Small fibre neuropathy: expanding the clinical pain universe

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Abstract

Small fibre neuropathy (SFN) is a disorder of thinly myelinated Aδ and unmyelinated C fibres. SFN is clinically dominated by neuropathic pain and autonomic complaints, leading to a significant reduction in quality of life. According to international criteria, the diagnosis is established by the assessment of intra-epidermal nerve fibre density and/or quantitative sensory testing. SFN is mainly associated with autoimmune diseases, sodium channel gene variants, diabetes mellitus, and vitamin B12 deficiencies, although in more than one-half of patients no etiology can be identified. Recently, gain-of-function variants in the genes encoding for the $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ sodium channel subunits have been discovered in SFN patients, enlarging the spectrum of underlying conditions. Sodium channel gene variants associated with SFN can lead to a diversity of phenotypes, including different pain distributions and presence or absence of autonomic symptoms. This suggests that SFN is part of a clinical continuum. New assessments might contribute to a better understanding of the cellular and molecular substrates of SFN and might provide improved diagnostic methods and trial designs in the future. Identification of the underlying mechanisms may inform the development of drugs that more effectively address neuropathic pain and autonomic symptoms of SFN.

Introduction

Knowledge of small fibre neuropathy (SFN) has advanced substantially over the last two decades, both at pathophysiological and clinical level. SFN is a condition that selectively involves thinly myelinated Aδ-fibres and unmyelinated C-fibres. It is clinically characterized by neuropathic pain, most frequently described as burning, shooting and/or prickling. Most cases present with a length-dependent or stocking-glove distribution,(*Tesfaye, et al., 2010*) although a non-length-dependent pattern of symptoms may also occur.(*Gemignani, et al., 2010b; Gorson, et al., 2008; Khan and Zhou, 2012; Khoshnoodi, et al., 2016*) Dysautonomic features may include dry eyes or mouth, orthostatic dizziness, bowel and micturition disturbances, a change of the perspiration pattern, accommodation problems, impotence, diminished ejaculation or vaginal lubrication, hot flushes, and/or cardiac palpitations.(*Lauria, 2005; Stewart, et al., 1992*)

In general, pure SFN does not show abnormalities in motor and large sensory nerve fibre function at neurological examination, while hyperalgesia and allodynia frequently accompany nociceptive and temperature sensation loss.(*Blackmore and Siddiqi, 2016*) In patients with pure SFN, nerve conduction studies reveal no signs of large nerve fibre involvement. In addition, over the last years, there has been increased awareness of chronic itch as a symptom of SFN.(*Brenaut, et al., 2015; Devigili, et al., 2014; Martinelli-Boneschi, et al., 2017; Misery, et al., 2014*) Muscle cramps have also been described to be a symptom of SFN, possibly reflecting the location of small nerve fibres as thermoreceptor and nociceptor muscle afferents.(*Lopate, et al., 2013; Mense, 1996*)

Epidemiology

To date, the only epidemiological study in SFN has been performed in the Netherlands. It showed an overall minimum incidence of 12 cases per 100,000 inhabitants per year with long-term persistent complaints.(*Peters, et al., 2013*)

Children can also suffer from SFN. Although SFN in children is difficult to diagnose because of the absence of normative data for intraepidermal nerve fibre density in children, several case reports have been published.(*Hoeijmakers, et al., 2016; Kafaie, et al., 2016; Oaklander and Klein, 2013; Wakamoto, et al., 1999*)

Quality of life

SFN leads to a significant reduction in the overall QoL,(*Bakkers, et al., 2014*) at least in part due to pain and autonomic symptoms. Thermal thresholds and reduced IENFD have been reported to correlate with the deterioration of QoL.(*Lin, et al., 2015*) A significant association was found between pain severity and health status and function.(*Schaefer, et al., 2014*) Furthermore, greater adjusted direct and indirect costs were reported at increasing levels of pain in idiopathic SFN.(*Schaefer, et al., 2014*)

Definition and diagnosis

The diagnosis of SFN is made according to a clinically-based definition, including symptoms and signs suggestive of SFN and their distribution.(*Hoeijmakers, et al., 2012a*) The diagnosis can be graded as follows:

- *Possible*: presence of length-dependent symptoms and/or clinical signs of small fibre damage;
- *Probable*: presence of length-dependent symptoms, clinical signs of small fibre damage, and normal sural NCS;
- *Definite*: presence of length-dependent symptoms, clinical signs of small fibre damage, normal sural nerve conduction study (NCS), and reduced intraepidermal nerve fibre density (IENFD) at the ankle and/or abnormal thermal thresholds.(*Cazzato and Lauria, 2017; Lauria, et al., 2012; Tesfaye, et al., 2010*)

However, this definition only includes length-dependent symptoms, whereas the spectrum of clinical signs has widened from the classical length- dependent SFN to include non-length-dependent patterns.(*Gemignani, et al., 2010b; Gorson, et al., 2008; Khan and Zhou, 2012; Khoshnoodi, et al., 2016*) Furthermore, according to this definition, the diagnosis SFN should be considered only in patients with pure or isolated impairment of the Aδ- and C-fibres. Patients with predominant features of small fibre neuropathy and clinical and NCS findings of large sensory fibre dysfunction should be considered to have a mixed (small and large fibre) sensory neuropathy, also described as predominant SFN. A correct classification of SFN is of importance, as it impacts the work-up for an underlying condition and the design of clinical trials.(*Cazzato and Lauria, 2017*)

Assessments

In the past years, new technologies for the assessment of peripheral neuropathies, including SFN, have become available.(*Gasparotti, et al., 2017; Lauria, et al., 2010b*) A number of diagnostic tools is available for the detection of SFN (Table 1). A distinction can be made in methods that quantify small nerve fibres and methods that test small nerve fibre function. New imaging techniques are likely to impact the diagnostic field in SFN as well.

Quantification of small nerve fibres

Skin biopsy

The diagnostic value of skin biopsy with IENFD in patients with clinically suspected SFN has been established and the method is generally considered the 'gold standard' for the diagnosis, though a true gold standard for SFN is lacking.(*Lauria, et al., 2010a; Lauria, et al., 2010b*) IENF are unmyelinated sensory endings with exclusive somatic function that arise from nerve bundles of the sub-papillary dermis.(*Lauria, et al., 2009*) They lose the Schwann cell ensheathment as they cross the dermal–epidermal junction,(*Boulais and Misery, 2008; Lauria, et al., 2004; Lauria, et al., 2014*) and widely express the capsaicin receptor, making them the most distal nociceptors. Skin biopsy is commonly taken with a 3-mm disposable punch, from the lower leg, 10 centimeters proximal from the lateral malleolus, within the territory of the sural nerve. By means of immunohistochemistry, IENF are visualized using antibodies against the protein gene product (PGP9.5), a cytoplasmic ubiquitin carboxyl-terminal hydrolase. The number of fibres crossing the dermal-epidermal junction is quantified, the length of the section is measured and the linear density of IENF per millimeter is obtained and compared with age- and gender-matched normative values.(*Lauria, et al., 2010a*) Recent studies have shown that right and left-side IENFD overlap in healthy subjects and in patients with length-dependent SFN, and that IENFD is stable when re-assessed within a 3-week period that is the time of epidermal renewal, through a follow-up biopsy in the same sensory territory.(*Lauria, et al., 2015*)
Disadvantages of skin biopsy are that the analysis is time-consuming and relatively costly, and that sensitivity is moderate. Indeed, some patients with symptoms of SFN may have normal IENFD and possibly represent pre-degenerative functional impairment of the nerve fibres.(*Devigili, et al., 2008*)
IENFD decreases with ageing,(*Lauria, et al., 2010a*) and values in upper arm and proximal thigh are significantly higher than in wrist and distal leg, respectively.(*Liu, et al., 2014*) One study performed to monitor IENFD during disease course in idiopathic SFN found similar rates of decrease in proximal and distal sites of the lower limb.(*Khoshnoodi, et al., 2016*) The

rates of IENFD decrease over time do not differ between idiopathic SFN, diabetic SFN and impaired glucose tolerance SFN.(*Khoshnoodi, et al., 2016*)

IENFD has been reported to be reduced also in other painful conditions, such as Guillain-Barré syndrome,(*Ruts, et al., 2012*) meralgia paraesthestica,(*Wongmek, et al., 2016*) notalgia,(*Lauria and Lombardi, 2007*) Ehlers-Danlos syndrome,(*Cazzato, et al., 2016*) and fibromyalgia,(*Kosmidis, et al., 2014*) and non-painful disorders, such as Parkinson's disease and related disorders,(*Kass-Iliyya, et al., 2015; Podgorny, et al., 2016; Schrempf, et al., 2016*) amyotrophic lateral sclerosis,(*Dalla Bella, et al., 2016; Nolano, et al., 2016; Truini, et al., 2015*) critical illness,(*Skorna, et al., 2015*) and peripheral arterial disease.(*Grone, et al., 2014*)

New techniques to determine the IENFD with indirect immunofluorescence,(*Provitera, et al., 2016*) automated PGP9.5 immunofluorescence staining (laboratory developed test),(*Van Acker, et al., 2016*) and 3D-analysis(*Dauch, et al., 2013*) have been reported. One study investigated the global spatial sampling in order to determine the epidermal nerve fibre length density (ENFLD) taking into account its biologic complexity.(*Karlsson, et al., 2013*) Results showed that ENFLD is comparable with IENFD in differentiating between SFN and healthy individuals.(*Karlsson, et al., 2013*)

In hairy skin, dermal nerve fibres are organized in small bundles. The bundles located just below the dermal– epidermal junction constitute the subepidermal neural plexus, from which fibres arise to reach the epidermis. Other bundles can be found in the deeper dermis. Most fibres are unmyelinated, and the minority of myelinated fibres are detectable in the upper dermis, usually close to hair follicles or vascular structures.(*Lauria, et al., 2014*) A method for the assessment of dermal nerves by measuring the overall length of the fibres was shown to be reliable in terms of diagnostic yield in patients with pure SFN.(*Lauria, et al., 2011*)

The skin is also rich with autonomic nerve fibres, innervating different autonomic structures such as sweat glands and pilomotor muscles. The innervation of dermal autonomic structures can be investigated using markers for adrenergic, noradrenergic, and cholinergic sympathetic fibres and vasodilatory peptidergic fibres.(*Lauria, et al., 2014*) Indeed, several methods have been described to obtain a morphometry of sweat gland and pilomotor muscle innervation.(*Gibbons, et al., 2009; Nolano, et al., 2010*)

Corneal Confocal Microscopy

Corneal Confocal Microscopy (CCM) is a method that visualizes the unmyelinated C-nerve fibres that originate from the trigeminal nerve and travel to the Bowman's membrane of the

cornea.(*Tavakoli, et al., 2008*) It allows an *in vivo* evaluation of disease or surgery-induced alterations of corneal nerves.(*Oliveira-Soto and Efron, 2001; Patel, et al., 2009*)

Four established parameters - corneal nerve fibre density (CNFD), corneal nerve branch density (CNBD), corneal nerve fibre length (CNFL) and corneal nerve fibre tortuosity (CNFT) – can be quantified by means of the software program CCMetrics. An international normative dataset of these corneal nerve fibre parameters has been published.(*Tavakoli, et al., 2015*)

CCM is a non-invasive tool with high repeatability.(*Petropoulos, et al., 2013*) Studies in patients with non-length dependent SFN(*Gemignani, et al., 2010a*) and length-dependent SFN(*Tavakoli, et al., 2010*) demonstrated a decrease in CNFD. However, these studies included small patient groups (6 and 25, respectively). Regeneration of the small fibres in the cornea was found in diabetic patients after kidney and pancreas transplantation (*Tavakoli, et al., 2013*) and after continuous subcutaneous insulin therapy in comparison with injections without improvement in the IENFD and QST. .(*Azmi, et al., 2015*)

CCM has been used to detect small fibre damage in other neurological diseases, such as Fabry's disease, chronic inflammatory demyelinating polyneuropathy, Charcot-Marie Tooth type 1A, and multiple sclerosis.(*Bitirgen, et al., 2017; Stettner, et al., 2016; Tavakoli, et al., 2012; Tavakoli, et al., 2009*) Conversely, research on patients with Parkinson's showed an increase in CNBD and CNFL.(*Kass-Iliyya, et al., 2015*)

Assessment of the function of small nerve fibres

Quantitative sensory testing

Quantitative sensory testing (QST) is a non-invasive psychophysical method that quantifies the thresholds of sensory perception carried by large and small nerve fibres.(*Dyck, et al., 1993*) QST is considered a diagnostic tool in SFN,(*Devigili, et al., 2008; Hoitsma, et al., 2003*) and consensus recommendations were provided for clinical use of QST,(*Backonja, et al., 2013*) emphasizing the need of a standardized protocol, adequate equipment, trained staff and use of normative values. The method of levels (ie a reaction time–independent method; the subject answers per stimulus whether a warmer or cooler temperature is sensed) has several advantages: there is no effect of stimulus temperature change rate, applicability is possible even in subjects with cognitive impairment and children, and repeatability is comparable or better compared to the method of limits (reaction time-dependent; pushing a button when a change in temperature or pain is sensed).(*Bakkers, et al., 2013; Kemler, et al., 2000; Pertovaara, et al., 1996; Yarnitsky and Ochoa, 1991*) The combination of bilateral

warm and cold thresholds of the hands and feet by the levels method probably provides the most optimal sensitivity and specificity.(*Bakkers, et al., 2015*)

Thermal threshold deterioration was associated with the intensity of pain in peripheral neuropathy.(*Ng Wing Tin, et al., 2014*) In diabetes without sensory large nerve involvement, a significantly lower IENFD and higher cold perception threshold were found in comparison with controls, irrespective of whether they had symptoms of polyneuropathy or not. However, a reduction of IENFD was the most frequent abnormal finding in the subgroup of patients with neuropathic symptom, and therefore seemed more sensitive as a diagnostic tool.(*Loseth, et al., 2008*)

Furthermore, QST requires the patient to be alert and cooperative, the test cannot discriminate between central and peripheral nervous system diseases,(*Maier, et al., 2010*) and may be influenced by malingering or other nonorganic factors.(*Dyck, et al., 1998; Shy, et al., 2003; Verdugo and Ochoa, 1993; Yarnitsky, et al., 1994*) For all these reasons, QST should be used in relation to the clinical context and in conjunction with other tests, and not alone for the diagnosis of a neurological lesion.(*Hansson, et al., 2007*)

Microneurography

Microneurography is used to record the activity of C-nociceptors and sympathetic fibres and to test the efficacy of different compounds in blocking abnormal on-going activity in both animal models and in patients.(*Serra, 2010*) The use of microneurography is increasing in disorders affecting the peripheral nervous system.(*Donadio and Liguori, 2015; Kleggetveit, et al., 2016; Liguori, et al., 2011; Ochoa, et al., 2005*) However, its application in clinical practice remains limited due to the technical challenges, the amount of time needed to perform the examination, the small number of nerve fibres that can be studied in any given patient, and the test awaits validation of diagnostic value.(*Mainka, et al., 2015*)

Nociceptive Evoked Potentials

Nociceptive evoked potentials can be used to investigate the conduction properties of small nerve fibres in a fashion not dependent on patients' cooperation and attention.(*Le Pera, et al., 2002*) These nociceptive evoked potentials can be generated by either radiant heat (laser-evoked potentials, LEPs) or contact heat (contact heat-evoked potentials, CHEPs). Both LEPs and CHEPs are based on selective of Aδ- and C-fibre activation, whereas induction of pain-related evoked potentials (PREPs) involves the preferential stimulation of Aδ-fibres.(*Merkies, et al., 2015*) Skin denervation induced by topical capsaicin causes the

decrease of LEP amplitude.(*Rage, et al., 2010*) LEPs are a validated technique to investigate the neural bases of nociception.(*Garcia-Larrea, et al., 2003; Mobascher, et al., 2009*) LEP amplitudes correlate with the reported intensity of perceived pain,(*Garcia-Larrea, et al., 1997*) and negatively with age.(*Truini, et al., 2005*) Moreover, it is modulated by opioids(*Hoeben, et al., 2012*) and pain expectation.(*Colloca, et al., 2008; Hird, et al., 2017*) Comparable to QST, LEPs cannot discriminate the site of pathology (peripheral nerves, plexus, roots, spinal cord or brainstem),(*Cruccu, et al., 2008*) and should therefore also be considered a supportive tool for diagnosing SFN.

Age- and gender adjusted normative values have been reported for the clinical use of CHEPs.(*Lagerburg, et al., 2015*) More recently, a strong correlation between CHEP amplitudes with the degree of skin innervation was found in a large SFN cohort.(*Wu, et al., 2017*) Patients with sensory neuropathy and an IENF loss have lower-amplitude CHEPs.(*Atherton, et al., 2007; Casanova-Molla, et al., 2011; Chao, et al., 2008*) However, CHEPs cannot be recorded in all healthy participants, which makes the clinical interpretation of absent CHEPs difficult.(*Lagerburg, et al., 2015*)

Intraepidermal electrical stimulation (IES) has also been described as a potential additional tool in detecting functional changes in Aδ-fibres and C-fibres in SFN,(*Inui and Kakigi, 2012; Kodaira, et al., 2014*) and in patients with neuropathic pain.(*Omori, et al., 2017*)

Imaging

Peripheral Nerve Ultrasound

Ultrasound (US) showed enlargement in cross-sectional area (CSA) of the sural nerve in SFN patients with reduced IENFD, compared with body mass index matched healthy controls,(*Ebadi, et al., 2015*) indicating changes in structure or morphology of larger nerve fibres in SFN. Possible explanations for this large nerve fibre enlargement include impaired axoplasmic flow in proximal (larger) nerve segments due to loss or injury of distal small nerve fibres, or sodium channel dysfunction, leading to axonal degeneration with axonal swelling.(*Persson, et al., 2016; Persson, et al., 2013*) Alternatively, changes in the extracellular space within peripheral nerves and/or change in non-neuronal connective tissue surrounding the axons may contribute. At present, more data are needed to establish the value of ultrasound as a diagnostic tool in SFN.

Magnetic Resonance Imaging

Non-invasive imaging techniques, such as functional magnetic resonance imaging (fMRI), are used to measure neuronal activity in humans in order to study regional activation in various parts of the brain in chronic pain states. The advantage of fMRI is the ability to ascribe function to specific brain regions. The resolution of fMRI images has become more detailed with increasing magnet strength. Skin denervation has been associated with abnormal recruitment of pain-related regions in the brain,(*Tseng, et al., 2013*) especially in diabetic neuropathic pain,(*Cauda, et al., 2010; Cauda, et al., 2009*) suggesting altered patterns of activation of the brain in painful neuropathy. Volume reduction was most notable in pain-processing regions, particularly the bilateral anterior cingulate cortices, which was associated with greater depletion of IENF.(*Hsieh, et al., 2015*) However, whether a specific activation pattern can be seen depends on many factors, such as type of brain imaging modality.(*Apkarian, et al., 2005*) It is conceivable that a particular type of pain (stimulus) may enhance a specific pain brain pattern, but patient-specific factors (ie gender, genetic and epigenetic factors) may influence the pain activation network.(*Cole, et al., 2010; Paulson, et al., 1998; Quiton and Greenspan, 2007*) Psychological modulation as well as chronicity of pain may influence the activation network, and should therefore be taken into account.(*Gracely, et al., 2002; Grachev, et al., 2000; Phillips, et al., 2003; Ploghaus, et al., 2000; Ploghaus, et al., 1999; Rainville, et al., 1997*)

Autonomic testing

Changes in peripheral autonomic nervous system function may be an early manifestation in SFN.(*Low, et al., 2006*) Dysfunction of the sudomotor system may result in an increase or decrease in sweat production, resulting in disturbances of thermoregulation. Traditional measurements of sudomotor function include thermoregulatory sweat testing, quantitative sudomotor axon reflex testing (QSART), silicone impressions, quantitative direct and indirect axon reflex testing, and the sympathetic skin response (SSR).(*Illigens and Gibbons, 2009*)

Thermoregulatory sweat testing

Thermoregulatory sweat testing is performed by increasing the ambient room temperature which in turn raises blood and skin temperature. The degree and extent of sweat production is then visualized with an indicator dye.(*Illigens and Gibbons, 2009*) The test is time-consuming, requires special equipment, and special preparation and treatment of the patient, and is therefore only performed in highly specialized centres, limiting the clinical applicability.

Quantitative sudomotor axon reflex testing (QSART)

QSART is used to evaluate postganglionic sympathetic cholinergic sudomotor function by measuring the axon-reflex mediated sweat response over time. QSART can be of value in the diagnosis of SFN.(*Namer, et al., 2013; Thaisetthawatkul, et al., 2013*) It has been suggested to add QSART as one of the core diagnostic tests, requiring abnormality on 2 measures for a diagnosis of SFN (clinical findings, QST, QSARTS, and skin biopsy. Though QSART can be of value in the diagnosis of SFN, normative data are needed to determine its usefulness for clinical practice.(*Cazzato and Lauria, 2017*)

Silicone impression method

The silicone impression method is used to evaluate the postganglionic sympathetic cholinergic sudomotor function by measuring the direct and axon-reflex mediated sweat response at specific time points.(*Stewart, et al., 1994*) Although the silicone impression method is probably the easiest method to perform in the clinical realm, artifacts may influence the test results.

Quantitative direct and indirect axon reflex testing

Quantitative direct and indirect axon reflex testing is a method to evaluate the postganglionic sympathetic cholinergic sudomotor function by measuring the direct and axon-reflex mediated sweat response in a dynamic fashion. The test is simple, but further studies are required to determine its diagnostic value in SFN.(*Illigens and Gibbons, 2009*)

Sympathetic skin response (SSR)

SSR is a measure of electrodermal activity and provides a surrogate measure of sympathetic cholinergic sudomotor function. Although easy to perform, there is high variability within and between subjects, and sensitivity and specificity of the method are low.(*Hoitsma, et al., 2003; Lacomis, 2002*)

Electrochemical skin conductance

More recently, the Sudoscan was developed. It is a simple, quick, painless and non-invasive quantitative test measuring C-fibre postganglionic sympathetic nerve function in sweat glands of the palms and soles of the feet, areas that contain a high density of these glands.(*Grandinetti, et al., 2007; Mao, et al., 2017; Nevoret and Vinik, 2015; Tesfaye, et al.,*

2010) The Sudoscan measures the electrochemical skin conductance.(*Bordier, et al., 2016; Nevoret and Vinik, 2015; Sato, et al., 1989*) Most studies on the Sudoscan have been performed in patients with diabetic neuropathy, demonstrating a decrease of electrochemical skin conductance and a correlation with small fibre dysfunction and neuropathic symptoms.(*Casellini, et al., 2013; Nevoret and Vinik, 2015; Parson, et al., 2013*) A recent review concluded that normative values are inconsistent across publications, and large combined data sets do not support a high sensitivity and specificity.(*Rajan, et al., 2018*) Therefore, the value of Sudoscan as a diagnostic tool for SFN still needs to be determined.

Neuropad

Another recently developed test, the Neuropad, was introduced to measure sweat production based on the colour change of a cobalt II compound.(*Ponirakis, et al., 2014*) Moderate sensitivity and specificity (68% and 49%, respectively) were found using the warm perception threshold as a reference method, and these were enhanced when the corneal nerve fibre length (CNFL) was used as a reference method (83% and 80% respectively). The contribution of this test to the diagnosis SFN needs to be established.

Stimulated skin wrinkling (SSW)

SSW is a test for sympathetic function based on changes of dermal arteriovenous tissue vasoconstriction of the digits. A negative digit pulp pressure will occur after a warm water bath for 30 minutes. Wrinkling would occur when epidermal skin is drawn down unevenly, because of its varying tautness.(*Wilder-Smith, 2004*) The eutectic mixture of local anaesthetics (EMLA©) cream can also be used as a vasoconstrictive factor with similar results.(*Hsieh, et al., 2007; Wilder-Smith and Chow, 2003; Willatts and Reynolds, 1985*) In clinical practice, SSW is usually performed in the hands and graded using a published 5-point-scale.(*Teoh, et al., 2008; Wilder-Smith, 2015; Wilder-Smith, et al., 2009*) Foot skin wrinkling is hardly ever performed, as wrinkling is poor because of higher sympathetic nerve activity to the lower limbs.(*Anderson, et al., 1987*) Reduced SSW was found in patients with diabetic neuropathy(*Clark, et al., 1984; Ping Ng, et al., 2013; Vasudevan, et al., 2000*) and in idiopathic SFN.(*Teoh, et al., 2008; Wilder-Smith, 2015; Wilder-Smith, et al., 2009*) However, the value of SSW as a diagnostic tool is currently limited.

Outcome measures

Surveys might help clinicians to diagnose and assess treatment responses. The 13-item SFN-

Symptom Inventory Questionnaire© (SFN-SIQ), an ordinal based multi-item composite measuring 13 SFN-related symptoms, was transformed through Rasch to an interval measure which can be used as a diagnostic screening tool enabling parametric analyses.(*Bakkers, et al., 2010; Brouwer, et al., 2015a*) Furthermore, a disease-specific 32-item SFN-Rasch-built Overall Disability Scale (SFN-RODS©) questionnaire was developed via Rasch analyses, suitable for detecting activity limitations and participation restrictions in patients with SFN.(*Brouwer, et al., 2015a*) A Small-Fibre Symptom Survey has also been developed with satisfactory psychometric properties, indicating potential future utility for surveying patient-reported symptoms; however, this is an ordinal scale, hampering meaningful calculations.(*Treister, et al., 2017*) Finally, the The Utah Early Neuropathy Scale was developed to evaluate the sensory signs and symptoms in sensory and small fibre nerve neuropathy, and may be a useful tool for clinical use and in trials.(*Singleton, et al., 2008*)

Underlying conditions and pathophysiology

SFN is associated with multiple diseases which can be categorized as metabolic, immune-mediated and infectious diseases, exposure to drugs and toxins, and genetic causes.(*Cazzato and Lauria, 2017; Lauria, et al., 2012*) In a large cohort of 921 patients, 75% of them did not have a known preselected comorbidity before the diagnostic workup. Immunological conditions were found in 175 patients (19%); other associated conditions were sodium channel gene variants (16.7%), 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%) (Figure 1).(*de Greef BT, 2017*) Systemic dysimmunity was more prevalent in idiopathic SFN patients than in the general population, though the pathogenic role of isolated autoantibodies remains uncertain.(*de Greef BT, 2017*) Another smaller study confirmed the presence of immunological abnormalities (eg ANA, ENA and celiac autoantibodies), whereas diabetes, prediabetes, and hypertriglyceridemia were not associated with SFN.(*Lang, et al., 2016*) A large study demonstrated that the prevalence of Fabry´s disease is irrelevant in adult SFN patients, a finding that allows excluding this genetic screening in patients with confirmed diagnosis of SFN.(*de Greef, et al., 2016*) Early degeneration of small nerve fibers can occur in the presymptomatic stage of patients carrying TTR mutations,(Masuda, et al., 2017) whereas patients with a symptomatic stage of familial amyloid neuropathy more likely present with a mixed neuropathy.(Adams, et al., 2016)

Even in patients with a known possible etiology, additional underlying causes can be found in 27% of patients.(*de Greef BT, 2017*) It is therefore recommended to screen patients with SFN at least for autoimmune diseases, diabetes mellitus including glucose intolerance, vitamin B12 deficiency and sodium channel gene variants, even when they already have a potential underlying condition at referral.

Voltage-gated sodium channelopathies in small fibre neuropathy

Voltage-gated sodium channels play an essential role in regulating the excitability of nociceptive primary afferent neurons. Three voltage-gated sodium channels, $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$, encoded by genes *SCN9A, SCN10A* and *SCN11A*, are preferentially expressed in peripheral neurons and are known to play a role in human pain disorders.(*Dib-Hajj, et al., 2013*)

Gain-of-function *SCN9A* variants have been described in three painful human pain conditions: inherited erythromelalgia (IEM), paroxysmal extreme pain disorder (PEPD) and SFN. By contrast, congenital insensitivity to pain (CIP) is associated with autosomal recessive loss-of-function *SCN9A* variants. Increased understanding of the pathophysiological mechanisms underlying sodium channelopathies(*Cummins, et al., 2009; Dib-Hajj, et al., 2017*) paved the way for the development of isoform-selective blockers as a targeted treatment modality.(*Alexandrou, et al., 2016; Cao, et al., 2016; Zakrzewska, et al., 2017*)

$Na_V1.7$ in inherited erythromelalgia

Inherited erythromelalgia (or erythermalgia; OMIM 133020; IEM) is characterized by attacks of bilateral symmetrical burning pain together with redness and warmth in the feet or hands. Moderate exercise and heat provoke and aggravate the attacks, whereas cold, rest and raising the affected limbs may provide relief.(*Drenth and Michiels, 1990; Drenth and Waxman, 2007; McDonnell, et al., 2016*) In most patients with IEM symptoms start in early childhood (prior to 5-6yrs of age); occasional families show an older age at onset.(*Burns, et al., 2005*) Except for reddening of the skin of affected body parts due to vasomotor dysregulation during attacks,(*Rush, et al., 2006*) autonomic symptoms, such as in SFN, has been rarely reported in IEM.(*McDonnell, et al., 2016*)

IEM is an autosomal dominant painful neuropathy, caused by variants in *SCN9A*.(*Burns, et al., 2005; McDonnell, et al., 2016; Michiels, et al., 2005*) Gain-of-function variants that shift activation of $Na_v1.7$ in a hyperpolarizing direction, slow deactivation, and enhance ramp currents cause IEM. Over 20 different IEM variants have been discovered in $Na_v1.7$, and

almost all variants investigated so far result in a hyperpolarizing shift of activation, allowing $Na_v1.7$ to open at lower potentials compared with the wild type,(*Ahn, et al., 2013; Choi, et al., 2010; Cregg, et al., 2013; Dib-Hajj, et al., 2005; Estacion, et al., 2013; Harty, et al., 2006; Kim, et al., 2013; Lampert, et al., 2009; Lampert, et al., 2006; Lampert, et al., 2008; Namer, et al., 2015; Novella, et al., 2007; Sheets, et al., 2007; Stadler, et al., 2015*) in familial cases,(*Cheng, et al., 2008; Choi, et al., 2010; Yang, et al., 2016; Yang, et al., 2004*) and children.(*Estacion, et al., 2013; Tanaka, et al., 2017*) This left shift of activation enhances excitability, intuitively explaining the pain phenotype.(*Choi, et al., 2006; Cummins, et al., 2004; Dib-Hajj, et al., 2005*) The phenotype, however, can be complex and variable,(*Cheng, et al., 2008; Drenth, et al., 2005; Gurkiewicz, et al., 2011; Han, et al., 2009; Han, et al., 2007; Han, et al., 2006; Meijer, et al., 2014*) even within families carrying the same variant.(*McDonnell, et al., 2016*) The I234T-variant, which causes IEM-like pain phenotype, exhibits a complex phenotype that includes automutilation (*Ahn, et al., 2010; Meijer, et al., 2014*) and bilateral congenital corneal anesthesia.(*Kim, et al., 2015*) These findings, which suggest both gain-of-function and loss-of-function at the clinical level for patients carrying this variant, are explained by the unusually large hyperpolarization of activation of the mutant channel, which produces a massive depolarization in the resting potential of some DRG neurons, thus silencing them.(*Huang, et al., 2018*) Several variants have been reported without functional testing.(*Dabby, et al., 2011; Skeik, et al., 2012*) Recently, a $Na_v1.8$ variant has been linked to a syndrome with clinical characteristics similar to IEM.(*Kist, et al., 2016*)

$Na_V1.7$ in paroxysmal extreme pain disorder

Paroxysmal extreme pain disorder (PEPD), previously known as familial rectal pain (OMIM 167400) is an inherited condition characterized by paroxysms of rectal, ocular, or submandibular pain with flushing. Patients with PEPD can also suffer from autonomic dysfunction leading to poor feeding and reflux, vomiting, tonic attacks, breath holding spells, and bradycardia that sometimes requires insertion of a pacemaker. PEPD is caused by gain-of-function $Na_V1.7$ variants that mostly result in impaired fast-inactivation. So far, ten variants in $Na_V1.7$ are known that cause PEPD.(*Choi, et al., 2011; Dib-Hajj, et al., 2008; Fertleman, et al., 2006; Imai, et al., 2015; Jarecki, et al., 2009; Suter, et al., 2015; Theile, et al., 2011*) It is thought that the variant induces a depolarizing shift of steady-state fast inactivation, hampering channel closure during action potential electrogenesis.

$Na_V1.7$ in channelopathy-associated insensitivity to pain

Patients with congenital insensitivity to pain (CIP) do not perceive physical pain (OMIM 243000). The difference between sharp and dull and hot and cold is felt, but the pain awareness is absent. Young children with CIP may accrue mouth or finger wounds due to repeated self-biting, may also experience multiple burn-related injuries, and may injure bones and joints without experiencing pain. They also have a complete loss of the sense of smell (anosmia). *SCN9A* homozygous missense and deletion variants have been described in these patients, who do not produce functional Nav1.7 channels, and has been linked to the absence of pain perception.(*Bartholomew, et al., 2014; Bogdanova-Mihaylova, et al., 2015; Cox, et al., 2006; Cox, et al., 2010; Goldberg, et al., 2007; Kurban, et al., 2010; Mansouri, et al., 2014; Nilsen, et al., 2009; Shorer, et al., 2001; Shorer, et al., 2014; Staud, et al., 2011*) Partial deletion of pain perception was also described.(*Yuan, et al., 2011*) The clinical phenotype of patients with reduced pain sensibility due to $Na_v1.9$-variants is different than $Na_v1.7$-associated CIP.(*King, et al., 2017; Phatarakijnirund, et al., 2016; Woods, et al., 2015*) Large hyperpolarizing shifts in the voltage dependence of activation in the mutated $Na_V1.9$ channels in these cases are associated with insensitivity to pain. This evokes a massive degree of membrane depolarization that renders DRG neurons hypoexcitable.(*Huang, et al., 2017*)

$Na_V1.7$ in small fibre neuropathy

The first gain-of-function variants in $Na_V1.7$ that change the properties of the channel and the excitability of DRG neurons were described in 2012 in skin biopsy- and QST-confirmed idiopathic SFN.(*Faber, et al., 2012a*) Unexpectedly, while there is a strong correlation between genotype and phenotype for many mutations, some patients carrying $Na_V1.7$ variants show a remarkable degree of genotype-phenotype variability. Thus a single $Na_V1.7$ variant can be associated with a range of clinical phenotypes, and the same clinical phenotype may be associated with multiple different variants.(*Brouwer, et al., 2014; Devigili, et al., 2014; Estacion, et al., 2011; Faber, et al., 2012a; Han, et al., 2012; Hoeijmakers, et al., 2015; Hoeijmakers, et al., 2012b; Hoeijmakers, et al., 2012c; Waxman, et al., 2014*) The I228M variant, for example, may present with facial pain, or with a distal SFN.(*Estacion, et al., 2011*) Most SFN variants in $Na_V1.7$ are associated with distal pain but the G856D variant was linked to a more complex phenotype of very severe pain, together with erythema, dysautonomia and small hands and small feet (acromesomelia).(*Hoeijmakers, et al., 2012b*) The IEM-associated G856R variant was recently also shown to be associated with impaired distal limb development, suggesting that

some gain-of-function variants of $Na_V1.7$ may adversely affect limb morphogenesis during development.(*Tanaka, et al., 2017*) Furthermore, some variants present with severe autonomic symptoms, while others do not. This differential effect of certain $Na_V1.7$ variants, rendering DRG neurons hyperexcitable and sympathetic ganglion neurons hypoexcitable, can be explained by the presence or absence of $Na_V1.8$ in dorsal root ganglion versus sympathetic ganglion neurons, respectively.(*Han, et al., 2012; Rush, et al., 2006*) In addition to providing a mechanistic basis for pain and autonomic symptoms in SFN, the presence of gain-of-function variants in Na_V channels may provide insights about the mechanisms that lead to degeneration of axons in SFN. *In vitro* studies have demonstrated that reverse-mode (Ca^{2+} -importing) Na/Ca exchange can be triggered by a small but sustained influx of Na^+ ions due to pathogenic sodium channel variants found in SFN patients, thereby impairing neurite outgrowth, suggesting a molecular mechanism of axon degeneration in SFN.(*Persson, et al., 2013*)

Multiple modulatory factors can shape the pain experience of patients carrying Nav1.7 gain-of-function mutations; for example, a recent study of two patients with IEM both carrying the same Nav1.7mutation but with different pain profiles, demonstrated that a variant of a second gene, in a potassium channel, can introduce a degree of resilience to pain.(*Mis, et al., 2018*) Moreover, Nav1.7 mutations may affect multiple cell types including some cells outside the nervous system. Some patients with painful SFN can develop diabetes years after SFN becomes clinically manifest. It has been speculated that $Na_v1.7$ variants, present in pancreatic ß-cells as well as DRG neurons, may increase susceptibility for development of diabetes via ß-cell injury and produce painful neuropathy via a distinct effect on DRG neurons.(*Hoeijmakers, et al., 2014*) This hypothesis remains to be experimentally tested.

*$Na_V1.8$ **in** small fibre neuropathy*

The $Na_v1.8$ sodium channel, expressed in DRG neurons and peripheral nerve axons, contributes most of the sodium current underlying the action potential upstroke and supports repetitive firing in response to sustained depolarization.(*Blair and Bean, 2002; Dib-Hajj, et al., 2017; Garrison, et al., 2014; Renganathan, et al., 2001*) Gain-of-function variants in $Na_V1.8$ have been found in patients with painful neuropathy,(*Faber, et al., 2012b*) which had an enhanced channel response to depolarization and produced hyperexcitability in DRG neurons, including reduced current threshold, increased firing frequency and spontaneous activity. Other $Na_V1.8$ variants also have been linked to SFN,(*Han, et al., 2014; Huang, et al., 2013*) some with a clinical phenotype that includes a clinical picture that suggests severe

dysautonomia.(*Dabby, et al., 2016*) Variants in $Na_V1.8$ were found in almost 5% of a group of 921 consecutive patients with SFN.(*de Greef BT, 2017*)

$Na_V1.9$ in small fibre neuropathy

$Na_V1.9$ is preferentially expressed in small-diameter DRG neurons, trigeminal ganglion neurons, and intrinsic myenteric neurons.(*Dib-Hajj, et al., 2015*) Several human pain disorders have been linked to dominant gain-of-function $Na_V1.9$ variants, including early-onset pain in distal extremities,(*Han, et al., 2017; Okuda, et al., 2016; Zhang, et al., 2013*) cold-aggravated pain,(*Leipold, et al., 2015*) and SFN.(*Huang, et al., 2014; Vijayan, et al., 2015*) The expression of $Na_V1.9$ in myenteric neurons can explain the gastrointestinal symptoms reported by patients harboring *SCN11A* variants.(*Han, et al., 2017*) Finally, gain-of-function variants in $Na_V1.9$ have been reported in patients with a complex clinical syndrome that includes insensitivity to pain.(*Leipold, et al., 2013; Phatarakijnirund, et al., 2016; Woods, et al., 2015*) The loss of pain sensibility in these cases arises from a massive depolarization of DRG neurons that inactivates the sodium channels in these cells and reduces their excitability.(*Huang, et al., 2017*)

Overlap between pain disorders

With the description of painful SFN caused by $Na_V1.7$ variants, it has become clear that the phenotype of $Na_V1.7$ variants expands, and that the boundaries between these phenotypes are not always distinct (Figure 2). Clinically, burning pain with a stocking-glove distribution is a common characteristic in SFN but is also seen in IEM.(*Faber, et al., 2012a; Yang, et al., 2004*) Facial and diffuse or widespread pain can be seen in SFN and PEPD,(*Estacion, et al., 2011; Faber, et al., 2012a; Fertleman, et al., 2006*) and also in IEM.(*Drenth and Waxman, 2007*) Although this suggests that the function of small nerve fibers are equally impaired, IEM usually is not characterized by a loss of ENFD.(*Mantyh, et al., 2016*)

Reddening of the skin can occur in both IEM and PEPD and, to a lesser extent, in SFN. One study suggested that the activity of mutant $Na_v1.7$ channels in smooth muscle cells and sympathetic fibres innervating skin vessels may contribute to this phenomenon.(*Rice, et al., 2015*) Mixed phenotypes of IEM and SFN, IEM and PEPD, or SFN and PEPD associated with one variant have been described. Amongst SCN9A variants, the R185H has been found in patients diagnosed with either PEPD.(*Meglic, et al., 2014*) or SFN.(*Faber, et al., 2012a*) The A1632E variant has been found in a patient with a mixed phenotype of IEM and PEPD, and causes a mixed physiological change in channel function, of hyperpolarized activation and

impaired fast inactivation of the channel, which are typically associated with IEM and PEPD, respectively.(*Estacion, et al., 2008*) The heterozygous L245V variant that was found in a large family with IEM did not affect channel activation, but instead resulted in incomplete fast inactivation and a small hyperpolarizing shift in steady-state slow inactivation, which is more characteristic for PEPD.(*Emery, et al., 2015*) Overall at the structural level, most IEM variants tend to be located within the domains I and II of the protein, while PEPD variants are commonly located in the domains III and IV. The structural dichotomy, while not present in every case, parallels the biophysical effects of the two types of variants.(*Cheng, et al., 2010*)

Electrophysiology and pathogenicity of voltage-gated sodium channels variants

Although we know that some variants in sodium channels $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ can cause pain disorders, it is important to discriminate disease-causing variants from disease-contributing variants and variants of uncertain significance.(*Waxman, et al., 2014*) IEM and PEPD are due to rare, high impact, fully penetrant variants in Nav1.7. The frequency of specific variants is still low in the SFN population, and one could argue whether these variants can be considered risk factors or variants contributing to the disease, but not causing the disease. The clinical utility of *in silico* mutation-prediction programs is at best moderate, since these algorithms do not always accurately predict changes in channel function.(*Waxman, et al., 2014*) Consensus has been reached that newly described gene variants of *SCN9A, SCN10A,* and *SCN11A* should be assessed in the context of phenotype, family history, *in-silico* analysis, and functional profiling of the variant channel, and urge that gene variants be interpreted cautiously within clinical practice in the absence of segregation with symptoms in a large kindred and/or a pathogenic functional signature showing clear pro-excitatory changes in channel physiology.(*Waxman, et al., 2014*)

Management

Primary goals of the management of neuropathic pain in SFN are to detect (potentially treatable) underlying causes, to eliminate risk factors, and to manage the pain. Patients with SFN typically suffer from severe neuropathic pain that may be difficult to treat. At present, therapeutic strategies are largely symptomatic. Three main categories of drugs are most commonly used for treating neuropathic pain: antidepressants, anti-epileptics, and opioids.(*Finnerup, et al., 2015*) Using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE), recommendations were made for the pharmacotherapy of neuropathic pain based on the results of a systematic review and meta-

analysis. There is a strong recommendation for use and proposal as first-line treatment for tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin, and gabapentin; a weak recommendation for use and proposal as second line for lidocaine patches, capsaicin high-concentration patches, and tramadol; and a weak recommendation for use and proposal as third line for strong opioids and botulinum toxin A. Topical agents and botulinum toxin A were recommended for peripheral neuropathic pain only. A substantial subset of patients with SFN is aged 65 years or older, and comorbidities and polypharmacy make neuropathic pain treatment more challenging.(*Brouwer, et al., 2015b*) At present treatment of neuropathic pain is often disappointing, leading overall to pain relief of about 50% in only one-half of the patients, and the drug often has to be discontinued due unpredictable side-effects. The recent genetic and functional findings in SFN may pave the way for the development of new analgesics, through both pharmacogenomic targeting of existing medication,(*Geha, et al., 2016; Yang, et al., 2017*) and the development of a new generation of specific sodium channel blockers.(*Alexandrou, et al., 2016; Cao, et al., 2016; Zakrzewska, et al., 2017*).

As pain is a complex symptom, in which not only physical factors but also psychological, neurophysiological, socio- economic and cultural aspects may influence the experience and continuation of pain, a multidisciplinary approach in line with the biopsychosocial model is required in optimizing treatment for the individual patient.(*McCarberg, et al., 2012*) Physical therapy modalities and rehabilitation techniques are important options.(*Akyuz and Kenis, 2014*) Moreover, supervised exercise in patients with metabolic syndrome showed a increased cutaneous regenerative capacity, suggesting potential benefits of peripheral nerve function.(*Singleton, et al., 2015*)

Conclusions

The universe of causes of SFN is expanding. Sodium channel gene variants associated with SFN have been linked to a spectrum of clinical presentations, including different pain distributions together with the presence or absence of autonomic symptoms. The observation of mixed or overlap phenotypes suggests that multiple different pain disorders, currently considered as clinically distinct, may be part of a physiological continuum or spectrum. The number of diagnostic tests for SFN is increasing, although the clinical relevance of many is still not established. With the discovery of sodium channel variants underlying SFN, the understanding of the pathophysiology of the disorder has increased. Variants in sodium channel genes have been found in a relatively small percentage of SFN

patients, and while their number is likely to increase, other genetic etiologies are likely to emerge. Recent progress is likely to inform the development of new treatments and provide a mechanism-based precision medicine approach to neuropathic pain.

Key points

- Small fibre neuropathy (SFN) predominantly affects thinly myelinated Aδ-fibres and unmyelinated C-fibres.
- Quality of life in patients with SFN is significantly reduced.
- Reliable diagnostic tests are available to assess function and structure of small nerve fibres, and new screening tools will likely become available
- Variants in *SCN9A, SCN10A* and *SCN11A,* which encode $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ sodium channel alpha subunits, are linked to a continuum of pain phenotypes that include SFN.
- A single pain phenotype may be caused by a range of variants and one specific variant may lead to a range of phenotypes, even within one family.
- Expansion in knowledge on the pathophysiology of SFN will inform the development of new therapies.

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Appendix

Contributions

All authors contributed equally to researching data for the article, discussion of content, writing the article, and to the editing and review of the manuscript before submission.

Review criteria

A literature search was performed to find studies and reviews published on SFN. If appropriate, historical papers were also included. PubMed search was performed using the keywords “small fibre (fibre) neuropathy”, in combination with any of the following keywords: “aetiology/etiology”, “pathogenesis”, “diagnosis”, “prognosis”, “treatment”, “skin biopsy”, “quantitative sensory testing”, “nerve conduction study (studies)”. Furthermore, the bibliographies of all articles published between 1997 and 2017 regarding SFN were checked. Only articles in published in English were included.

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Table

Table 1. Diagnostic tests in Small Fibre Neuropathy

Table 1. Diagnostic tests in SFN
*Quantification of small nerve fibres
Skin biopsy
intra-epidermal nerve fibre density (IENFD)
dermal nerve fibre length
sweat gland and pilomotor muscle innervation
Cornea confocal microscopy
corneal nerve fibre density (CNFD)
corneal nerve branche density (CNBD)
corneal nerve fibre length (CNFL)
corneal nerve fibre turtuosity (CNFT)
*Functionality of small nerve fibres
Quantitative sensory testing
assessment of large and small sensory nerve fibre function
Microneurography
assessment of activity of C-nociceptors
Nociceptive Evoked Potentials
generation by laser (LEPs), contact heat (CHEPs) or pain-related (PREPs)
intra-epidermal electrical stimulation (IES)
*Imaging
Peripheral Nerve Ultrasound
(Functional) Magnetic Resonance Imaging
*Autonomic Testing
Thermoregulatory sweat testing
Quantitative sudomotor axon reflex testing (QSART)
Silicone impression method
Quantitative direct and indirect axon reflex testing
Sympathetic skin response (SSR)
Electrochemical skin conductance
Neuropad
Stimulated skin wrinkling (SSW)

Legends of figures

Figure 1. Prevalence of underlying causes in patients with SFN

Immunological causes: 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.

Figure 2. The triangle of *SCN9A*-related pain disorders

SFN = small fibre neuropathy, IEM = inherited erythromelalgia, PEPD = paroxysmal extreme pain disorder. Modified from Hoeijmakers, thesis: Small fibre neuropathy and sodium channels: a paradigm shift, 2014, chapter 9, figure 1.(*Hoeijmakers, 2014*)

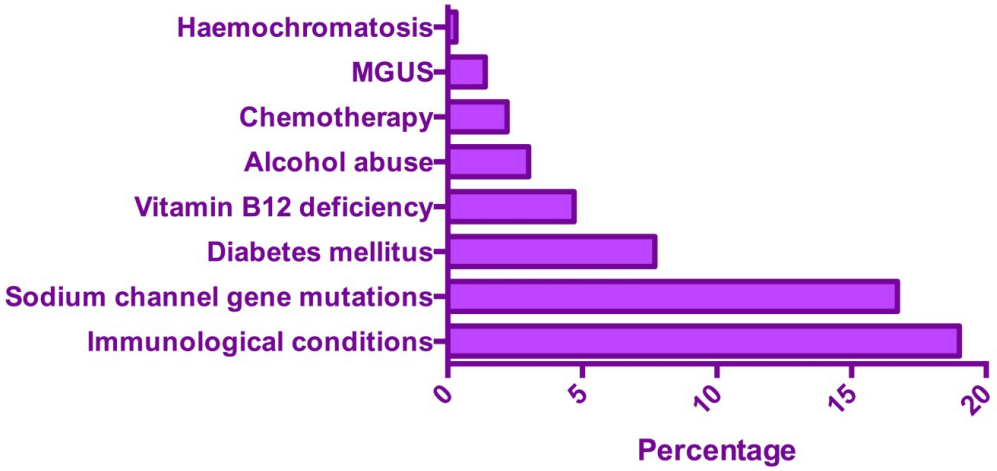

Figure 1. Prevalence of underlying causes in patients with SFN
Immunological causes: Sarcoidosis, Sjogren's disease, coeliac disease, other autoimmune diseases, and abnormal immunological laboratory findings (antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, monoclonal gammopathy, soluble interleukin-2 receptor, anti-tissue transglutaminase, and anti-Extractable Nuclear Antigen Antibodies)
MGUS: monoclonal gammopathy of undetermined significance.

151x77mm (220 x 220 DPI)

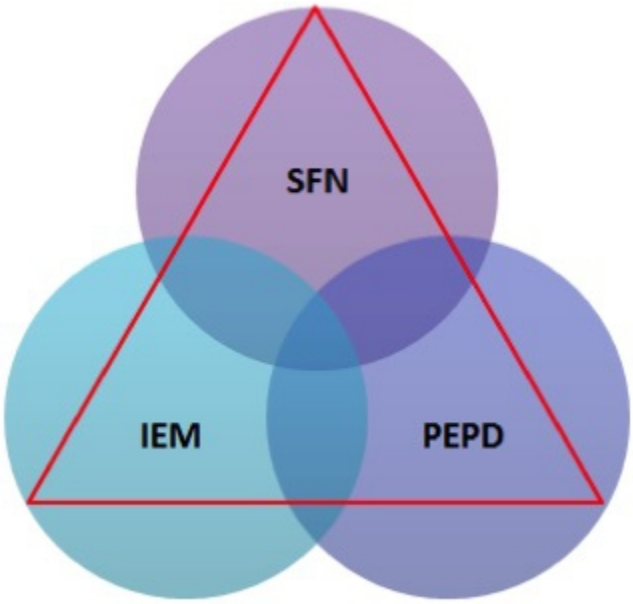

Figure 2. The triangle of SCN9A-related pain disorders
SFN = small fibre neuropathy, IEM = inherited erythromelalgia, PEPD = paroxysmal extreme pain disorder.
Modified from Hoeijmakers, thesis: Small fibre neuropathy and sodium channels: a paradigm shift, 2014, chapter 9, figure 1.(Hoeijmakers, 2014)

133x117mm (72 x 72 DPI)