirus disease 2019 pandemic, but also new auto-antibodies in SFN have been demonstrated. Identifying patients with immune-mediated SFN can be challenging, since contrary to the classical distal sensory phenotype, a nonlength-dependent pattern is more common.
Besides the etiologies of classical SFN, small fiber pathology is increasingly described in diseases without the typical neuropathic pain features of SFN, sometimes called syndromic SFN. However, the clinical relevance is not yet fully understood.

Summary
The expansion of the etiologies of SFN continues and brings more insight in possible targets for treatment. The clinical presentation may vary as a result of the underlying condition.

Keywords
etiology, immune-mediated, small fiber neuropathy, small fiber pathology

INTRODUCTION

Small fiber neuropathy (SFN) is a peripheral nerve condition in which the thin myelinated Aδ- and unmyelinated C-fibers are damaged. In classical SFN, the clinical picture is characterized by a length-dependent pattern of positive and negative sensory symptoms, including neuropathic pain, allodynia, hyperalgesia, and pinprick or thermal hypoesthesia. In addition, autonomic complaints may be present. In pure SFN, signs of large nerve fiber dysfunction are excluded, both in clinical examination and nerve conduction studies [1–3]. The diagnostic workup for SFN consists of a skin biopsy for determination of the intraepidermal nerve fiber density (IENFD) at the distal leg and quantitative sensory testing to investigate the thermal sensation. After the diagnosis SFN is made, at least additional laboratory tests and a chest X-ray will be performed to search for possible associated conditions, since some of them are treatable [4]. The last decades, the list of possible underlying causes has been grown rapidly (Table 1). The acquired etiologies can be classified into metabolic, immune-mediated, infectious, toxic, and drugs-related conditions [4–6]. In particular, autoimmune diseases, diabetes mellitus including glucose intolerances and vitamin B12 deficiencies are more prevalent in patients with SFN compared to the general population [4]. Some of these conditions can also cause a pure large nerve fiber neuropathy or mixed-fiber neuropathy. In addition, the last decade, the knowledge of hereditary causes of SFN is increasing, with a special focus on sodium channelopathies. In about 15% of patients a (potentially) pathogenic voltage gated sodium channel (VGSC) gene variant in *SCN9A*, *SCN10A* or *SCN11A* can be

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KEY POINTS

- The etiologies of SFN can be classified into metabolic, immune-mediated, infectious, toxic, drugs-related, and hereditary conditions.
- In immune-mediated SFN a nonlength-dependent sensory pattern is more common than the classical distal phenotype.
- Immune-mediated SFN is related to underlying systemic diseases and various auto-antibodies, or can develop postinfectious and postvaccination.
- Small fiber pathology is increasingly described in diseases without the typical SFN phenotype, including neurodegenerative disorders and various pain syndromes.

found [4,7]. Since erythromelalgia and warmth-induced pain are the only discriminative clinical features between SFN patients with and without VGSC variant, genetic screening should be considered in all patients with pure SFN, independently of the symptoms and signs [7]. Targeted treatment with sodium channel blockers has already shown promising results [8,9▪]. Despite the screening for several diseases, in more than 50% of cases in which symptoms of SFN are the presenting complaints, no underlying condition can be found and is therefore considered as idiopathic SFN [4].

The expansion of the etiologies of SFN continues and several hypotheses are made about the pathophysiological mechanisms. Understanding these processes, will provide new targets for treatment. In recent years, special attention has been paid to immunological etiologies, partly due to the coronavirus disease 2019 (COVID-19) pandemic. Identifying patients with immune-mediated SFN can be challenging, since contrary to the classical distal sensory phenotype, a nonlength-dependent pattern is more common [10▪▪]. Besides, small fiber pathology is increasingly described in diseases without the typical neuropathic pain features of SFN, sometimes called syndromic SFN [5]. The clinical relevance is not yet fully understood.

This paper will provide an updated review of the developments in the etiologies of SFN over the past 18 months.

IMMUNE-MEDIATED SMALL FIBER NEUROPATHY

Immune-mediated SFN can develop in different circumstances. It can be a manifestation of an underlying systemic disease, like sarcoidosis [11▪,12▪] or Sjögren syndrome [13▪,14▪]. In addition, various auto-antibodies have been linked to SFN, in the absence of systemic diseases [15▪,16▪▪,17▪▪]. Besides, postinfectious and postvaccination cases of SFN have been described, in which immune-mediated mechanisms are supposed to be causative [18▪,19▪,20▪,21▪,22▪,23▪,24▪,25▪,26▪].

Although immune-mediated SFN can present with a length-dependent phenotype, a nonlength dependent pattern with a proximal, patchy, asymmetrical or diffuse sensory distribution, probably caused by a ganglionopathy of the small neurons of the dorsal root ganglion neurons, is often associated with an underlying immunological disease [10▪▪] (Fig. 1). A disadvantage of the standard diagnostics of SFN in diagnosing nonlength dependent SFN, is the distal site the skin biopsy is taken for determination of the IENFD. In case of a proximal sensory distribution, the distal skin biopsy can be normal, potentially unjustified rejecting the diagnosis SFN. To date, normative values for proximal IENFD are not available [10▪▪].

When immune-mediated SFN is suspected, immunotherapy seems to be the treatment of first choice. Several case reports about SFN with an underlying systemic disease showed variable positive results of treatment with intravenous immunoglobulins (IVIG), plasma exchange, high dosed steroids or biologicals [10▪▪,11▪,13▪]. However, randomized controlled trials in these patient groups are lacking. Because immunologic mechanisms have been speculated also to contribute to idiopathic SFN, a double-blind randomized controlled trial evaluating the efficacy and safety of IVIG versus placebo in patients with idiopathic SFN has been performed recently. No significant effect on pain or other SFN related symptoms was shown in patients treated with IVIG, compared to the placebo group [27▪]. This does not mean that IVIG is not effective in any form of immune-mediated SFN. More knowledge about the exact etiologies and pathophysiological mechanisms in the different forms of immune-mediated SFN, will allow the clinicians to choose for more targeted treatment with probable higher success rates.

Systemic diseases

Sarcoidosis is one of the systemic diseases, in which the association with SFN has been quite clear for many years [11▪]. In contrast to the rare granulomatous neuropathies, with granulomatous inflammation and signs of perineuritis in nerve biopsies, SFN in much more common in sarcoidosis and considered to be the result of a systemic immune-mediated inflammation. To identify the clinical and histological correlates of SFN in sarcoidosis patients, a

Table 1. Associated conditions in small fiber neuropathy.

Acquired	
Metabolic	
	Diabetes mellitus
	Impaired glucose tolerance
	Hyperlipidemia
	Hypothyroidism
	Vitamin B12 deficiency
	Folate deficiency
	Metabolic syndrome
Immune-mediated	
	Sarcoidosis
	Sjögren syndrome
	Celiac disease
	Systemic lupus erythematosus
	Monoclonal gammopathy
	Inflammatory bowel disease
	Paraneoplastic
	Auto-antibodies
	Postinfectious
	Postvaccination
Infectious	
	Human Immunodeficiency Virus
	Hepatitis C
	Lyme neuroborreliosis
	Chagas disease
	COVID-19
Toxic and drugs-related	
	Metronidazole
	Nitrofurantoin
	Linezolid
	Statins
	Flecainide
	Bortezomib
	TNF inhibitor
	Alcohol
	Thallium
	Hypervitaminosis B6
Hereditary	
	Sodium channelopathies (*SCN9A, SCN10, SCN11A*)
	COL6A5 mutations
	Fabry disease
	Familial amyloidosis
	Hemochromatosis
	Tangier disease
	Friedreich ataxia
	Hereditary sensory autonomic neuropathies
Syndromic	
Pain syndromes	
	Fibromyalgia
	Chronic pelvic and bladder pain
	Irritable bowel syndrome
	Complex regional pain syndrome type I
	Elhers-Danlos syndrome
Neurodegenerative disorders	
	Parkinson's disease
	Multiple system atrophy
	Amytrophic lateral sclerosis

The table is based on the reviews of Hoeijmakers *et al.* [6] and Cazzato *et al.* [5], and on the large cohort study of de Greef *et al.* [4].
Recent literature findings of the conditions in bold are discussed in the current review.

prospective study included 50 patients with lung sarcoidosis and 25 healthy controls [12▪]. The SFN Screening List (SFN-SL) was used for clinical evaluation, in which autonomic complaints were frequently reported. In addition, all patients underwent a distal skin biopsy. A negative correlation between the IENFD and SFN-SL score was demonstrated.

As possible mechanism for the autonomic dysfunction in sarcoidosis, another study hypothesized that antiganglionic acetylcholine receptor (gAChR) antibodies could cause an autoimmune autonomic ganglionopathy [28▪]. In three patients with severe dysautonomia, anti-gAChR antibodies were found. A larger study population is needed to validate the results.

Auto-antibodies

Fibroblast growth factors (FGFs) are proteins that are involved in the development and regeneration of the peripheral nervous system. One specific receptor, FGF receptor 3 (FGFR3), plays a role in axonal development and regeneration. Antibodies against FGFR3 were already linked to purely sensory-predominant neuropathies or neuronopathies. A

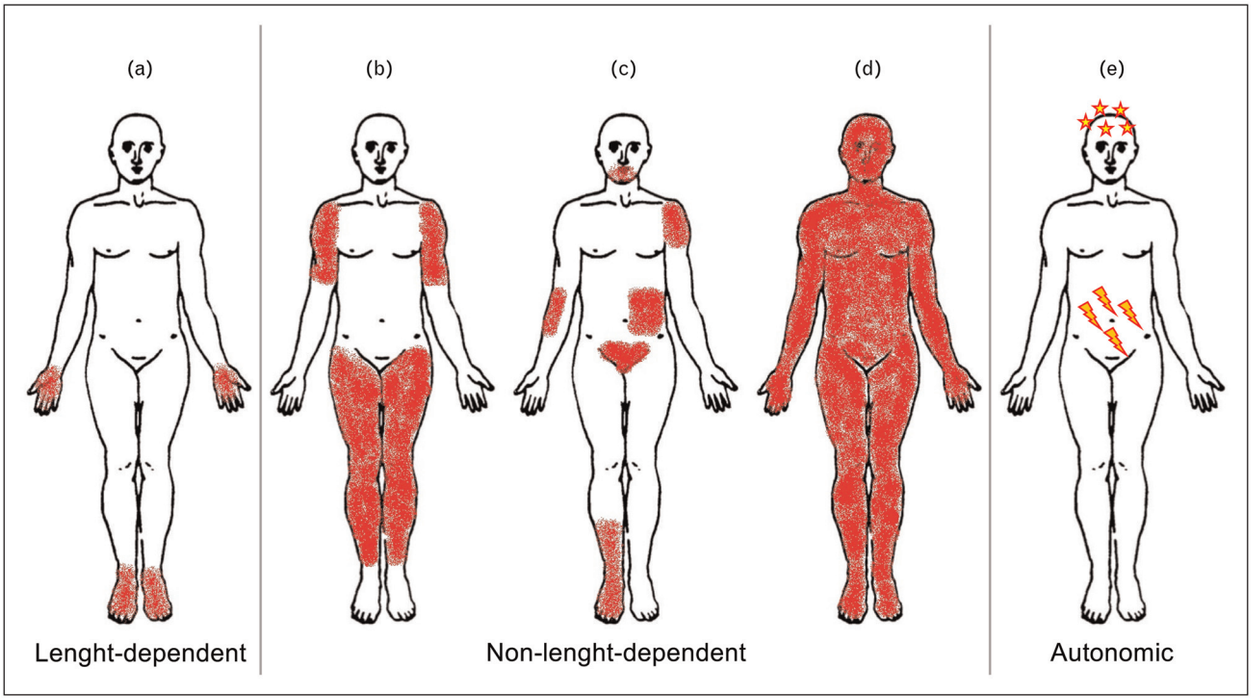

FIGURE 1. Different phenotypes of small fiber neuropathy. The phenotype of small fiber neuropathy can be classified into a classical sensory length-dependent pattern (a), sensory nonlength-dependent pattern (b, c, and d) or predominantly autonomic phenotype. The specific SFN phenotype can provide direction for the underlying etiology. SFN, small fiber neuropathy.

recently conducted retrospective study, showed a broader clinical spectrum with involvement of both small and large fibers, sensory, and motor fibers, and the trigeminal nerves [15▪].

Antiplexin D1 antibody (plexin D1-IgG) specifically binds to small neurons in the dorsal root ganglia. Former studies reported the presence of plexin D1-IgG in patients with neuropathic pain and an underlying neuroinflammatory diseases, and in idiopathic trigeminal neuralgia. In a new study of the same research group, 63 patients with probable SFN and 55 healthy controls were screened for serum plexin D1-IgG by ELISA. Plexin D1-IgG was found in eight SFN patients and was absent in healthy controls. IgG from three plexin D1-IgG positive patients was intrathecally injected into mice, causing mechanical and/or thermal hypersensitivity. Mice injected with IgG of healthy controls showed no hypersensitivity. In addition, an activation marker was significantly more abundant in mice injected with patients' immunoglobulin G (IgG) compared to mice injected with healthy control IgG, confirming the pathogenicity of the antibody [16▪▪].

In contrast to the aforementioned studies, which both focused on one specific auto-antibody, a larger study used a novel high-throughput model to search for new auto-antibodies in idiopathic SFN patients [17▪▪]. By a protein microarray platform that consisted of over 1600 proteins selected on the basis of involvement in the immune system, sera of 58 SFN patients (58.6% idiopathic) and 20 healthy controls were screened. In addition, a validation cohort of 33 SFN patients (54.5% idiopathic) was included. Novel antibodies MX1 (interferon-induced GTP-binding protein MX1), debrin-like protein and keratin type II cytoskeletal 8 were specifically found in idiopathic SFN. Both a length-dependent- and nonlength-dependent pattern was described in those patients. Limitations of the study were the small sample size and the definition of definite SFN, in which an abnormal skin biopsy was not required. Validation studies and an in-depth analysis of these autoantibodies are needed to elucidate the meaning for clinical practice [17▪▪].

In general, it is debatable if the auto-antibodies that have been demonstrated in SFN are disease causing, or are that they a result of the immunological processes that occur after small nerve fiber damage.

COVID-19 related small fiber neuropathy

Severe acute respiratory syndrome coronavirus 2 or COVID-19 infection has been associated with a broad spectrum of cerebrovascular, neuropathic and autonomic features. Also, painful SFN has been

linked to COVID-19. In the past, direct neurotoxic effects of viruses, including Human Immunodeficiency Virus and hepatitis C have been described to play a role in the development of SFN [5]. Additionally, immune-mediated processes have been postulated to cause nerve damage, especially when the symptoms appear not directly at the start of the infection. A case series of 13 patients, who all developed new-onset paresthesias within 2 months following a COVID-19 infection, suggested a similar postinfectious acute neuropathy or postviral autoimmune phenomenon [18▪]. In six of these patients the IENFD at the ankle was decreased together with specific SFN sensory symptoms and signs. Two of them also suffered from dysautonomia. All patients were treated with symptomatic pain treatment. None of them received immunotherapy. After eight to ten months of follow-up, the complaints of most patients were relatively well controlled. It was striking that the severity of the COVID-19 infection was not associated with the development of SFN.

As the COVID-19 pandemic progressed, a better understanding of Post-Acute Sequelae of COVID-19 or long COVID was reached. Also, in these complex of symptoms, SFN seems to play a role [19▪,20▪]. A case series of nine patients with PACS after a mild COVID-19 infection showed multisystem involvement, including skin biopsy proven SFN with evident dysautonomia [19▪]. In another study, in which 17 patients with long COVID, that were referred for peripheral neuropathy screening, were evaluated, abnormal skin biopsies were found in 63% of patients and disturbed autonomic function tests in 50%. Some of these patients were treated with IVIG or corticosteroids. Although they reported significant improvement of complaints, also spontaneous recovery in patients without treatment was shown [20▪]. In most SFN patient reports concerning long COVID, autonomic complaints are more pronounced than the sensory symptoms [21▪,22▪,23▪]. Especially, postural orthostatic tachycardia syndrome is frequently mentioned [21▪,23▪]. However, since autonomic complaints can be caused by various conditions, one should be careful to attribute the symptoms directly to SFN.

Not only COVID-19 itself is associated with the development of SFN, but also post COVID-19 vaccination, sensory and autonomic complaints caused by skin biopsy proven SFN have been described [24▪,25▪,26▪]. Within one month after administration, both virus vector vaccines and mRNA vaccines resulted in neuropathic and autonomic symptoms. In some cases, spontaneous recovery after weeks was seen [24▪,25▪]. In other patients, treatment with oral corticosteroids seemed to speed up recovery. In non-recovering patients, IVIG treatment after five to nine months resulted in full recovery within two weeks [25▪].

Although the course of developing SFN after a COVID-19 infection or COVID-19 vaccination suggests an immunological mechanism, it may also be a coincidence due to the high number of infections and vaccinations during the pandemic. The case studies describing a positive effect of immunotherapy on SFN are too limited to serve as evidence.

SYNDROMIC SMALL FIBER NEUROPATHY

The term syndromic SFN is used when small fiber pathology is present without the typical neuropathic features of SFN [5]. In neurogenerative diseases, like Parkinson's disease or multiple system atrophy, a reduced IENFD and abnormal quantitative sensory testing have been described [29▪,30▪,31▪]. In a study evaluating 59 Parkinson's disease patients, a decreased IENFD was negatively correlated with an autonomic symptom questionnaire [29▪]. In addition, small fiber pathology has been suggested in various chronic pain syndromes, both with and without signs of dysautonomia, including irritable bowel syndrome, complex chronic pelvic pain and bladder pain syndrome [32▪,33▪,34▪]. The most discussed condition that can be considered as syndromic SFN is fibromyalgia and will be further explained below.

Fibromyalgia

Fibromyalgia and SFN have in common that both conditions lead to chronic pain. Although pain in SFN is clearly neuropathic, there are different thoughts about the specific type of pain in fibromyalgia. Originally, it was considered to be nociplastic and musculoskeletal. However, recent studies showed also evidence for a neuropathic character. Several questionnaires have been used to screen for neuropathic pain. A nationwide study performed in Italy, recruited 749 fibromyalgia patients fulfilling the Fibromyalgia Research Criteria [35▪]. All patients completed the Neuropathic Pain Symptoms Inventory (NPSI). This questionnaire consists of 10 questions, which allow to discriminate and quantify five different neuropathic pain dimensions using a numeric rating scale from 0 to 10. In about two-thirds of patients the NPSI indicated severe neuropathic pain and almost half of the patients reported autonomic complaints [35▪]. In another study, the Pain Detect Questionnaire (PDQ) and Douleur Neuropathique (DN4) were used to evaluate the neuropathic pain features in 80 fibromyalgia patients [36▪]. The PDQ identifies the temporal pattern of pain, pain irradiation and

characteristic symptoms of neuropathic pain. The DN4 consists of 10 dichotomously answered items concerning typical neuropathic qualitative symptoms and an objective neurological evaluation of hypoesthesia and allodynia. In addition, a rheumatologist was asked to give a clinical judgment on the presence or absence of neuropathic pain features. In 37.5% of patients the clinical evaluation was positive for the presence of neuropathic pain. A good concordance between clinically evaluation and questionnaires for identifying neuropathic pain features was reached. The DN4 demonstrated a better agreement with the clinical judgment compared to the DN4 [36▪].

The presence of neuropathic pain in both fibromyalgia and SFN can make it challenging to differentiate between these conditions, especially when SFN patients present with a nonlength dependent pattern [37▪]. An additional complicating factor is that diagnostic tests to detect small fiber pathology can also be abnormal in fibromyalgia. In up to half of the patients fulfilling the criteria of fibromyalgia a decreased IENFD can be found. Multichannel laser evoked potentials, that can be used to test small nerve fiber function, have been shown not to correlate sufficiently with small nerve fiber impairment in fibromyalgia [38▪]. Although the value of corneal confocal microscopy to quantify the corneal nerve fiber density in diagnosing SFN is still uncertain, a case series of 28 female patients diagnosed with fibromyalgia, showed a strong negative correlation between corneal nerve density and SFN sensory and autonomic symptoms [39▪]. If similar diagnostic tests indeed show small nerve fiber pathology in both fibromyalgia and SFN, there is need for better discriminatory tests. The keratinocyte transcriptome signature might be helpful in this [40▪▪]. In 26 SFN and 26 fibromyalgia patients, the RNA sequencing of keratinocytes showed a diverse transcriptome signature with differentially expressed protein coding genes.

The theories about the underlying pathophysiological mechanisms in fibromyalgia are evolving. Dorsal root ganglia pathology has been proposed in both SFN and fibromyalgia [41▪]. On the other hand, central sensitization might play a greater role in fibromyalgia, and peripheral abnormalities in SFN [42▪].

After all, SFN and fibromyalgia seem to be different entities. The clinical findings and diagnostics tests that can help to differentiate between both should be better defined and further developed. Together with a better understanding of the pathophysiology, it will facilitate to start appropriate treatment in time [37▪].

CONCLUSION

In the past 18 months, the knowledge about etiologies in SFN has been further expanded. Special attention has been paid to associated immunological conditions, with a predominantly nonlength dependent phenotype. In addition to the various etiologies of classical sensory SFN, small fiber pathology has extensively described in diseases without the typical neuropathic pain features of SFN. In the upcoming years it is expected that the causal relationship between the etiologies and SFN, and the underlying pathophysiological mechanisms will be further elucidated. Especially for hereditary causes, new developments are expected. Eventually, these findings will provide new targets for treatment.

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- ▪▪ of outstanding interest

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