

SMALL FIBER NEUROPATHY: SENSORY, AUTONOMIC OR BOTH

Christopher Gibbons, MD, MMSc , FAAN

Introduction

A review of basic information about small fiber neuropathy (SFN) as well as recent scientific advances will be highlighted within this course. The program will focus on incorporating new scientific information while organizing the information to be within the context of clinical practice.

The term 'small fiber neuropathy – or SFN' refers to disorders that selectively damage the unmyelinated and thinly myelinated sensory and autonomic nerve fibers in the peripheral nervous system. Although SFN is often considered synonymously with painful neuropathies that damage nociceptive C-fibers, a larger spectrum of disorders exist. Painless loss of nociceptive C-fibers and damage to peripheral autonomic nerve fibers may also occur and broaden the spectrum of disorders that are considered a SFN.¹

Small fiber neuropathies include a group of disorders that predominantly affect peripheral fibers of the small somatic and autonomic variety. Many disorders, such as diabetes or amyloidosis, may damage both large and small subsets of nerve fibers so are not usually considered an isolated 'small fiber neuropathy' although they will commonly have small nerve fiber involvement. However, there are specific scenarios where small nerve fibers will be selectively damaged, even in diabetes, and these will be discussed in more detail.

Clinical History and Examination Findings

Many disorders will cause a length dependent loss of small nerve fibers that results in the familiar stocking and glove involvement as the disease progresses.^{1,2} Damage and loss of small nerve fibers in the distal extremities will result in a decrease in function in the affected area. This may be reported as loss of thermal or pain sensation. Patients may report numbness, painless injuries or inability to sense cold objects or hot water. Damage to distal autonomic nerve fibers may result in loss of sudomotor (sweating) function in the affected regions.³ Counterintuitively, patients may report hyperhidrosis (increased sweating) in more central regions because of compensatory sweat production to maintain thermoregulatory capacity. Loss of distal autonomic vasomotor control may result in color changes to the skin, or loss of distal thermoregulation. The skin over the affected region may appear dry, shiny, atrophic or discolored. Greater involvement of autonomic nerves in a length dependent fashion can result in erectile dysfunction, resting tachycardia, gastroparesis, constipation or urinary retention.⁴

Some small fiber neuropathies may present in a non-length dependent fashion.² Symptoms of somatic sensory loss will occur in the affected region. Loss of autonomic nerve fibers in a non-length dependent fashion may result in more dramatic changes to autonomic function resulting in symptoms of orthostatic intolerance, dry mouth, dry eyes, gastroparesis, constipation or urinary symptoms.

Examination findings may be isolated to disturbances in thermal or pain sensitivity, with preserved strength, reflexes, vibration and proprioception. These relatively minimal findings on examination often prove difficult for the non-neurologist to detect.

Neurophysiology: Nerve conduction studies and electromyography

By definition, isolated small fiber neuropathies will have little, if any, large fiber involvement. Nerve conduction studies and electromyography will not typically reveal any clinically relevant abnormalities, although may be appropriate in ensuring that large fiber involvement is not present. It should be noted that many disorders, such as diabetes, will have both large and small fiber involvement. Any abnormalities to nerve conduction studies will reflect the damage to large myelinated nerve fibers, and will not confirm or deny the presence of small fiber nerve damage.

Quantitative sensory testing

The use of a standardized method to deliver thermal or vibratory stimuli to detect the threshold at which an individual can detect sensation is known as quantitative sensory testing (QST). It is a well-established and well validated approach to detect evidence of a neuropathy. A variety of instruments can be used, but the more

rigorous and labor intensive methods tend to provide the greatest reliability and reproducibility. Unfortunately this can often require 1-2 hours to complete testing for a single patient.⁵ QST has not gained widespread acceptance in clinical practice due to the length of time required for testing and a lack of reimbursement for the testing procedure. Other major limitations include the psychophysical nature of the test: a subject must be awake and alert to respond to stimuli. Fatigue, cognitive impairment, medication effects, central nervous system lesions and even malingering cannot be distinguished from impaired sensory perception.⁶

Skin biopsy

Skin biopsy has become the pathologic gold standard used for the diagnosis of a small fiber neuropathy.¹ The biopsy site with most widespread normative data includes the distal leg 10 cm above the lateral malleolus.⁷ Other biopsy sites typically include the lateral distal thigh, the lateral proximal thigh and the instep of the foot. It should be noted that skin biopsies can be obtained from any region, but may not have normative values. In neuropathies with focal unilateral involvement, biopsy of the contralateral, unaffected site can serve as a control. Established counting methods are used to quantify the density of intra-epidermal nerve fibers (IENFD). Standard guidelines and worldwide normative data are available and commercial laboratories have brought this technology into the hands of general practitioners.^{1,7} Clinically, skin biopsies appear to be used both to rule in a diagnosis of small fiber neuropathy, but also to rule out a diagnosis of small fiber neuropathy in patients with complaints suggestive of neuropathy, but no confirmatory exam findings.⁸ In cases where the skin biopsy is normal, a negative result redirects management towards other items on the differential diagnosis.⁸ It should be noted that the vast majority of patients with small fiber neuropathy do not require a skin biopsy for diagnosis; the history and examination findings are sufficient for confirmation in almost all cases. Quantitation of other nerve fiber subtypes, such as deeper dermal fibers, sudomotor fibers around sweat glands and pilomotor fibers contained within arrector pilorum muscles have been described.^{9,10} These techniques may provide valuable insight into selective autonomic neuropathies that may not be detected using standard counting of intra-epidermal nerve fibers. It should be noted that methods to quantify the dermal and autonomic nerve are not as well established or accepted as the analysis of IENFD. Despite these limitations, the utility of skin biopsies to investigate a variety of neuropathies continues to grow.

Small Fiber Neuropathies

Discussion of the differential diagnosis of small fiber neuropathy will be covered in the lecture slides. In this section, updates on new developments are provided.

Treatment Induced Neuropathy of Diabetes (TIND)

Also previously described as 'insulin neuritis', 'diabetic neuropathic cachexia' or 'acute painful diabetic neuropathy', this disorder occurs in individuals with type 1 or type 2 diabetes with history of uncontrolled hyperglycemia and an abrupt improvement in glycemic control.¹¹⁻¹³ Glucose control can occur with the use of insulin, oral hypoglycemic medications or severe dietary restriction. There is an associated fall in glycosylated hemoglobin (A1C) ≥ 2 percentage points or more over a 3 month period of time. Greater rates of decrease in the A1C are associated with more severe symptoms and more profound neuropathy.¹³ Clinically, individuals present with the abrupt onset of burning and shooting neuropathic pain in a length dependent fashion (although it can be non-length dependent pain in those with the largest drops in A1C) 2-6 weeks after improvement in glucose control.¹¹ Autonomic dysfunction is present in the majority of individuals, but may be masked by the severity of the neuropathic pain. Patients will often have a normal neurologic examination with the exception of hyperalgesia and allodynia in the distribution of pain.¹¹ Nerve conduction studies are typically normal. Older individuals with type 2 diabetes may already have a mild underlying neuropathy with absent ankle reflexes and reduced distal vibratory sensation, but this likely predates the development of TIND. Treatment of the neuropathic pain can be very difficult despite polypharmacy, but often does improve spontaneously after 12-24 months.¹¹ Individuals with type 1 diabetes may also show clinical improvement to autonomic symptoms and function over this period of time, it is unclear if individuals with type 2 diabetes have the same degree of recovery.¹¹

Sodium Channel Mutations

There have been several disorders associated with sodium channel 1.7 (Nav1.7). Inherited erythromelalgia is a disorder of severe pain, typically present in the feet, with associated color changes that is precipitated by warmth and relieved by cooling. A number of publications have directed attention to the association between Nav1.7 mutations and an inherited pattern of erythromelalgia.¹⁴⁻¹⁷ Although these cases are relatively few in number, they have highlighted the clinical heterogeneity associated with sodium channel mutations and have provided direct support for the use of sodium channel antagonists, such as carbamazepine, in the treatment of these pain disorders.

A study from the Netherlands in 2012 reported that 28.6% of individuals with idiopathic painful small fiber neuropathy expressed a *gain of function* mutation to voltage gated sodium channel 1.7 (NAV1.7) of the SCN9A gene.¹⁸ These individuals have evidence of hyper-excitability dorsal root ganglia and also endorse evidence of autonomic dysfunction.¹⁸ In a follow up study, the authors have also identified patients with painful small fiber neuropathy that has a gain of function mutation to NAV1.8 (gene SCN10A).¹⁹ The patients showed a typical loss of immunostaining for distal epidermal nerve fibers by skin biopsy, and had a clinical history consistent with idiopathic small fiber neuropathy. Although these mutations are of intense scientific interest, the genetic testing for these abnormalities is not readily available at this time. Therefore the clinical implications and recommendations for treatment of these disorders is still a work in progress. However, it should be expected that over the next few years a number of genetic tests may become available and rapidly changing recommendations are to be expected.

Impaired Glucose Tolerance and Metabolic Syndrome

The association between glucose dysregulation, in the form of impaired glucose tolerance or impaired fasting glucose and small fiber neuropathy, has been known for over a decade.^{20, 21} However, extensive debates about whether these findings are causative or associated have raged through the literature.²²⁻²⁷ A number of interesting findings have been reported recently in patients with predominantly small fiber neuropathy and glucose dysmetabolism. In the MONICA/KORA study, 28% of individuals with diabetes had neuropathy, 13% of individuals with impaired glucose tolerance had neuropathy, 11.3% with impaired fasting glucose had neuropathy and 7.4% of controls had neuropathy.²⁷ These findings suggest an association, but not causation, between pre-diabetes and neuropathy.

Several studies have now linked metabolic syndrome, with both hyperlipidemia and hyperglycemia as independent risk factors for the development of neuropathy.²⁸⁻³⁰ These findings are of particular interest because patients with pre-diabetes often present with small fiber neuropathy that may improve with treatment of the underlying disorders.^{24, 25} To date, no clear recommended guidelines on treatment of pre-diabetes and neuropathy have been established. However, the burden of evidence implicating glucose dysmetabolism and hyperlipidemia with multiple long term complications suggests early interventions are important in preventing development of diabetes and a host of other complications.

Sarcoid

Pain is common in patients with sarcoidosis. A recent report describes symptoms suggestive of small fiber neuropathy in 2/3 of individuals with sarcoidosis and no other identified causes of neuropathy.³¹ Unlike other small fiber neuropathies, sarcoidosis can frequently cause a non-length dependent neuropathy and may present with migratory symptoms of burning, numbness, allodynia and paresthesias.³² Symptoms often progress over time.

Postural Tachycardia Syndrome

Postural tachycardia syndrome (POTS) is a disorder characterized by an excessive increase in heart rate with standing associated with orthostatic intolerance.³³ The disorder is comprised of many heterogeneous etiologies, although a number of reports now suggest that a subset of individuals (approximately 1/3 from a specialized neuropathy tertiary referral center) with POTS have an associated small fiber neuropathy.³⁴⁻³⁷ One recent small study reported evidence of a small fiber neuropathy in 9 of 24 patients diagnosed with postural tachycardia syndrome (POTS).³⁸ The study reported that patients with neuropathic POTS had very different autonomic characteristics during testing than those individuals without evidence of an underlying neuropathy. Although the underlying mechanism has not been elucidated, these findings could suggest an autoimmune etiology that could be amenable to intervention in some POTS patients. It is not clear that the vast number of people presenting with POTS have a small fiber neuropathy, this is a problem that will require further investigation.

Fibromyalgia

There have been recent reports that small fiber neuropathy was seen in some patients with fibromyalgia.³⁹ The findings do suggest an association, but not causation. However, these results have significant implications for the pathophysiologic basis for fibromyalgia, particularly the painful aspects of the disorder, which has been largely written off as a 'wastebasket' diagnosis with little in the way of pathologic findings to support the diagnosis. If these findings are confirmed in a larger population of patients with fibromyalgia, this may lead to more targeted therapy that may improve long term outcomes.

Treatment

Treatment of small fiber neuropathy will be targeted toward the underlying disease and will be covered in more detail in the provided slides. Treatments of any associated neuropathic pain or autonomic dysfunction will improve quality of life, but will not alter the natural history of the disease.

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