Maastricht University

Improving assessments in the diagnosis of small fiber neuropathy

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CHAPTER 10

IMPACT PARAGRAPH

In this chapter, a reflection is presented on the scientific impact of the results of the research described in this thesis.

The field of chronic neuropathic pain medicine is currently facing enormous challenges. The incidence of chronic neuropathic pain is increasing worldwide, particularly in the developed world. Epidemiological studies have shown that the prevalence in the general population may be as high as 7 to 8%[1,2], accounting for 20 to 25% of individuals with chronic pain. As a result, chronic neuropathic pain is imposing a growing burden on Western societies in terms of cost of medical care and loss of productivity. From a health care perspective, the total average annual costs of clinically referred patients undergoing skin biopsy and/or quantitative sensory testing (QST) in proven small fiber neuropathy (SFN) in 2020 amounted to €29.8 million and from a societal perspective €147.7 million (submitted, own data). The development of objective measurements of neuropathic pain is critical to improve pain management in the long-term to determining modulation of the nervous system that may take place over time. Due to the current inadequate treatments for pain currently available, these patients represent a major concern for the public health system.

Diabetes is one of the main causes of painful neuropathy, up to 25% of diabetic patients with moderate to severe pain in most. Patients are limited in their general functioning and their ability to sleep and often experience anxiety and depression.[3] As a consequence, high health care costs due to hospitalizations and outpatient visits are seen. The total annual cost of diabetic peripheral neuropathy (DPN) and its complications in the United States was estimated to be between 4.6 and 13.7 billion US dollars. Up to 27% of the direct medical cost of diabetes may be attributed to DPN.[4] Moreover, (severe) painful DPN had significantly greater healthcare resource utilization and costs than patients with diabetes only.[5] In addition, the painful symptoms cause impaired work productivity and annual lost productivity cost increased with pain severity.[6] Estimated annual productivity losses based on several European countries were €5.646, €10.552, and €16.597 for mild, moderate, and severe painful DPN, respectively.[6] Previous retrospective studies show that 1-year excess health costs for DPN, can be high as $8500.[7]

Listening to patients

Medicine and medical research starts with questions and concerns that are originated from experiences of people's life. Without a patients' story or request for help, we have no work to do. Therefore, the patients' clinical picture is the

starting point for medical research and ask questions like 'why', 'how', 'when' etc, the so-called gold circle but now applied in health care.

Improving assessments

It is important to recognize as general practitioner and consultant the clinical picture of SFN and/or pain related syndromes. Doing research and publishing both negative and positive results will help to develop more knowledge and to get more publicity. If a clinical picture is not recognized, patients undergo additional investigations that might be irrelevant and misdiagnosis arises driving costs of health care. From a patients' perspective, the overuse of diagnostic tests is considered as annoying and time-consuming. Patients frequently report that, even the pain is still present after diagnostics, clarity of the clinical picture and its diagnosis is more important for them.

In this thesis, we intended to explore the value of additional diagnostic tests in order to improve the diagnostic algorithm of SFN. Nowadays, patients are referred to our center, Maastricht University Medical Center+ (Maastricht UMC+), since we are the most experienced center with a unique setting in the Netherlands for diagnosing SFN. Even more, patients from abroad are seen in our center. Because of this, the waiting list for patients before they are invited for diagnostic testing can run up to 12 months. Ideally, if we find more simple, cheaper, sensitive and easily applicable tests to diagnose SFN, diagnostics does not have to take place in our expertise center but could be applied in every center in our country, or internationally. In the literature, CCM and SSW seemed promising existing diagnostic tools to quantify small nerve fibers in the eyes and test the autonomic function of these fibers, respectively. We concluded in this thesis that both tests do not have an additional value in the diagnostic process of SFN. Further investigation should be done in order to find their diagnostic position. Specifically, research has to be focused on the improvement of the skin wrinkling analysis and/or the applicability of CCM in SFN subgroups (i.e. those with glucose intolerance) or as a biomarker after pharmacological treatments.

However, until now, we still need to focus on the skin biopsy and temperature threshold testing since this is the 'golden standard' for the diagnosis of SFN and no other test to date have changed this pattern.

Treatment options

The current treatment approaches in neuropathic pain are essentially 'educated trial and error' where specific treatments are offered, usually within the focus of a clinical domain (e.g. interventional, alternate, behavioral etc). Even within treatment domains (e.g. pharmacological), medications are tried, nearly a random trial for each individual, beginning with the least invasive treatment and progressing along an increasing gradient of treatment side effects to find a strategy that provides some measure of relief. In addition to be inefficient, this 'trial and error' approach may create conditions under which subsequent treatments are less or more effective than if administered to naïve patients, so effective solutions may be missed or not fully understood.

Understanding pathogenicity

The knowledge in genetics is growing. Previous studies showed that in more than 50% of SFN is idiopathic.[8] Patients should be explained that idiopathic SFN does not mean that their complaints does not have a cause. However, they should be told that our knowledge is limited, meaning that not all causes ("cryptogenic status") are detected yet. In this thesis, we showed that a variety of genetic components can be an underlying condition and/or risk factor for SFN. This means that SFN might have a familial component, which can help diagnosing SFN in family members with the same complaints. Zebra-fish models can help us to understand the relation between specific DNA change and pain severity. Furthermore, these models help us to figure out whether existing and new pharmacological treatments could relief pain (behavior). We also reported that new, valid and rapid techniques are applicable for the detection of genetic mutations and should therefore be implemented in the overall diagnostics for SFN.

Overall, the PROPANE-study had a strong translational value that can be identified both in the diagnostic and treatment approaches to neuropathic pain. The approach to neuropathic pain as a whole condition influenced by a genetic background, irrespective of the clinical feature, led to include subgroups of patients with peculiar phenotypes, like itch or diffuse pain, in whom the diagnosis has been defined and a new gene has been identified thus far.

Respecting social impact

Although it is important to focus on the pathogenicity of neuropathic pain, we should bear in mind that patients with neuropathy cannot wait until we have found personalized solutions in pain relief. So, attention for their daily functioning in life is inevitable.

Chronic neuropathic pain, which means pain more than six weeks, is a society problem with important consequences for the functioning of the human being. For many patients, pain interferes with social activities such as household, work or family activities. A rehabilitation process could help patients to adjust with chronic neuropathic pain, such as therapies with Graded Exposure and/or Graded Activity. However, there is no literature to support this and more research should be done on integrated biopsychosocial interventions in patients with SFN.

Research and innovation might focus on creating effective ways of monitoring and evaluating neuropathic pain symptoms. For example, fill out diaries on a mobile device with the possibility to monitor *on distance* the pain and level of functioning (activities and participation) might help to intervene when it is needed and most efficient. This method is not expensive (beside data storage), costs a patient little time and helps interventions being more effective than before.

Nowadays, value-based healthcare is important, where we try to provide new diagnostic tests or other ways to improve health care, and in particular with low costs. Still, the emphasize of good clinical practice should be in the contact with a patient and not in lowering health care costs.

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