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Small fiber neuropathy

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CHAPTER 8

SUMMARY, GENERAL DISCUSSION, AND FUTURE PERSPECTIVES

Neuropathic pain in patients with small fiber neuropathy (SFN) is difficult to control. To provide more specific treatments, with higher efficacy and fewer side effects, more knowledge is needed regarding the underlying pathophysiological mechanisms and conditions related to SFN. This thesis provides insight in the incidence of underlying SFN conditions in a large cohort of patients and presents data on potential mechanisms related to SFN, which is reflected in some studies investigating possible targeted therapeutic approaches in this debilitating condition. In the following, a summary of the chapters in this thesis will be provided, followed by future perspectives highlighting some caveats and unsolved needs in SFN.

Summary and general discussion.

Chapter 1 is an introduction in which general information about SFN is presented. The anatomy and function of the peripheral nerves is briefly described. Subsequently, the symptoms and diagnosis of SFN are clarified. In literature, various diseases have been suggested being related to SFN. These conditions and, specifically, the role of voltage-gated sodium channels are discussed. Finally, the current approach, from diagnostic to therapeutic management of neuropathic pain is addressed. The aims and outline of the thesis are presented in this chapter as well.

Associated conditions in SFN and pathophysiological mechanisms

SFN is a condition that reflects the complaints related to small nerve fiber damage. It is a "horrible condition that drives some patients crazy due to the excruciating continuously ongoing pain", as pointed out by a patient and agreed upon by many others suffering from SFN. Key questions are why specifically these nerve fibers get damaged and what the possible underlying pathophysiological mechanism would be. Various articles have been written regarding the possible underlying causes potentially related to SFN. Numerous diseases have been mentioned to be causal to SFN, however, most of these being based on cohort studies or case studies without providing any pathophysiologic evidence to develop SFN. For most of the diseases mentioned in literature potential treatments are available, justifying the need to test patients with SFN for the presence of such potentially related conditions. However, extensive diagnostic testing in SFN is not always the solution, and physicians should examine the burden to patients and related costs on the one hand, versus the benefits of an elaborative diagnostic approach on the other hand.

Chapter 2 illustrates elegantly the disadvantages of standard execution of additional tests having little if any benefit at all. Fabry disease is a metabolic disease that results in an accumulation of globotriaosylceramide (lyso-GB3) in different cell types, including the heart, kidneys, skin, and also neurons.[1,2] Some patients with Fabry disease suffer from burning or shooting pains in hands and feet. Therefore, it was thought that SFN could be the first symptom of Fabry disease as has been previously reported.[1-5] In a large cohort of patients (n=725) with pure SFN, we investigated the presence of Fabry disease and found no patients with this concomitant illness.[6] This finding suggests that pure SFN is unlikely to be the first expression of Fabry disease in adult patients, which contradicted literature on the presence of Fabry in

pure SFN.[7,8] Screening for Fabry disease in patients with SFN leads to high health care costs and may even provide confusing test results within a patient when one of the diagnostic tests turn out to be inconclusive, while the others are negative. Hence, we conclude that in patients with pure SFN, without other signs or symptoms of Fabry disease (like cardiac involvement, kidney involvement, or skin abnormalities), the screening for Fabry disease can be left out. However, this should always be chosen with great care, since this illness is treatable. It is suggested to re-evaluate those patients with additional involvement of other organs during evaluation over time and reconsider this testing if needed.

Patients that were referred to our center with the suspicion of SFN, have not only been tested for Fabry disease, but also for many other potentially related conditions based on literature review as presented in Table 1.[8-18]
The absence of Fabry disease in our cohort of patients with SFN triggered the thought of investigating the prevalence of other conditions too, which is presented in **Chapter 3**. In the SFN cohort (n=921), the most prevalent conditions were: autoimmune diseases (including abnormal immunological laboratory findings) in 19% of the patients, sodium channel gene variants (including variants with uncertain clinical significance, possibly pathogenic, probably pathogenic or pathogen variants)[19] in 16.7%, diabetes mellitus in 7.7%, impaired glucose tolerance in 9.7%, and vitamin B12 deficiencies in 4.7%. All of these conditions were more prevalent than reported in the general Dutch population. Besides, even though some patients already had a known condition related to SFN before screening, additional underlying conditions related to SFN were found in 26.7% of these patients.[20]

These findings are considered the first step in investigating the relationship between SFN and most prevalent underlying conditions found. More research is suggested to investigate and provide knowledge on the pathophysiology and mechanisms behind this relationship. This might eventually lead to more targeted treatments, as are discussed in chapters 5-7. Even though there are a lot of conditions present in patients with SFN, in the cohort of the study no underlying condition could be found in 53% of the patients, which is congruent with reported literature.[14,21-23] The findings also tell us that even though someone may have an illness that might contribute to SFN (e.g. diabetes mellitus) one should still examine the patient for other additional conditions that may co-contribute to its existence.

Table 1. Underlying conditions of SFN mentioned in literature.

Metabolic Diabetes mellitus Impaired glucose tolerance Rapid glycaemic control Hyperlipidaemia Hypo-/hyperthyroidism Chronic kidney disease Vitamin B12 deficiency	**Infectious** Human immunodeficiency virus (HIV) Hepatitis B/C Leprosy Lyme disease Epstein-Barr virus Influenza Critical illness or severe sepsis Herpes simplex infection Mycoplasma pneumonia Rubella Antecedent viral infection Syphilis Rabies vaccination Varicella Diphtheria Chagas disease Botulism	**Hereditary** Sodium channel gene mutations Primary erythermalgia Fabry disease Haemochromatosis Familial amyloidosis Hereditary sensory autonomic neuropathies Autosomal recessive hereditary neuropathy Pompe disease Ross syndrome Tangier disease Friedreich ataxia Cerebrotendinous xanthomatosis Familial burning feet syndrome Spinocerebellar Ataxia 3 Charcot-Marie-Tooth Mitochondrial disease Acute intermittent porphyria Generalized anhidrosis
Immune-mediated Sarcoidosis Sjögren syndrome Celiac disease Inflammatory bowel disease Monoclonal gammopathies Systemic lupus erythematosus Paraneoplastic neuropathy Rheumatoid or psoriatic arthritis (Primary) Amyloidosis Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) Vasculitis Guillain-Barré syndrome Autoimmune autonomic ganglionopathy Scleroderma Behcet disease Churg-Strauss syndrome Anti-sulfatide antibodies Anti-trisulfated heparin disaccharide antibodies	**Neurotoxic exposure** Alcohol abuse Chemotherapeutic agents Antiretroviral agents Pyridoxine (vitamin B6) intoxication Statins Antiarrhythmic drugs (flecainide, amiodarone) Antibiotics (metronidazole, nitrofurantoin, linezolid, ciprofloxacin) Industrial, environmental, and marine toxins (including heavy metals like thallium and lead) Ingestion of Clostridium botulinum toxin Tumour necrosis factor α inhibitors	**Idiopathic** Idiopathic small fiber neuropathy Burning mouth syndrome Fecal urgency and rectal hypersensitivity Complex regional pain syndrome **Other** Fibromyalgia Parkinson disease Postural orthostatic tachycardia syndrome Restless legs syndrome

Legend to table 1. This tables summarizes all the different conditions that are mentioned in the literature to be associated with SFN.

For some of the above-mentioned conditions, data have been provided regarding a pathophysiological mechanism leading to small nerve fibers damage. Some of these conditions are briefly discussed in the following:

- Diabetes mellitus (DM) is one of the best-known underlying diseases of painful neuropathies. It is believed that hyperglycemia-mediated superoxide overproduction may lead to micro vascular complications via various pathways.[24] But also other mechanisms of action are described, like an increase in inflammatory markers in the dorsal root ganglia (DRG).[25] However, even though these mechanisms might explain how the small nerve fibers are damaged, it still leaves us with some questions. Part of the patients with diabetes mellitus will develop a painful neuropathy as a complication of the disease, while others develop a non-painful neuropathy, and another subset does not develop a neuropathy at all. Moreover, next to neuropathic pain, also nociceptive pain occurs in DM.[26] Nociceptive pain is a result of injury of tissues, for example because of ischemia damaging the blood vessels and tissues. Which factors contribute to the susceptibility for developing a painful neuropathy are largely unknown. This also illustrates that a condition may be related to SFN, but may not directly cause SFN.[27]
- Sodium channels play an important role in neuropathic pain. The SCN9A-, SCN10A-, and SCN11A-gene are encoding for $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ respectively, which are preferentially expressed in the peripheral nerves and the DRG neurons. Gain-of-function mutations in these genes are found in around 15% of the patients with SFN[20,28] and can cause increased firing frequency and spontaneous firing of the neurons of the DRG.[29-34] These changes may lead to a decreased neurite length, but no DRG neuron death occurs.[29]

Even though the screening of underlying conditions in patients with SFN is very comprehensive, in half of the patients, no conditions can be found and these patients are still idiopathic after an extensive diagnostic work up.[20-22] This might suggest that there are still unknown internal/external mechanisms that cause damage to the small nerve fibers, such as other gene mutations leading to hyperexcitable neurons or intracellular deficits leading to a disturbed axonal transport.

Treatment of neuropathic pain in SFN

About 5-10% of the general population is suffering from neuropathic pain,[35] which is caused by a disease or lesion that affects the somatosensory nervous system.[36] Patients with SFN are suffering from excruciating neuropathic pain, having a negative impact on their quality of life.[37] Therefore adequate treatment is desirable. There are different types of drugs that are used to reduce the symptoms of SFN, i.e. anticonvulsants, antidepressants, opioids, and topical agents. In **chapter 4**, the different therapeutic possibilities are mentioned with their known pathophysiological aspects, side effects and precautions. Especially in the elderly, a large proportion of patients with SFN (19% begins at the age of 65 years or older), the treatment is more challenging because of frequent comorbidity and the use of co-medication.[38] Therefore, other first-line treatments or another regimen of use of neuropathic agents might be considered compared to younger patients.

Even though several drugs are available for the treatment of neuropathic pain, and practical treatment algorithms are available, still only 50% of the patients have demonstrated a 50% reduction of their pain experience, often with disturbing side effects.[38,39] One of the crucial things is that all these medications are not very specific and are only used to reduce the symptoms, but not heal the patients or the small nerve fibers' damage. Therefore, we are in desperate need for new and more targeted treatment options.

Lacosamide is an anticonvulsant that selectively acts on the sodium channel $Na_v1.3$, $Na_v1.7$, and $Na_v1.8$. Next to this selectivity in sodium channels, lacosamide spares the channels with a normal activity and only inhibits the currents of hyperexcitable neurons. Thereby, it binds to the channels with a slow- or fast-inactivated state.[40-46] Lacosamide has not been tested before in patients with SFN. In studies with painful diabetic neuropathy however, a reduction in neuropathic pain was found, although not robust.[47-50] In **chapter 5**, the rationale and the design of the Lacosamide-Efficacy-'N'-Safety in SFN (LENSS-study) is explained in detail.
The LENSS-study was a randomized, double-blinded, placebo-controlled crossover trial. The primary objective of this study was to evaluate the efficacy of lacosamide versus placebo in subjects with *SCN9A*-associated SFN. The primary efficacy endpoint was defined as at least a 1-point decrease on the daily pain intensity numerical rating scale (PI-NRS) and the secondary efficacy endpoint at least a 2-point decrease. These efficacy outcomes were chosen as such based on the IMMPACT recommendations.[51] Other secondary objectives were the evaluation of the safety and tolerability of lacosamide, and the effect of lacosamide versus placebo on autonomic symptoms, daily sleep interference, and quality of life.
To assure that the study results could be interpreted with sufficient power and because *SCN9A*-associated SFN is relatively rare, a crossover trial design was chosen. Another advantage of the crossover design was that the influence of confounders (e.g. age, gender distribution) could be reduced, since every patient will be his/her own control, an extremely important entity in a heterogeneous condition like SFN. Patients were given a dose of 200mg BID of lacosamide (and placebo in the other treatment period). This dose was selected based on previous studies, where it was shown that 200mg BID was effective and the side effects were acceptable, in contrast to a dose of 100mg BID which had few side effects but was less effective and 300mg BID which was effective however caused a lot of side effects.[52] The treatment period for both lacosamide and placebo had duration of eight weeks. This was chosen because of the knowledge that the analgesic effect of the pain medication may take several weeks to occur.[53]

In **Chapter 6** the results of the LENSS-study are described.[54] In total 24 patients received lacosamide and 23 of them placebo. In 58.3% the average pain decreased with at least 1 point on the PI-NRS during the lacosamide period, compared to 21.7% during the placebo period (p-value = 0.0045, with an odds ratio of 5.65 and a 95% confidence interval of 1.83-17.41). A decrease of at least 2 point on the PI-NRS was found in 33.3% in the lacosamide period and in 8.7% in the placebo period (p-value = 0.0244, with an odds ratio of 10.58 and a 95% confidence interval of 1.63-68.63). Additionally, in the lacosamide group, 33.3% reported that their general condition improved, versus 4.3% in the placebo group (p-value = 0.0156), captured with the Patients' Global Impression of Change (PGIC) questionnaire. Other secondary

outcomes showed that there was a significant positive effect on the daily sleep interference and there was a significant decrease in surface pain. In contrast, there was no significant improvement on quality of life or autonomic symptoms. The most common side effects of lacosamide were dizziness (41.7%), nausea (25.0%), and headache (25.0%), which is in agreement with the known adverse event profile reported, although these were addressed as being mild.[52] However, these complaints were also the most frequent adverse event during the placebo period (17.4% for all three complaints). Furthermore lacosamide was safe to use.
The results of this study are in line with the clinical experience that the current treatment possibilities cause a 50% reduction of the complaints in 50% of the patients.[39,55] Based on the theoretical background of the working mechanism of lacosamide on this specific group of patients, a larger effect could be expected. Even though the effect was similar than in other drugs, in our study patients were allowed to continue most of their pain medication, and therefore the treatment effect may even be bigger in drug-naïve patients. Whether lacosamide is also beneficial in SFN patients without SCN9A mutations, remains to be investigated.
One can also question if the right outcome measure has been used to investigate the efficacy of the medicine. For this study, the primary efficacy endpoint was at least 1-point decrease on the PI-NRS, based on guidelines for painful neuropathic studies.[51] There are a lot of different outcome measures regarding measuring the effect on pain, the 1-point or 2-point decrease on the PI-NRS can be used, but also a 30% or 50% reduction from baseline on the PI-NRS is mentioned.[51] Perhaps we should not look at these numbers since these are simple ordinal metrics with no numerical value, but we have to start listening to our patients and take their response's addressing voices into account. A patient score going from 8 to 7, does not per se mean anything, since the patient may still feel terrible. Or what if a patient's pain goes from 6 to 5, but they feel much better? Therefore, we should focus more on patients' response questionnaires like the Patients' Global Impression of Change (PGIC) addressing the clinical meaningfulness of their personal experience rather than looking at these insignificant numbers or multidimensional scales.[56 57]
In the LENSS study, no significant effect of lacosamide on the autonomic symptoms was found. An explanation could be that the side effects that are caused by using lacosamide mask the effect of lacosamide on the autonomic symptoms, because they are comparable; for example, dizziness is an autonomic symptom, but also a side effect of lacosamide. So the questionnaire to register autonomic symptoms might be influenced by the presence of similar side effects.
The influence of small fiber neuropathy on the quality of life of these patients has been investigated earlier.[37] The biggest declines were found in the domains of physical role of functioning and body pain.[37] By decreasing the intensity of pain in these patients with lacosamide, it could be expected that the quality of life would increase because the role of body pain would decrease. However, in this study this was not found, not even in the pain domain, which could be explained by a study period that was too short (8 weeks) to notice a significant reduction in quality of life.
To conclude, the study showed that lacosamide is an effective, safe and tolerable treatment for *SCN9A*-associated SFN. However, the study has to be confirmed in a larger cohort and in patients without an SCN9A-variant before proposing the therapeutic use of this drug.

The LENSS-study is an example of a study that investigates a drug that is more targeted than other current available treatment possibilities for SFN. However, a targeted approach is only possible when the target is known. As mentioned earlier, in a large proportion of patients with SFN no underlying conditions have been found. However, the question is what to do if there is no defined underlying condition? In patients with SFN, a role of the immune system is suggested in those with associated diseases, such as sarcoidosis, Sjogren disease, and celiac disease.[23,58,59] Also the presence of inflammatory changes,[60] autoantibodies,[61,62] and elevated cytokines[63] provide some support for the hypotheses that in SFN the immune system plays an important role, even in absence of immune-mediated diseases. Without knowing the specific disturbance in the immune system, there are treatment possibilities based on this hypothesis. Based on literature review, some open-labelled studies in patients with painful neuropathies treated with intravenous immunoglobulin (IVIg) have shown substantial relief, justifying the exploration of IVIg as a new treatment modality in SFN in a more extensive manner.[64,65]

Chapter 7 describes a randomized, double-blinded, placebo-controlled, parallel study evaluating the efficacy and safety of IVIg in patients with predominant SFN complaints.[66] The study design has been adopted from the landmark paper of IVIg in the treatment of patients with chronic inflammatory demyelinating polyradiculoneuropathy (ICE trial),[67] starting with a loading dose of IVIg of 2g/kg body weight given over 2-5 days. After that, patients will be receiving a maintenance dose of 1g/kg body weight IVIg every three weeks for three months, with an extension period after the randomization period of three months to determine the long-term effect of IVIg on pain. This is the first randomized clinical trial that will be investigating the efficacy, safety, and tolerability of IVIg in patients with idiopathic SFN. Patients randomized to placebo, will get the same treatment regimen. The study is currently running and aims to include 60 patients. The primary outcome will be a 1-point decrease change in the PI-NRS from baseline. Secondary outcomes will be 2-point decrease change in the PI-NRS from baseline, the influence of IVIg on autonomic symptoms, daily sleep interference, and quality of life. Because all of these outcome measures are based on questionnaires, also an objective outcome measure has been included, namely the cornea confocal microscopy.[68] This is a technique that can detect nerve fiber loss but also nerve fiber regeneration, investigated thoroughly in patients with diabetes mellitus.[69,70] In this sub-study, only patients with an abnormal skin biopsy and no underlying conditions (idiopathic SFN) will be examined. If IVIg is proven to be effective, more insight could be obtained to examine the underlying pathophysiology in patients with idiopathic SFN.

Future perspectives

In this thesis, more insight is provided regarding the underlying conditions that are prevalent in patients with SFN. In addition, new treatments are investigated, not only to give more possibilities for patients to reduce their complaints, but also to gain more insight into the pathophysiology of SFN. So all studies that are described in this thesis contribute to the knowledge on SFN, but also generate more research questions, which can be investigated in the future.

Diagnostics and clinical outcome measures

The complaints of SFN are mostly subjective feelings, which are difficult to measure objectively. At the moment, skin biopsy and temperature threshold testing are used to confirm the diagnosis of SFN.[9,18] However, the intensity of pain, different pain sensations, quality of life, and autonomic symptoms should all be evaluated by questionnaires because of the lack of an objective measurement. This could lead to biased results, as mentioned above in the LENSS study, where the influence of lacosamide on autonomic symptoms might be influenced by the occurrence of side effects, which are not differentiated through the questionnaire. Future studies should aim to develop a tool that can measure the autonomic function.

In addition to objectifying more symptoms of SFN, it would be very worthwhile to have a diagnostic tool, which can be used in clinical trials.

Skin biopsy is used at the moment as the golden standard to diagnose SFN, together with the temperature threshold testing. However, the sensitivity of the skin biopsy is moderate. When the intraepidermal nerve fiber density (IENFD) is normal in patients with possible SFN, it could suggest that there is no SFN, but it is also possible that there is a pre-degenerative functional impairment of the small nerve fibers, which cannot be detected with the current skin biopsy method. It is known that the IENFD decreases with increasing age[71] and the IENFD is stable within a 3-week period and for right and left side.[72] The decreasing IENFD in aging might be due to the aging of the central nervous system.[73]

A small study investigated the longitudinal trend of the IENFD in patients with idiopathic SFN (n=25), found no different degree of decrease in IENFD compared to patients with SFN and diabetes mellitus or glucose intolerance.[74] It would be of interest to compare the decrease in IENFD in patients with (complaints of) SFN and healthy subjects. Besides, the proximal/distal IENFD ratio can give more insight and be of value for diagnosing SFN.[75] Currently, the distal IENFD is used for diagnosing SFN. The ratio between the proximal and distal IENFD is investigated sparsely. One study showed that there was a greater reduction in the IENFD of the distal leg compared with the thigh, resulting in an elevated proximal/distal IENFD ratio, compared to healthy controls.[76,77] The use of the longitudinal course of the distal IENFD and/or the use of the proximal/distal IENFD ratio, in addition to the current one-time distal IENFD might be an enrichment for the diagnostic workup for SFN.

Skin biopsy is an invasive, time-consuming and expensive method for diagnosing SFN. In the Bowman's membrane of the cornea, the nerve endings of the unmyelinated C-fibers from the trigeminal nerve can be seen.[78] Corneal confocal microscopy (CCM) is a non-invasive method that detects these nerve fibers and nerve fiber loss in the cornea, with a high repeatability.[79]

This method has been primarily applied in patients with diabetes mellitus.[80] In two small studies, a decrease in the corneal nerve fiber density was found in patients with SFN.[69,81] Subsequently, it was also shown that CCM was not only useful to prove nerve fiber loss, but also nerve fiber regeneration after pancreas and kidney transplantation in patients with diabetes mellitus.[70] Therefore, CCM might be useful as a diagnostic tool to diagnose (non-length-dependent) SFN, and perhaps also as an objective outcome measure in clinical trials. Because of this, the CCM was included in the IVIG in SFN study.

All of the above-mentioned methods are based on the peripheral mechanisms that are known in SFN. However, this focus should be widened to also understand other potential pathophysiological mechanisms of pain in these patients like the (central) processing of pain stimuli. This entity is thought to be very complex, including different regions of the brain, like the cortex, subcortical structures and the midbrain.[82] In addition, chronic pain may lead to structural changes in the brain.[83] The pattern of these changes may differ among different pain syndromes and may be reversible.[84] Functional imaging of the brain has shown specific brain activity patterns in patients with pain.[85,86] To date, there is no objective tool to measure pain, but only questionnaires are available like the neuropathic pain scale (NPS), Pain Intensity Numeric Rating scale (PI-NRS), or the Visual Analogue Pain Scale (VAS). Functional MRI (fMRI) data can provide more insight into the specific pathways of neuropathic pain in SFN. Additionally, the fMRI can possibly be used in the future as a biomarker for evaluation in clinical trials. This technique may also elucidate differences that might reflect the heterogeneity of SFN, as has been demonstrated in patients with migraine.[87]

The finding of new biomarkers could be very helpful in conditions like SFN.[88] With the finding and presence of biomarkers, patients can be stratified in different groups, new treatment targets arise, and more personalized treatments can be given.[89] Besides, specific biomarkers can create an opportunity to grade disease severity, which is not possible at current stage.

In the literature some biomarkers are linked to neuropathic pain. Post-transcriptional regulator molecules, microRNAs, are reported to be dysregulated in patients with pain.[90] MicroRNAs are crucial micro-modulators of normal cellular homeostasis, and dysregulation has been associated with different conditions such as cancer,[91] cardiovascular diseases,[92] and neurodegenerative disorders.[93] In animal pain models, microRNA modulation is present in different levels, like the sciatic nerve, DRG, spinal dorsal horn and the brain.[90] Additionally, it has been found that microRNAs control sodium channel expression.[94] Besides the finding that microRNAs have a potential of being a specific biomarker for neuropathic pain, it could possibly also create new therapeutic possibilities, as shown in animal models.[95,96] Because microRNAs are present in all biofluids, it can be searched for in patients with SFN in the blood or in the cerebrospinal fluid as is done in other pain conditions.[97,98]

Also cytokine-related biomarkers have been found in neuropathic pain, for example anti-tumor necrosis factor (TNF)-α. Upregulated TNF-α is believed to play a role in the development, facilitation, and maintenance of neuropathic pain.[99-103] Thereby, it is shown that agents that antagonize TNF-α can reduce pain-behavior in animal models.[104,105]

A totally different biomarker that is mentioned in literature, is objectifying the hyperexcitability of the small nerve fibers, for example with microneurography. The finding that in patients with neuropathic pain due to peripheral neuropathy a large proportion of the nociceptors had a

significant ongoing activity, led to the hypothesis that microneurography could be a biomarker for pain.[106] Microneurography can record the peripheral C-nociceptors in humans and aminals,[107] which make it an interesting method to be used in clinical trials.

A targeted approach can be used to search for the above-mentioned biomarkers in SFN. An untargeted approach can also be considered, although this has some advantages and disadvantages. This cohort of patients is probably very heterogeneous, which might make it very difficult to find a specific biomarker, compared with subgroups (for example idiopathic SFN patients with abnormal skin biopsy). However, this group is very suitable because of the large sample size for modern statistical techniques, like machine learning with which biomarkers can be identified out of large datasets.[108,109]

To find these biomarkers, different methods are described, for example metabolomics or proteomics. Metabolomics is the profiling of metabolites, with nuclear magnetic resonance spectroscopy,[110] mass spectrometry,[111] gas chromatography,[112] or liquid chromatography.[113,114] The analysis can be targeted (quantitative analyses of a substrate or product metabolites of a target protein), untargeted (overview of whole-cell metabolic patterns), or metabolic profiling can be performed (quantitative analyses of a set of pre-defined metabolites). Proteomics is the quantitative analyses of the composition of proteins in a cell, tissue, or organism.

A recent study investigated metabolomics and proteomics in sciatic nerves in diabetic and healthy control rats. Alterations in the metabolic lipids were found, which were more present distal than proximal. In addition, increased proteins were found in the sural nerve and not more proximal.[115] These findings gave more insight in the consequences of diabetes mellitus and the influence on the nerve fibers. This is one example of how metabolomics or proteomics can provide more insights in underlying pathophysiological mechanisms, but may also reveal specific biomarkers.

In many diseases, the correlation between subjective and objective measures is weak.[116] Thereby, subjective measurements are highly variable and therefore only really useful when the effect of an intervention is large. The invention of objective tools to measure the function of the nerve fibers or autonomic symptoms or the discovery of biomarkers is therefore an important step. However, we should also focus on the opinion of the patients and listen to what they have to say. What does improvement of a biomarker following treatment mean if the patient is still having the same complaints? Do we conclude that our treatment is effective or not? Therefore, we should, besides objective measurements, include the opinion of the patient (like the PGIC). Or maybe the disability and functionality of patients should be taken more into consideration, with for example the small fiber neuropathy Rasch-built overall disability (SFN-RODS) as an option.[117] Moreover, the opinion of the patient should also be used in designing studies, making decisions, and evaluating treatments. With this we can shift our focus from statistical significance to clinical relevance.[118] Shared-decision making is defined as an approach where patients and clinicians share the best available evidence in order to make a decision, where patients are supported to consider different options and point out their preference.[119,120]

Lately, shared-decision making is more and more used in clinical practice. However, it has been known for a long time that patients prefer to have experts perform the problem-solving tasks,

but wish to take an active role in decision making.[121] Shared-decision making was first proven to be effective in serious or life-threatening conditions, when different therapies exist with different benefits and risks.[122,123] Shared decision-making is also useful in situations where outcomes are uncertain. For neuropathic pain, current treatment possibilities are not satisfactory at the moment, as discussed earlier. Therefore, when patients with SFN start using one of these therapies, the result is uncertain (trial and error approach). It is shown that the implementation of shared-decision making in pain management will increase the satisfaction of patients.[124,125] Because pain is a multidimensional entity, shared-decision making could lead to a more bearable experience of their complaints.

In studies, quantitative data is often used without the presence of qualitative data. Quantitative data consists of close-ended information, such as rating scales and other questionnaires. On the other hand, qualitative data consists of open-ended information that is gathered for example by interviews and focus groups. The addition of qualitative data can be used to elaborate, clarify, or build on findings from other methods, but also for looking at a research question from different angels, for example from a patients perspective or other caregivers. With this we can evaluate why patients think their quality of life is diminished, or which other things they experience because of SFN. Or focus groups with clinical experts from different disciplines can be organized, to develop new ideas, insights or theories. So for some research questions a single research method might not be enough.[126] Mixed methods analyses are used to combine these two types of data by triangulation.[127] The combination provides strengths that can neutralize the weaknesses of both quantitative (weak knowledge of context) and qualitative (biased interpretations) research.

Mixed methods analyses and shared-decision making are two examples in which patients and physicians are 'forced' to talk and listen to each other. However, also the communication between patients themselves should be stimulated. Patient can give advice or share experiences with each other. It would be beneficial to create a platform in which patients can be in contact with each other, but also caregivers and physicians should be a part of this. Working together can on the one hand improve the patient care, but on the other hand also gain new ideas or insights. In epilepsy, for example, it is shown that an online platform benefits in finding other patients experiencing the same symptoms and learning more about the symptoms and treatments.[128]

In line with this, one could also think about making a mobile application wherein patients can monitor their complaints, for example with questionnaires or diaries.

Associated conditions and pathophysiology

To confirm if some underlying conditions, which are found in patients with SFN, are really a cause of the disease, more studies should be conducted. In diabetes mellitus, a lot of animal studies are already performed.[129-131] This should also be executed (more) for other conditions like vitamin B12 deficiencies and autoimmune disorders. When knowing the exact underlying pathophysiology of these conditions, this could lead to possible treatment options. The advantage of interfering with these pathways with for example targeted drugs, is that the disease could possibly be solved and the nerve fibers can be regenerated, instead of symptom reduction as we do with our current practice.

When potential underlying mechanisms are hypothesized, animal models can give evidence for this. For example, mouse models can be used, in which some mice are exposed to the hypothesized underlying mechanism, and the others don't. After that, differences can be visualized, like pain, anxiety, and distress.[132] It would also be interesting to investigate if all animals exposed to that mechanism develop the same complaints. Animal models can also be used to see the effect of different levels of biomarkers, again to prove their causality.[133] In models for sodium channel gene mutations, often zebra fish are being used.[134] In these, transfected lines can be created, with the mutation of interest, and compared to the wild types. On the one hand, these animal models can be used to search and prove underlying mechanisms. On the other hand, they are of importance for testing different treatment possibilities.

The finding of mutations in the sodium channels $Na_v1.7$,[32] $Na_v1.8$,[33] and $Na_v1.9$,[34] was a large breakthrough in SFN, and has led to more insight in the pathophysiology, and to new treatment possibilities, for example with pharmacogenomics.[135] In addition, this has led to the idea that maybe other sodium channels or other mechanisms might also be responsible for neuropathic pain in SFN. In DRG, sodium channels $Na_v1.3$ and $Na_v1.6$ are also present and seem to have a role in pain as well.[28,136-140]

However, sodium channels are working together with other channels and have some corresponding characteristics. Potassium and calcium channelopathies have also been associated with pain.[141]

To investigate which other gene mutations are present in patients with chronic neuropathic pain, next generation sequencing (NGS) like whole exome sequencing (WES) or whole genome sequencing (WGS) can be used as an untargeted approach, while the analysis of candidate genes can be a useful targeted method. The PROPANE study group aimed to identify why patients with a common associated condition can have different phenotypes, for example a painful or painless neuropathy in patients with DM. The findings of this study will be published soon, hopefully providing us more insights into the genetic background.[34,142] The advantage of WES analyses is that not only preselected variants can be found, so it is an example of an unbiased molecular-genetic approach.[143] With this, new insights can be gained and a possible explanation for the 50% of idiopathic patients can be found. However, WES analyses also have disadvantages. With this technique, various variants will be found in even only one person. When searching for common variants in a cohort, even more different results will arise. For this, again machine learning or clustered data analyses can solve this, to search for correlations even between different variants in relation to patient's personal determinants like age, gender, educational level, habits, occupation, etc.

Although sodium channel gene mutations have been proven to be responsible for the clinical picture in a proportion of patients suffering from SFN, it is remarkable that there is a marked clinical heterogeneity between these patients, even when the same mutation is found.[144] Furthermore, in some patients a trigger (like a viral infection, trauma, operation, severe exercise, pregnancy of vaccination) precedes the clinical symptoms. Since all these factors demand a lot of energy of the body, dysfunction of mitochondria might be an explanation. In case the energy supply or reserves are not sufficient, this may lead to nerve damage. Both in the central and in the peripheral nervous system neurons have a high-energy demand, which

is reflected by the high number of mitochondria in these cells.[145] Especially unmyelinated neurons and the nerve endings contain mitochondria.[146,147] Dysfunctional mitochondria or a disturbed migration of healthy mitochondria to the nerve endings can result in a disturbance of different steps in the oxidative phosphorylation. Peripheral neuropathic pain has been shown to be a result of ATP-depletion, an elevation of free radicals or inadequate calcium buffering in the cell.[146] When the ATP-production is too low this might lead to a dysfunctional Na^+/K^+-pump, leading to abnormal firing of the neurons.[147] A combination of a high sodium influx in sodium channel gene mutations and dysfunctioning mitochondria, will lead to a reverse-mode Na^+/Ca^{2+} exchange because of the increased intracellular sodium level, resulting in import of calcium into the cell, rising to toxic levels and causing cell death.[148-150]
But also defects in the mitochondrial dynamics might contribute to the origin of SFN. Since most patients show a length-dependent pattern, disturbances in the axonal transport or mitochondrial fusion or fission could be responsible for the nerve endings damage.[150-152] Already, in other hereditary neuropathies of the Charcot-Marie-Tooth spectrum these mechanisms have been shown to be pathogenic.[151] Both DNA-analysis of mtDNA or nuclear DNA responsible for the mitochondrial dynamics genes might be of interest in SFN.
Also epigenetic mechanisms might play a role in the pathophysiology of SFN.[153] These mechanisms can enhance or suppress gene expressions, without altering the primary DNA sequence.[154] This may explain why some people are carrying for example an SCN9A-gene mutation, without having complaints, while a different person with the same variant does have complaints of SFN. It may also provide the explanation for the development of SFN symptoms later in life in patients carrying a sodium channel gene mutation. Epigenetics may therefore be an important link between acquired and hereditary causes.

Treatment

There is high demand for new treatment possibilities. The current available medications are not effective in all patients and have side effects that can be very bothersome.
At this time, more targeted treatments are being investigated. Lacosamide is a sodium channel blocker that is selectively blocking sodium channels $Na_v1.3$, $Na_v1.7$, and $Na_v1.8$.[42] At present, sodium channel blockers with a high selectivity for $Na_v1.7$ are being investigated. Such a selective sodium channel blocker was studied in trigeminal neuralgia.[155] Even though this was a $Na_v1.7$-selective and state-dependent sodium channel blocker, the response in pain reduction was again similar as the current medications, a 50% reduction in paroxysms in 60% of the patients with the use of the selective sodium channel blocker, compared to 21% in the placebo group. In addition to the comparable pain effect, additionally side effects occurred similar to the side effect profile of current available medications, e.g. headache and dizziness. So it might be a utopia to expect that a selective and targeted approach always will lead to better efficacy and fewer side effects. This might be explained by the idea that some underlying conditions of SFN are not causative alone, and thereby other pathways play a role at the same time. A more recent study investigated a different $Na_v1.7$ blocker in a randomized, placebo-controlled, double-blinded study.[156] However, this agent showed no statistically significant decrease in the average pain score. Besides, the effect was even lower than seen in pregabalin study. The past years, a lot of patents are treated with sodium channel blockers.[157] The future

will show if this is the right direction and the solution for patients with SFN. One could also speculate whether studies combining different agents could provide via different action mechanisms more relief to the experience of pain.

Until now, it is still unclear why some patients respond to treatment and others don't. For this, it would be very useful to have some patient-specific factors known that influence the drug response. A recent study started to search for associations between underlying conditions and the response on neuropathic pain medication. They found that diabetes mellitus had an impact on the effect of anticonvulsants and the duration of pain had an impact on the effect of antidepressants on neuropathic pain.[158]

The genetic and functional findings in SFN may lead to the development of new targeted treatments. This can also be supported by pharmacogenomics. As mentioned earlier, not all patients with SFN respond to the current available treatments in the same way and even the side effects differ between patients. Pharmacogenomics may be an additional tool to predict the variability in treatment efficacy and side effects.[159] A few experiments already showed that with pharmacogenomics, it could be predicted if the hyperexcitability of nerve fibers due to a specific *SCN9A* mutation is reduced by a specific treatment, or not.[160,161] With these results, eventually prediction models can be developed to be used in daily clinical practice. In the long term, this may lead to higher satisfaction of the patients and lower health care costs. However, when it is predicted that a specific treatment should work in specific patients, naturally this should still be proven in practice, as for example is done in patients with erythromelalgia.[162]

Targeting the sodium channels may be of interest in patients having mutated channels (about 15% of the patients), though other patients may also benefit from sodium channel blockers. In over 50% of the SFN patients no underlying condition can be found. However, for new treatment possibilities for these idiopathic patients, we should think about possibilities that are beyond the current knowledge of the pathophysiology. One of these new ideas is the use of intravenous immunoglobulins in SFN. The results of the IVIg in SFN study will become available in 2019. If positive, a lot of new research questions will arise, to figure out how this treatment works in these patients, which patients would benefit, and what treatment regime should be used and for how long. To ensure health insurance coverage and registration of IVIg as a treatment option for patient with SFN, clear evidence of the efficacy should be available, and probably future confirmation studies should also investigate the cost-effectiveness of this treatment. In extension to this study, the benefit of other immunomodulating therapies in SFN may also be hypothesized

Corticosteroids are working via various mechanisms, for example inhibition of the T-cell-dependent immunity and interfering with cytokines of which TNF-α is an example.[163] As mentioned earlier, there are suggestions that TNF-α is a biomarker in neuropathic pain, so corticosteroids might be effective. An example from current practice is the use of prednisone in patients with post-herpetic pain,[164] as well as reduction of the pain resulting from a vasculitic neuropathy in HIV.[165] There are also studies that investigate the role of biologicals as an alternative for chemical substances in chronic pain. Monoclonal antibodies (mAbs) are very specific and have a high affinity.[166] However, the mAbs should attack the right targets to be effective. There are mAbs that inhibit TNF-α, interleukin-1 or interleukin-6, in immune-mediated conditions as rheumatoid arthritis. Therefore, it should be investigated if these are

still effective in diminishing non-inflammatory pain.[167] Biologicals can provide more specific and therefore safer alternatives in the future, though the high costs of these therapies are a limit to wide-spread use.

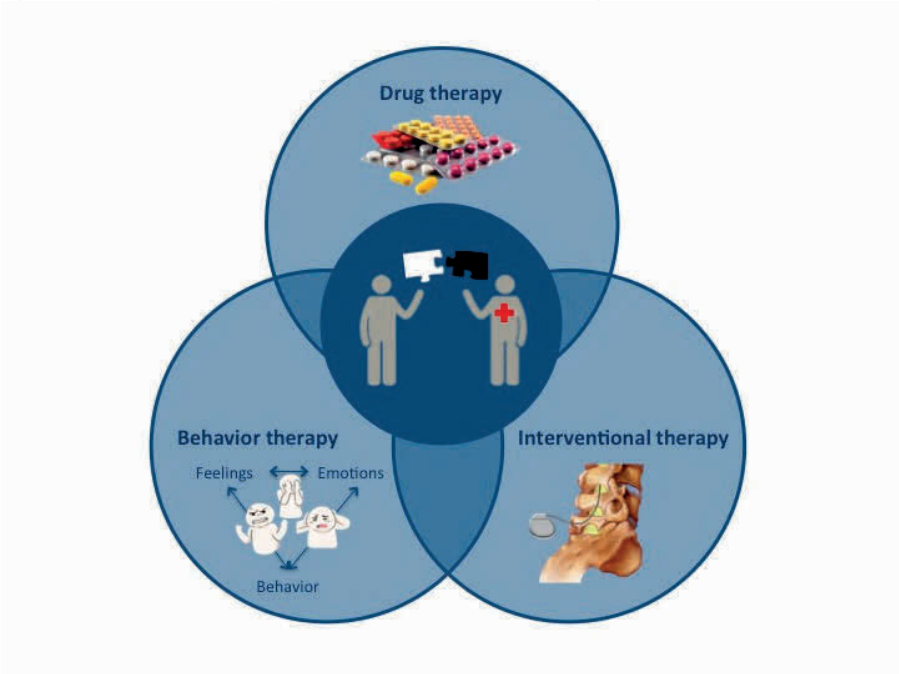
To take it one step further, maybe not only chemical or biological agents should be investigated more in the future, but it would be of interest to look more in depth into interventional methods, or combinations of these. Spinal cord stimulation could lead to a reduction of pain in chronic pain patients, based on the gate control theory and general principles of segmental pain inhibition.[168-170] Or, should we even move more upwards, to the brain, for new interventions? It is hypothesized that abnormal synchronization between brain networks in chronic pain can be disrupted by deep brain stimulation DBS.[171] Finally, repetitive transcranial magnetic stimulation is a noninvasive neuromodulation technique, which can possibly improve the efficacy of conventional medical treatments in chronic pain patients.[172]

Besides trying to treat SFN or diminish the symptoms, attention should be given to the consequences of the symptoms on patients' wellbeing. As described earlier, patients with SFN have a decreased quality of life,[37] but also affective disorders like anxiety or depression have a high prevalence.[173] High levels of depression and anxiety may worsen pain and pain-related disability.[174] Therefore, trials regarding the effect of interventions focused on mood disorders or coping with pain are of great interest. Mindfulness therapy has been described to improve pain, as well as depression symptoms and quality of life.[175] Furthermore, several trials have been performed with graded exposure or graded activity therapy in chronic pain, for example in chronic back pain.[176,177] There is some evidence that both of them may be effective, however, these therapies are not tested yet in patients with SFN.

The oldest known non-pharmacological method for relieving pain is music.[178] Pain can be diminished by passive music listening, called music-induced analgesia. Thereby, music can also diminish stress, depression and distress.[179] Even a 70% greater probability of reporting a pain decrease of at least 50% and a reduction in opioid medication as a result of music listening is reported.[179] In addition, changes on functional MRI are found.[178]

In patients with chronic neuropathic spinal cord injury pain, it is found that multidisciplinary cognitive behavioral programs improved pain intensity, pain-related disability, anxiety and participation.[180] So finally, why use only one method, when combining therapeutic strategies (figure 1) might be even better?[181]

Figure 1. Multimodal treatment possibilies and shared-decision making.



Legend to figure 1. This figure represents the mulitmodal treatment possibilities and shared-decision making in SFN.

Conclusions

SFN is a condition resulting in a heterogeneous cohort of patients. Not only the complaints can differ between patients, there is also a variety of underlying conditions that can possibly cause damage to the small nerve fibers. However, in a substantial part of the patients no underlying potential cause can be demonstrated. The knowledge that some conditions are more prevalent in patients with SFN compared to healthy subjects, like diabetes mellitus (including impaired glucose tolerance), autoimmune diseases (including abnormal immunological laboratory findings), sodium channel gene mutations, and vitamin B12 deficiencies, could lead to more specific research in the future. Unraveling the exact pathophysiological pathways behind these conditions leading to SFN perhaps may lead to better treatment options. As an example, the finding of sodium channel gene mutations, led to a more selective treatment with lacosamide, which can be used possibly in the future as a treatment option for a broader group of patients with SFN after confirmative studies have been performed. More specific treatments might result in better pain relief with fewer side effects. However, new insights may also lead to the finding that SFN might not be caused by one mechanism on its own, but it is a more complex process. In all cases, other multimodal new therapeutic strategies should be considered in the approach of SFN, as it is a debilitating disorder.

As already mentioned in the introduction of this thesis, our aim is to work from the perspective of the patients, searching for associated conditions and biomarkers, revealing the pathophysiological mechanisms behind this, which may lead to new treatment possibilities; the entire process should be evaluated with the patients, and this cycle can then be repeated. From bench to bedside and back again: translational research is of great importance to finally rule out SFN.

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CHAPTER 9

NEDERLANDSE SAMENVATTING

Dunnevezelneuropathie (DVN) is een aandoening waarbij pijn op de voorgrond staat. Dit is het gevolg van een beschadiging van de aller dunste zenuwvezels (dun-gemyeliniseerde Aδ-vezels en ongemyeliniseerde C-vezels), die normaal gesproken voor de registratie van pijn en temperatuur zorgen. Bij DVN ervaren patiënten neuropathische pijn, die meestal in de voeten begint. Daarnaast kan DVN ook autonome klachten veroorzaken, zoals duizeligheid, droge ogen, maag- en darmklachten en hartkloppingen. De combinatie van deze klachten leidt vaak tot een sterke verminderde kwaliteit van leven.
De diagnose DVN wordt gesteld op basis van typische klachten, in combinatie met een verlaagde intra-epidermale zenuwvezeldichtheid in het huidbiopt en/of een afwijkend temperatuurdrempelonderzoek. De behandeling is meestal symptomatisch, waarbij het vaak lastig is de neuropathische pijn onder controle te krijgen. Om meer specifieke behandelingen aan te kunnen bieden, met een hogere werkzaamheid en minder bijwerkingen, is meer kennis nodig omtrent de onderliggende pathofysiologische mechanismen en aandoeningen die geassocieerd zijn met DVN. Dit proefschrift geeft inzicht in de incidentie van onderliggende aandoeningen bij DVN in een grote groep patiënten met daarbij de mogelijke onderliggende mechanismen. Op basis hiervan zijn twee studies opgezet om een meer gerichte behandeling voor deze invaliderende aandoening te onderzoeken.

Hoofdstuk 1 is een introductie waarin algemene informatie over DVN wordt gegeven. De anatomie en functie van de perifere zenuwen wordt kort beschreven. Vervolgens worden de symptomen en de diagnose van DVN uitgelegd, zoals ook kort hierboven besproken is. In de literatuur worden verschillende aandoeningen in verband gebracht met DVN. Deze aandoeningen en in het bijzonder de rol van spanningsafhankelijke natriumkanalen worden besproken. Ten slotte wordt de huidige aanpak beschreven van diagnose tot de behandeling van neuropathische pijn.

Geassocieerde aandoeningen bij DVN en pathofysiologische mechanismen

DVN is een aandoening waarbij klachten ontstaan door beschadiging van de dunne zenuwvezels. Een patiënt beschreef het als: "vreselijke aandoening die sommige patiënten gek maakt vanwege de ondraaglijke, voortdurend aanhoudende pijn", waar vele anderen die lijden aan DVN zich in herkennen. De vraag is waarom specifiek deze dunne zenuwvezels beschadigd raken en wat het mogelijke onderliggende pathofysiologische mechanisme zou kunnen zijn. Er zijn diverse artikelen geschreven over onderliggende aandoeningen die gerelateerd zouden kunnen zijn aan DVN. Verschillende ziekten zijn genoemd als oorzaak van DVN, maar dit is meestal gebaseerd op kleine cohortstudies of casestudies zonder dat pathofysiologisch bewijs is geleverd over hoe dit leidt tot DVN. Voor een aantal aandoeningen die in de literatuur worden genoemd, zijn mogelijke behandelingen beschikbaar, wat het rechtvaardigt om patiënten met DVN op de aanwezigheid van deze aandoeningen te testen. Voor diagnostische testen moeten de lasten voor de patiënten en de bijbehorende kosten afwegen tegen de voordelen van een uitgebreide diagnostische aanpak.

Hoofdstuk 2 toont de nadelen van het standaard uitvoeren van aanvullende testen die weinig of geen toegevoegde waarde hebben. De ziekte van Fabry is een metabole ziekte die resulteert

in een opeenstapeling van globotriaosylceramide (lyso-GB3) in verschillende cellen, waaronder cellen van het hart, de nieren, de huid en ook de zenuwen. Sommige patiënten met de ziekte van Fabry lijden aan brandende of schietende pijn in handen en voeten. In de literatuur wordt beschreven dat DVN een eerste symptoom van de ziekte van Fabry kan zijn. Aangezien de aandoening behandelbaar is, zou testen voor deze aandoening van belang kunnen zijn. In een groot cohort van patiënten (n = 725) met pure DVN (zonder beschadiging van de dikke zenuwvezels), hebben we bij niemand de ziekte van Fabry aan kunnen tonen. Deze bevinding suggereert dat pure DVN waarschijnlijk niet de eerste uiting van de ziekte van Fabry bij volwassen patiënten is, in tegenstelling tot wat er eerder in de literatuur werd vermeld. Screening op de ziekte van Fabry bij patiënten met DVN leidt tot hoge kosten voor de gezondheidszorg en kan zelfs verwarrende testresultaten opleveren bij een patiënt, wanneer bijvoorbeeld één van de diagnostische testen een twijfelachtige uitslag geeft en de rest goed is. Daarom concluderen we dat bij patiënten met pure DVN, zonder andere tekenen of symptomen van de ziekte van Fabry (zoals betrokkenheid van het hart, nieren of huidafwijkingen), de screening op de ziekte van Fabry kan worden weggelaten. Dit moet echter altijd met de grootste zorg worden besloten, aangezien het een behandelbare ziekte betreft. Het voorstel is om de patiënten die in de loop der tijd betrokkenheid van andere organen ontwikkelen opnieuw te evalueren en eventueel dan alsnog te testen.

Patiënten die naar ons centrum worden verwezen met het vermoeden van DVN, worden niet alleen getest op de ziekte van Fabry, maar ook op vele andere potentieel gerelateerde aandoeningen op basis van literatuuronderzoek **(hoofdstuk 3)**. In het DVN-cohort (n = 921) waren de meest voorkomende aandoeningen: auto-immuunziekten (inclusief afwijkende immunologische laboratoriumuitslagen) bij 19% van de patiënten, natriumkanaalmutaties (inclusief varianten met onzekere klinische betekenis, mogelijk pathogene, waarschijnlijk pathogene of pathogene varianten) bij 16,7%, diabetes mellitus bij 7,7%, gestoorde glucosetolerantie bij 9,7% en vitamine B12-tekort bij 4,7%. Al deze aandoeningen kwamen meer voor dan beschreven in de algemene Nederlandse bevolking. Hoewel bij sommige patiënten al voorafgaand aan de screening een aandoening aanwezig was die gerelateerd is aan DVN, werd alsnog bij 26,7% van deze patiënten een andere onderliggende aandoening aangetroffen.

Bovenstaande bevindingen zijn de eerste stap in het onderzoek naar de relatie tussen DVN en de meest voorkomende onderliggende aandoeningen. Meer onderzoek is nodig om kennis te verkrijgen over de mogelijke onderliggende pathofysiologische mechanismen. Dit kan uiteindelijk leiden tot meer gerichtere behandelingen, zoals besproken in hoofdstuk 5-7. Hoewel verschillende aandoeningen bij patiënten met DVN voorkomen, kon in het cohort van de studie bij 53% van de patiënten geen onderliggende aandoening worden gevonden, wat overeenkomt met eerder gerapporteerde studies. De bevindingen van de studie laten ook zien dat, hoewel iemand misschien een ziekte heeft die kan bijdragen aan DVN (bijv. diabetes mellitus), een patiënt nog steeds moet worden onderzocht op andere onderliggende aandoeningen.

Voor sommige van de bovengenoemde aandoeningen is al wat bekend over het pathofysiologisch mechanisme dat leidt tot beschadiging van dunne zenuwvezels.

- Diabetes mellitus (DM) is een van de bekendste onderliggende aandoeningen bij pijnlijke neuropathieën. Er wordt verondersteld dat hyperglycemie-gemedieerde superoxide-overproductie op verschillende manieren kan leiden tot microvasculaire complicaties. Maar ook andere werkingsmechanismen worden beschreven, zoals een toename van inflammatoire markers in de dorsale ganglia (DRG). Hoewel deze mechanismen kunnen verklaren hoe de dunne zenuwvezels beschadigd raken, het laat nog steeds enkele vragen onbeantwoord. Slechts een deel van de patiënten met DM ontwikkelt een pijnlijke neuropathie als een complicatie van de ziekte, terwijl anderen een niet-pijnlijke neuropathie ontwikkelen, en een ander deel helemaal geen neuropathie ontwikkelt. Bovendien treedt, naast neuropathische pijn, ook nociceptieve pijn op bij DM. Nociceptieve pijn is een gevolg van een beschadiging van weefsels, bijvoorbeeld vanwege een verminderde doorbloeding die de bloedvaten en weefsels beschadigt. Welke factoren zorgen voor de ontwikkeling van een pijnlijke neuropathie zijn grotendeels onbekend. Dit laat ook zien dat een aandoening mogelijk gerelateerd is aan DVN, maar dat het DVN mogelijk niet direct veroorzaakt.
- Natriumkanalen spelen een belangrijke rol bij neuropathische pijn. Het SCN9A-, SCN10A- en SCN11A-gen coderen respectievelijk voor de natriumkanalen $Na_v1.7$, $Na_v1.8$ en $Na_v1.9$, die voornamelijk tot uiting komen in de perifere zenuwen en de dorsale ganglioncellen. Gain-of-function-mutaties in deze genen werden gevonden bij ongeveer 15% in een DVN cohort en kunnen leiden tot een verhoogde frequentie van vuren en spontaan afvuren van de neuronen van de DRG. Deze veranderingen kunnen leiden tot een afname van de lengte van de zenuwen.

Hoewel de screening naar onderliggende aandoeningen bij patiënten met DVN zeer uitgebreid is, wordt bij de helft van de patiënten geen onderliggende aandoening gevonden. Bij deze patiënten is de oorzaak ondanks uitgebreid diagnostisch onderzoek nog steeds onbekend, wat idiopathische DVN genoemd wordt. Waarschijnlijk spelen bij deze groep patiënten voor nu nog onbekende interne en/of externe mechanismen een rol bij het ontstaan van schade aan de dunne zenuwvezels. Hierbij kan gedacht worden aan mutaties in andere genen of verstoringen in het axonaal transport.

Behandeling van neuropathische pijn bij DVN

Ongeveer 5-10% van de algemene bevolking lijdt aan neuropathische pijn, die wordt veroorzaakt door een ziekte of beschadiging die het somatosensorische zenuwstelsel aantast. Patiënten met DVN lijden aan ondraaglijke neuropathische pijn, welke een negatieve invloed heeft op hun kwaliteit van leven. Daarom is een betere behandeling erg gewenst. Er zijn verschillende soorten medicijnen die worden gebruikt om de symptomen van DVN te verminderen, waaronder anticonvulsiva, antidepressiva, opioïden en lokale behandelingen. In **hoofdstuk 4** worden de verschillende behandelingsmogelijkheden benoemd met hun bekende werkingsmechanismen, bijwerkingen en voorzorgsmaatregelen. Bij 19% van de patiënten met DVN beginnen de klachten op een leeftijd van 65 jaar of ouder. Vooral bij ouderen is de

behandeling van DVN uitdagender vanwege vaker voorkomende comorbiditeit en het gebruik van co-medicatie.
Hoewel verschillende medicijnen beschikbaar zijn voor de behandeling van neuropathische pijn heeft slechts 50% van de patiënten een pijnreductie van 50%, waarbij daarnaast vaak vervelende bijwerkingen aanwezig zijn. Een van de redenen voor deze teleurstellende resultaten is dat de huidige medicijnen niet erg specifiek zijn en alleen worden gebruikt om de symptomen te verminderen, maar niet om de patiënten of de beschadiging van de dunne zenuwvezels te genezen. Daarom is er dringend behoefte aan nieuwe en meer gerichte behandelingsmogelijkheden.

Lacosamide is een medicijn dat wordt gebruikt bij de behandeling van epilepsie. Lacosamide werkt specifiek op het natriumkanaal $Na_v1.3$, $Na_v1.7$ en $Na_v1.8$. Naast de werking op deze specifieke natriumkanalen, bespaart lacosamide de kanalen met een normale activiteit en remt het alleen de overactieve zenuwen. Het bindt aan de kanalen met een langzame of snel-geïnactiveerde toestand. Lacosamide is nog niet eerder getest bij patiënten met DVN. In studies met pijnlijke diabetische neuropathie werd een vermindering van neuropathische pijn gevonden, hoewel deze resultaten niet heel overtuigend waren. In **hoofdstuk 5**, wordt de motivering en het ontwerp van de Lacosamide-Efficacy-'N'-Safety in SFN (LENSS-studie) in detail uitgelegd.
De LENSS-studie was een gerandomiseerde, dubbel-geblindeerde, placebo-gecontroleerde cross-over studie. Het primaire doel van deze studie was om de werkzaamheid van lacosamide versus placebo te evalueren bij patiënten met *SCN9A*-geassocieerde DVN. Het primaire eindpunt om de werkzaamheid te testen, werd gedefinieerd als een daling van ten minste één punt op de numerieke beoordelingsschaal voor de dagelijkse pijnintensiteit (PI-NRS) ten opzichte van baseline. Het secundaire eindpunt om de werkzaamheid van lacosamide te testen, was een afname van ten minste 2 punten. Deze uitkomstmaten voor de werkzaamheid werden als zodanig gekozen op basis van de IMMPACT-aanbevelingen. Andere secundaire doelstellingen waren de beoordeling van de veiligheid en verdraagbaarheid van lacosamide en het effect van lacosamide versus placebo op autonome klachten, dagelijkse invloed van pijn op het slapen en de kwaliteit van leven.
Omdat *SCN9A*-geassocieerde DVN zeldzaam is, werd gekozen voor een cross-over design. Een ander voordeel van het cross-over design was dat de invloed van andere bijdragende factoren (bijvoorbeeld leeftijd en geslacht) kon worden verminderd, omdat elke patiënt zijn/haar eigen controle was. Dit is belangrijk omdat DVN een heterogene aandoening is. In de studie kregen patiënten tweemaal daags een dosering van 200 mg lacosamide (en placebo in de andere behandelingsperiode). Deze dosering werd gekozen op basis van eerdere onderzoeken, waarbij werd aangetoond dat tweemaal daags 200 mg lacosamide effectief was en de bijwerkingen aanvaardbaar waren. Daarentegen bleek dat een dosering van 100 mg tweemaal daags minder effectief te zijn met weinig bijwerkingen en dat een dosering van 300 mg tweemaal daags effectief was maar veel bijwerkingen veroorzaakte. De behandelingsperiode voor zowel lacosamide als placebo was acht weken. Dit werd gekozen vanwege het feit dat het pijnstillende effect van de medicatie enkele weken kan duren.

In **Hoofdstuk 6** worden de resultaten van de LENSS-studie beschreven. In totaal kregen 24 patiënten lacosamide en 23 van hen placebo. Bij 58,3% nam de gemiddelde pijn af met tenminste 1 punt op de PI-NRS tijdens de lacosamide-periode, vergeleken met 21,7% tijdens de placebo-periode. Een afname van de gemiddelde pijn van ten minste 2 punten op de PI-NRS werd gevonden bij 33,3% van de patiënten in de lacosamide-periode en bij 8,7% in de placebo-periode. Bovendien rapporteerde 33,3% in de lacosamidegroep dat hun algemene toestand verbeterde, versus 4,3% in de placebogroep, gemeten met de Patients' Global Impression of Change (PGIC). Andere secundaire uitkomsten toonden aan dat er een significant positief effect was van lacosamide op de dagelijkse invloed van pijn op slaap en dat er een aanzienlijke afname van de oppervlakkige pijn was. Er was geen significante verbetering van de kwaliteit van leven of autonome symptomen. De meest voorkomende bijwerkingen van lacosamide waren duizeligheid (41,7%), misselijkheid (25,0%) en hoofdpijn (25,0%), wat overeenkomt met de bekende gerapporteerde bijwerkingen van het medicijn; deze bijwerkingen werden als mild beschouwd. Deze bijwerkingen waren ook de meest frequente tijdens de placebo-periode (17,4% voor alle drie de klachten). Bovendien was lacosamide veilig om te gebruiken.
De resultaten van deze studie zijn in overeenstemming met de klinische ervaring dat de huidige behandelingsmogelijkheden een 50% vermindering van de klachten geven bij 50% van de patiënten. Een groter effect werd verwacht, op basis van de theoretische achtergrond van het werkingsmechanisme van lacosamide op deze specifieke groep van patiënten. In onze studie konden patiënten voor het grootste deel hun eigen pijnmedicatie blijven gebruiken. Daarom zou het behandelingseffect van lacosamide misschien zelfs groter kunnen zijn bij patiënten die (nog) geen medicatie gebruiken. Of lacosamide ook effectief is bij DVN-patiënten zonder *SCN9A*-mutaties moet nog worden onderzocht.
Een vraag is of de juiste uitkomstmaat is gebruikt om de werkzaamheid van het medicijn te onderzoeken. Voor deze studie was het primaire eindpunt om de werkzaamheid te meten ten minste 1 punt afname van de gemiddelde pijn op de PI-NRS, gebaseerd op richtlijnen voor studies naar pijnlijke neuropathieën. Er zijn veel verschillende uitkomstmaten voor het meten van het effect op pijn, de 1-punts of 2-punts afname van pijn op de PI-NRS kan worden gebruikt, maar ook een vermindering van 30% of 50% ten opzichte van de baseline op de PI-NRS wordt vermeld. Deze schalen hebben als nadeel dat het ordinale maten zijn; de getallen die worden gegeven hebben dus geen numerieke waarde. Dat maakt rekenen met dergelijke getallen niet goed mogelijk. Bovendien weten we niet goed wat een klinisch relevant verschil is. Wanneer een pijnscore van een patiënt van een 8 naar een 7 gaat, betekent dat op zichzelf niets, omdat de patiënt zich nog steeds verschrikkelijk kan voelen. Of wat als de pijn van patiënten van 6 naar 5 gaat, maar ze voelen zich veel beter? Daarom moeten we ons meer richten op de klinische betekenis van de persoonlijk ervaring van patiënten, zoals gemeten met de PGIC, in plaats van onbelangrijke getallen of multidimensionele vragenlijsten te gebruiken.
In de LENSS-studie werd geen significant effect van lacosamide op de autonome symptomen gevonden. Een verklaring zou kunnen zijn dat de bijwerkingen die worden veroorzaakt door het gebruik van lacosamide het effect van lacosamide op de autonome symptomen maskeren, omdat ze vergelijkbaar zijn. Zo is duizeligheid bijvoorbeeld een autonome klacht, maar ook een bijwerking van lacosamide. De vragenlijst om autonome symptomen te registreren kan daarmee zijn beïnvloed door de aanwezigheid van vergelijkbare bijwerkingen.

De invloed van dunnevezelneuropathie op de kwaliteit van leven van deze patiënten is eerder onderzocht. De sterkste verminderingen van de kwaliteit werden gevonden in de domeinen van fysieke rol van functioneren en lichaamspijn. Door de pijnintensiteit met lacosamide te verlagen, zou het te verwachten zijn dat de kwaliteit van leven toeneemt omdat de invloed van lichaamspijn op de kwaliteit van leven zou afnemen. In deze studie werd dit echter niet gevonden, zelfs niet in het pijndomein. Dit kon mogelijk verklaard kon worden doordat de studieperiode van 8 weken te kort was om een significante vermindering van de kwaliteit van leven op te merken.

Tot slot toonde de studie aan dat lacosamide een effectieve, veilige en goed te verdragen behandeling is voor *SCN9A*-geassocieerde DVN. Het onderzoek moet echter worden bevestigd in een groter cohort en bij patiënten zonder een *SCN9A*-variant voordat het gebruik van dit medicijn kan worden aanbevolen als algemene behandeling bij DVN.
De LENSS-studie is een voorbeeld van een onderzoek dat een geneesmiddel onderzoekt dat specifieker gericht is dan andere momenteel beschikbare behandelingsmogelijkheden voor DVN. Een gerichte aanpak is echter alleen mogelijk als het doelwit ook bekend is. Zoals eerder vermeld, worden bij een groot deel van de patiënten met DVN geen onderliggende aandoeningen gevonden. De vraag is echter: wat wat als er geen onderliggende aandoening wordt gevonden? Bij patiënten met DVN wordt een rol van het immuunsysteem gesuggereerd bij patiënten met geassocieerde aandoeningen zoals sarcoïdose, de ziekte van Sjögren en coeliakie. Ook de aanwezigheid van inflammatoire veranderingen, auto-antilichamen, en verhoogde cytokines, bieden ondersteuning voor de hypothese dat het immuunsysteem bij DVN een belangrijke rol speelt, zelfs bij afwezigheid van immuun-gemedieerde ziekten. Een aantal open-label studies, waarbij pijnlijke neuropathieën werden behandeld met intraveneuze immunoglobulinen (IVIg), tonen een aanzienlijke verlichting van de pijn. Dit heeft geleid tot het idee om IVIg als nieuwe behandelingsmethode bij DVN verder te onderzoeken.

Hoofdstuk 7 beschrijft de opzet van een gerandomiseerde, dubbel-geblindeerde, placebo-gecontroleerde, parallel studie waarin de werkzaamheid en veiligheid van intraveneuze immunoglobulinen (IVIg) wordt geëvalueerd bij patiënten met DVN. Het onderzoeksdesign is hetzelfde als van een belangrijke studie van IVIg bij de behandeling van patiënten met chronische inflammatoire demyeliniserende polyradiculoneuropathie (de ICE trial). In de studie wordt gestart met een oplaaddosering van IVIg van 2g/kg lichaamsgewicht gedurende 2-5 aaneengesloten dagen. Daarna krijgen patiënten elke drie weken een infuus met een onderhoudsdosering van 1g/kg lichaamsgewicht IVIg gedurende drie maanden. Daarna worden patiënten gedurende drie maanden gevolgd om het lange-termijneffect van IVIg op pijn te bepalen. Dit is de eerste gerandomiseerde klinische studie die de werkzaamheid, veiligheid en verdraagbaarheid van IVIg bij patiënten met idiopathische DVN zal onderzoeken. Patiënten die gerandomiseerd zijn voor placebo, krijgen hetzelfde behandelingsschema. Het onderzoek loopt momenteel en heeft als doel 60 patiënten te includeren. De primaire uitkomstmaat zal een 1-puntsdaling op de PI-NRS ten opzichte van baseline zijn. Secundaire uitkomsten zijn 2-puntsdalingen op de PI-NRS ten opzichte van baseline, de invloed van IVIg op autonome symptomen, dagelijkse invloed van pijn op slaap en kwaliteit van leven. Omdat al

deze uitkomstmaten gebaseerd zijn op vragenlijsten, is ook een objectieve uitkomstmaat meegenomen, namelijk de cornea confocale microscopie. Dit is een techniek die het verlies van dunne zenuwvezels en de regeneratie van zenuwen in het hoornvlies kan meten. Deze techniek is uitvoerig onderzocht bij patiënten met diabetes mellitus. In deze studie zullen alleen patiënten met een afwijkend huidbiopt en zonder onderliggende aandoeningen (idiopathische DVN) worden onderzocht. Als aangetoond kan worden dat IVIg effectief is bij DVN, kan mogelijk ook meer inzicht worden verkregen om de onderliggende pathofysiologie te onderzoeken bij patiënten met idiopathische DVN.

In hoofdstuk 8 worden de resultaten van dit proefschrift ter discussie gesteld en aanbevelingen gedaan voor toekomstig onderzoek.