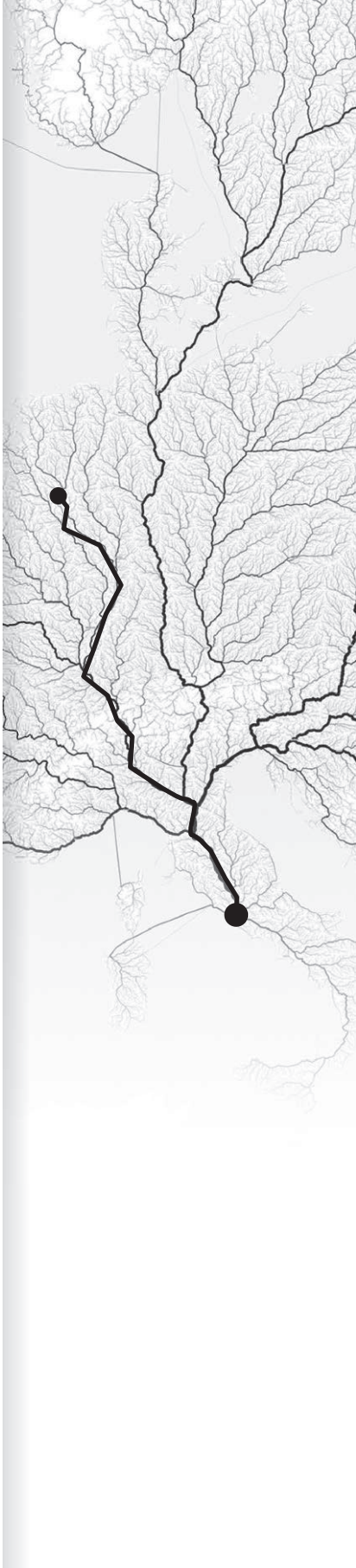
Small fiber neuropathy

CHAPTER 10

VALORIZATION ADDENDUM



Valorization is the utilization of the scientific knowledge in practice and the act of making research results appropriate and useful in order to enhance opportunities for others to use them.[1] It is a process with the aim to create societal impact in any way. This thesis provided more knowledge about the underlying conditions and possible treatments for patients with small fiber neuropathy (SFN). In this chapter I will discuss the clinical and societal relevance of these findings.

Small fiber neuropathy

Patients with SFN suffer from excruciating neuropathic pain and autonomic symptoms. The combination of complaints leads to a severe decrease in quality of life.[2] Between 2006 and 2011, the overall minimum incidence was calculated to be 12 cases /100,000 inhabitants/year and the overall minimum prevalence of SFN was 53 cases/100,000.[3] The last years, SFN has received more attention and recognition, possibly leading to higher incidence and prevalence numbers. Because many general practitioners and physicians still do not recognize the disorder, patients often visit multiple specialists to search for answers, and it usually takes a long time before the diagnosis is confirmed. SFN leads to substantial direct and indirect costs.[4,5] For example, current available treatments only diminish the pain of 50% of the patients, with many side effects. This may lead to a long search for the right treatment per patient. Patients may be interested in the prognostic information that testing provides, even if it is not used to guide treatment.[6] Establishing a diagnosis as explanation for unexplained pain may result in reassurance, acceptance, understanding, and more insight in their future perspectives.[6] In contrast, not performing diagnostic testing may lead to a continued search for an explanation, with increased medical consumption, resulting in higher costs on the longer term (both medical and non-medical, e.g. absenteeism). An adequate diagnosis may also be relevant to patients in terms of self-management and positive health.[7]

Associated conditions in SFN

There are several studies reporting many different conditions to be associated with SFN. However, most of these studies lack evidence for the underlying pathophysiological mechanisms. The endless list of associated conditions mentioned in literature leads to a large number of diagnostic tests, often with low yield. A proper guideline is needed describing the tests that should be performed to cover the conditions that are associated with SFN. For such a guideline, knowledge about the prevalence of these diseases in SFN patients is needed. This thesis describes the negative and positive consequences of testing different conditions mentioned in literature. In some studies, it is claimed that SFN could be a first sign of Fabry disease. However, in a large cohort of patients with SFN, no patients were diagnosed with Fabry disease. The diagnostics for this condition included three different tests, which led to cases in which one of the test had a doubtful result, but the other two tests were negative. These results may lead to confusion within and between physicians, but even more to confusion and uncertainty for the patient. The costs of these diagnostic tests were high. On the other hand, Fabry disease is a treatable disease, which brings up an ethical dilemma when deciding not to test patients for this condition. As a follow-up to this study, we investigated the prevalence of other conditions based on a literature study in a large cohort of patients with SFN. With these

results, we were able to generate recommendations for other physicians regarding additional testing in patients with SFN, like diabetes mellitus, glucose intolerance, vitamin B12 deficiency, immunological abnormalities, and sodium channel gene mutations. With this information, a physician can make a more evidence-based decision on required additional testing.
There is a growing interest in the hypothesis that early treatment might lead to less chronification of pain.[8,9] Additionally, screening might lead to early detection of an underlying condition, and the possibility to prevent further damage to the nerve fibers. If so, proper and early diagnostics are crucial. However, screening tests are only justified when benefits outweigh drawbacks.[10] A physician should always make a decision based on the benefits for the patients on the one hand and the burden (physical and mental) and costs on the other hand.

New treatment possibilities for SFN
The results about the prevalence of underlying conditions in SFN also lead to new research questions. The underlying pathophysiological mechanisms are still largely unknown. Better understanding of the mechanisms may provide new targets for treatment, with a greater probability of pain reduction and less side effects, finally resulting in a better quality of life. This would also have a positive effect on reduction of health-related costs.[4]
Both the lacosamide (LENSS) study and the IVIg in SFN study are examples of studies that investigate the efficacy and safety of specific therapies in SFN, based on the mechanisms of action. Although already registered for the treatment of other conditions, both of these agents were never tested before in this specific group of patients.
The LENSS-study provided evidence for lacosamide being an effective treatment option for patients with *SCN9A*-associated SFN. Besides patients with *SCN9A*-associated SFN (in 8.5% of all SFN patients), it is thought that also other patients, without a mutation, may benefit from sodium channel blockers, like lacosamide, because sodium channels play an important role in the generation and conduction of pain signals in the small nerve fibers. This hypothesis needs to be confirmed in a larger cohort of SFN patients without sodium channel gene mutation. At the moment, more selective sodium channel blockers are being tested in clinical studies.
The LENSS-study is an example of targeted treatment that is studied because of the discovery of the sodium channel gene mutations in SFN.[11-13] However, in around 50% of the patients with SFN, no underlying condition can be found at screening, as presented in this thesis. In these cases, no targets for treatment are available. In the IVIg in SFN study, we treat idiopathic SFN patients with IVIg based on supposed immunological mechanism that might play a role in the development of SFN in general. In case the study proves that IVIg is effective in these patients, this may lead both to a new treatment possibility and a new mechanisms of action in SFN.

Conclusion
This thesis provides more knowledge about the underlying conditions associated with SFN. These results have led to recommendations for which underlying condition to test. This thesis also presents two treatment options with lacosamide and IVIg, also enabling us to gain further knowledge about the underlying mechanisms, and possibly leading to more targeted treatments in the near future.

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