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Small-Fiber Neuropathy: Answering the Burning Questions

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Introduction

Peripheral nerves form a massively parallel bidirectional network that transmits information from the outside world to the central nervous system (CNS) and then back to the rest of the body. Peripheral nerves, made up of axons wrapped with Schwann cells (glial cells that provide electrical insulation), are the longest cells. The axons of a 100- μ M-wide sensory neuron cell body can span the distance between the toes and the brain, nearly 2 meters in some humans (and longer in giraffes and whales). Virtually all assembly of macromolecules and organelles occurs in the cell body, and items needed in the axons must travel these long distances (and sometimes back again) by axonal transport. Any disruption of the cytoskeletal machinery [for example, microtubules, actins, kinesins, or dyneins (see [Andersen Perspective](#) and "[Engine Trouble](#)")] or energy supply (oxygen, glucose, adenosine triphosphate, nicotinamide adenine dinucleotide, or mitochondria) required to keep axonal transport functional can thus cause distal axonal damage. Not surprisingly, such disturbances, known as axonopathies or neuropathies, are not rare. They are characterized by Wallerian degeneration, a mechanical breakdown of the axon and ensheathing myelin (a specialization of Schwann-cell plasma membranes), of the portion of the nerve fiber distal to the disruption. The more distant a portion of axon from its cell body, the more chance of interruption, so most axonopathies affect the distal-most portions of axons first.

The resulting symptoms depend on the functions of the "sick" axons, and thus vary because different types of fibers have highly specific functions that are reflected somewhat in their form. Morphologically, axons are classified as either myelinated (A fibers) or unmyelinated (C fibers). Myelin forms only on axons wider than 1 μ m; rapid transmission of signals in myelinated axons occurs by saltatory conduction between regions of exposed axon called nodes of Ranvier. Unmyelinated or "small-fiber" axons are enclosed within invaginations of the Schwann-cell membranes. Myelination increases axonal conduction velocity; unmyelinated C fibers conduct signals at about 1 m/s, whereas thickly myelinated A fibers conduct signals at 40 to 100 m/s. Large-diameter fibers transmit urgent messages to muscles and allow sensation of innocuous stimuli, such as touch, vibration, and one's own movements (proprioception). Symptoms of large-fiber neuropathies, whether axonal or myelin related, include weakness, numbness, tingling, or loss of balance. Small fibers mediate the involuntary autonomic functions and perception of noxious stimuli of various types (nociception or pain). Characteristic symptoms of small-fiber damage include pain, loss of pain and temperature sensation, and/or autonomic symptoms such as sweating or difficulty with sexual function, bladder or bowel control, or blood-pressure regulation. Generalized peripheral nerve dysfunctions

(polyneuropathies) can affect one or more types of axon, but regardless, symptoms start at the farthest point from the neuronal cell bodies, usually in the feet. Small fibers may be more vulnerable to conditions that affect transport than are large-diameter fibers because they need to propagate axon potentials along their entire length rather than by saltatory conduction between nodes of Ranvier as myelinated fibers do. At any rate, small-fiber symptoms are a common and early manifestation of many polyneuropathies. Unfortunately, small-fiber neuropathies are harder to detect and test for than large-fiber neuropathies. Inadequate ability to test for and diagnose small-fiber neuropathies has impeded patient care and research, but new tools offer promise.

Clinical Symptoms of Small-Fiber Polyneuropathies

As adults age, they become more vulnerable to the development of small-fiber polyneuropathies. The onset is usually heralded by pain in both feet, often first on the soles. Sensory loss or numbness, which seems to require more nerve damage, appear later. If the condition worsens, the symptoms spread proximally as shorter axons also become affected. The hands become symptomatic at about the same time as leg symptoms ascend to the mid-calf (known as a "stocking and glove" distribution). If even short fibers are damaged, symptoms can affect the torso and head. Small-fiber sensory symptoms are a mixture of numbness (sensory loss) and pain described variously as superficial and burning, deep aching, pins-and-needles, electrical shocks, or knifelike stabbing. Innocuous contact (such as with clothing or bedclothes) can become painful, as during sunburn. Small-fiber symptoms often worsen at night (when there are few distractions) and in the cold.

Damage to autonomic small fibers is also common (1). Patients can develop symptoms of vascular dysregulation, such as swelling or color and temperature changes in their feet. Their skin may become thin and shiny because keratinocyte mitosis rates depend on small-fiber innervation (2). With widespread involvement, internal organ dysregulation can develop, such as impaired gastrointestinal motility (diarrhea or constipation), bladder or sexual dysfunction, and, rarely, blood-pressure abnormalities or cardiac dysrhythmias. Of course, many polyneuropathies affect other types of axons to a greater or lesser extent, so large-fiber symptoms such as weakness, muscle atrophy or fasciculations, or loss of touch, balance, or proprioception can appear as well.

Clinical Evaluation of Small-Fiber Polyneuropathies

A detailed patient history is the best way to identify these conditions. Questions about onset, progression, distribution, and characteristics of symptoms can provide clues. Patients should be questioned about symptoms of other diseases or conditions associated with small-fiber polyneuropathy (see below). Although a detailed general and neurologic examination is mandatory, the results are sometimes frustratingly normal. Pure small-fiber polyneuropathy leaves patients with normal strength and muscle bulk, normal reflexes, and many normal sensory functions. Deep tendon reflexes are a large-fiber function that remain normal. Distal loss of pinprick sensation is perhaps the most common diagnostic abnormality, along with the abnormal foot appearance mentioned above.

What Are the Causes of Small-Fiber Polyneuropathies?

In affluent societies, the most frequent cause of small-fiber polyneuropathies is diabetes. New evidence suggests that even very early and mild glucose dysmetabolism ("pre-diabetes" or "[metabolic syndrome](#)") is enough to cause small-fiber neuropathy (3). Two- or three-hour glucose tolerance tests have been shown to be more sensitive than one-time measurements of serum glucose or glycosylated hemoglobin. Several toxins, including alcohol, preferentially affect small fibers. Either nutritional deficiency or direct alcohol toxicity can contribute. Other toxins that preferentially affect small fibers include arsenic and metronidazole (an antibiotic) (4).

Like all other tissues, small fibers are sometimes attacked by the body's own defense mechanisms in the autoimmune neuropathies. All of the generalized autoimmune diseases, such as lupus, can damage small

fibers. Sjögren's syndrome, an autoimmune disease whose prominent symptoms include dry eyes and mouth, can damage either the axons or cell bodies (sensory ganglionopathy) of small fibers (5). Antibody-mediated autoimmune small-fiber neuropathies are best understood in the context of the monoclonal gammopathies, conditions in which abnormal clones of immune cells produce high concentrations of antibodies, which sometimes target nerve tissues. Ten percent of patients with idiopathic peripheral neuropathy have evidence of monoclonal gammopathy, an incidence six times as high as the general population (6). Patients with amyloidosis produce abnormal proteins that are deposited in various body parts and disrupt normal cellular activities. Painful small-fiber nerve involvement can predominate early on, but eventually all nerve fiber types are involved (7).

Several genetic causes of small-fiber neuropathy have been identified. The hereditary sensory and autonomic neuropathies (HSANs) comprise a heterogeneous group of inherited neuropathies that disproportionately affect small- and large-fiber sensory neurons. Genetic defects have been identified in some families with HSAN-I (8), HSAN-II (9), and HSAN-III (familial dysautonomia) (10), but most genetic neuropathies come from as-yet-undiscovered mutations. Patients with a strong family history of painful neuropathy might consider having these specific genetic tests, offered at specialized centers including Massachusetts General Hospital. Sodium channel mutations have recently been identified in erythromelalgia, a rare autosomal dominant disorder in which exercise or warmth can cause crises of distal burning pain, swelling, and redness due to inappropriate vasodilation of skin capillaries that have lost the small-fiber axons that normally control their function (11). Other inherited diseases cause small-fiber neuropathy, among other symptoms. Fabry disease is an X-linked recessive disorder in which affected boys lack the enzyme necessary to metabolize ubiquitous lipid-based compounds (12). Shooting leg pains from small-fiber neuropathy can be the presenting symptom. In Fabry disease, there is a genetic abnormality of the enzyme alpha-galactosidase A. It is still not understood how this causes neuropathy. Poor nerve perfusion leading to ischemia of the axon of the nerve (13) and abnormal lipid accumulation compromising the function of the cellular membrane (14) are both thought to contribute to axonal destruction.

Several viruses and infectious diseases commonly cause large and small-fiber sensory neuropathy, including human immunodeficiency virus (15) and leprosy (16). Shingles (also known as herpes zoster, which is caused by reactivation of the varicella-zoster virus that produces chicken pox), produces severe sensorineural damage usually limited to the dermatome (area of skin) innervated by a single sensory ganglion. Shingles is estimated to affect up to one quarter of Americans during their lifetimes, almost all of them over age 40. Because the incidence of shingles is directly proportional to age, geriatric patients are at very high risk of developing shingles and of being left with postherpetic neuralgia, the chronic neuralgic pain condition that can persist after rash healing.

Despite best efforts, in many small-fiber neuropathies, the cause is not identifiable. In this situation, particularly if the diagnosis has been confirmed by electrophysiological testing or skin or nerve biopsy (see below), it is reasonable to consider immunosuppressive treatment for putative autoimmune disease. Because pharmacological immunosuppression can have serious adverse effects, the decision is not easy.

A recent prospective study of diabetic patients indicated that, apart from glycemic control, neuropathy prevalence was independently associated with potentially modifiable cardiovascular risk factors, including a raised serum triglyceride concentration, increased body-mass index, smoking, and hypertension (17). Presumably anything that interferes with microcirculation can damage the vulnerable distal axon. It will be interesting to see if these relations also appear in nondiabetic patients.

The proposed mechanisms of disruption of normal small-fiber nerve function are multifactorial and include (i) focal nerve ischemia (a low-oxygen state usually caused by insufficient blood flow) (18); (ii) an inflammatory process possibly mediated by cytokines (19); and (iii) abnormalities of oxidative metabolism in the distal axon (20).

Diagnostic Tests

The standard for diagnosing disease of peripheral nerves is identifying evidence of reduced or slowed axonal conduction. Unfortunately, this diagnostic modality is only sensitive enough to measure large-fiber nerve function because the action potentials of small fibers are too small and scattered to be detected. Because small fibers do not innervate neuromuscular junctions, results from electromyography (a test that measures the response of muscle to nerve stimulation) usually remain normal unless large fibers are damaged as well.

Neurodiagnostic skin biopsy is the emerging standard for the diagnosis of small-fiber neuropathy. Skin biopsy measures intraepidermal nerve fiber density and morphology and appears to be a sensitive measure of nerve fiber integrity. Neurodiagnostic skin biopsy is as effective as or more effective than other diagnostic tools in assessing small-fiber nerve function and can be repeated multiple times, so small-fiber nerve loss can be monitored over time for disease progression or treatment efficacy. Neurodiagnostic skin biopsy has been shown to be even more sensitive than the more traditional sural nerve biopsy, in which all or part of a patient's sural nerve is surgically removed from the lower leg and sent for pathological analysis (21), presumably because a more distal portion of the axon is sampled. The procedure's safety profile is excellent, with no serious adverse events reported yet, even in patients with advanced neuropathy.

The skin biopsy involves removing a full-thickness "punch sample" from anesthetized skin. The standard size is 3 mm in diameter, which creates a sample large enough to handle but leaves a wound small enough to heal without suturing. Some laboratories use suction to create an epidermal blister that is then cut off (22). This procedure is less traumatic but does not sample the dermis. To increase sensitivity, the biopsy site is most commonly the distal leg. Some laboratories compare results from both proximal and distal sites to look for a proximal-distal gradient. Selected vertical sections of skin are then immunolabeled with antibody that binds protein gene product (PGP) 9.5, a ubiquitin hydrolase that is a verified panaxonal marker (Fig. 1). Localization of epidermal PGP9.5 immunolabeling to axons has been ultrastructurally verified. Quantitative data are obtained from the epidermis where axons individuate. Almost all PGP9.5 immunoreactive epidermal neurites have been identified as nociceptors (see "[The Burden of Pain on the Shoulders of Aging](#)"), making this method particularly germane in painful conditions (23).

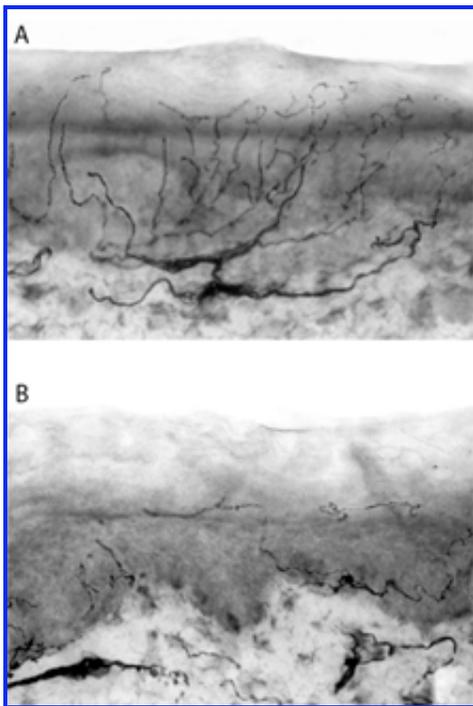


Fig. 1. PGP9.5-immunolabeled nerve endings in punch skin biopsies. Representative labeled vertical skin-biopsy sections from (A) a normal subject and (B) a subject with painful small-fiber neuropathy. Note the paucity of nerve endings in (B). Both are from the standard site on the distal leg 5 cm above the ankle. [Reproduced from (36) with permission from Elsevier.]

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Since the description of its utility as a marker for epidermal nerve fibers in human skin, the skin biopsy has been used for identification of small nerve fibers in the dermis and epidermis in a range of small-fiber neuropathies. A major advantage of skin biopsy followed by visualization of nerve fibers using PGP9.5 immunolabeling is the capacity for quantitation of epidermal innervation by small nerve fibers. Because skin is a regenerative organ, the skin biopsy test can be repeated over time.

Sural nerve biopsy, until recently the standard for diagnosing small-fiber neuropathy, requires ultrastructural examination of small fibers within a nerve biopsy specimen. There are several limitations to this technique in that (i) most nerves have motor function and cannot be sampled without detrimental effect; (ii) nerve biopsies cannot be repeated to monitor disease progression or the effects of therapy; and (iii) the procedure has standard operative complications as well as risk of nerve damage. There is increasing appreciation of the potentially disabling sensory loss and even chronic pain that sural biopsy can cause (24). Again, skin biopsy appears more sensitive than sural nerve biopsy in identifying small-fiber neuropathies (21). However, nerve biopsies offer substantially more tissue than skin biopsies, particularly if a muscle biopsy is performed in parallel. Samples of peripheral nerve are easy to obtain and may reveal specific pathological findings (such as vasculitis, infection, demyelination, or neoplastic cells) that are unlikely to be detected in skin biopsy.

Quantitative somatosensory testing (QST) uses calibrated tools to assess the function of all the sensory modalities. The smaller caliber nerves are evaluated by measuring pain and temperature (hot and cold) thresholds, and larger caliber nerves are evaluated by measuring thresholds for perception of vibration, joint position, and touch. This is done by touching patients' skin with stimuli of defined characteristics, such as a computer-controlled probe that can heat or cool to specific temperatures. The effectiveness of QST is limited because it requires subject cooperation and is inherently subjective, as it relies on the reported interpretation of sensory stimulation from the subject (25). In addition, it is difficult to establish universal standards between systems because of differences in electrode size, the site of stimulation, the frequency and rate of change of the stimulus, and the environment of the test laboratory. An additional limitation is that sensory stimuli *in vivo* activate combinations of sensory receptors (that is, the peripheral ends of sensory neurons), so QST in reality cannot isolate single types of receptors (26). All of these difficulties limit the reproducibility of this sensory test, and there is little published data that compares the reproducibility of the different systems.

Two algorithms have been developed for QST in an effort to standardize accurate and reproducible sensory thresholds: the method of limits and the method of levels. In the method of limits, the subject is exposed to an increasing or decreasing intensity of stimulus and is asked to report as soon as it is detected. Using this algorithm, sensory thresholds tend to be higher and more variable than the method of levels, partly because of variation in the subject's reaction time (26). In the method of levels, the subject is exposed to stimuli of a constant intensity and is asked to indicate whether or not the stimulus is felt. This algorithm is more time consuming and, although the results are not biased by the subject's speed of response, it is susceptible to errors from decreased attention by the subject (26).

Quantitative sudomotor axon reflex testing involves the use of acetylcholine to activate the nerves in the skin to cause a sweating response. The volume of sweat is then measured and categorized as being normal or abnormal. Although this test appears to be sensitive and reproducible, the highly specialized equipment required is not available in most health care facilities (27).

A number of other tests with variable sensitivities have been developed to measure the viability of the small-fiber nerve system, including (i) a test that measures the skin sweat response to a warm environment (thermoregulatory sweat test) or to electrical stimuli (sympathetic sweat test); (ii) a test that measures inconsistencies in the distribution of skin temperature in a given area (skin vasomotor temperature testing); (iii) laser Doppler monitoring of blood flow in capillaries in the skin (laser Doppler flowmetry) (28); and (iv) a test that measures the blood-pressure response and heart-rate response to changes in body position

(cardiovascular reflex test). Developing tools to objectively measure small-fiber function, especially in the context of pain, is an ongoing area of research.

Therapy

Infrequently, the underlying cause of small-fiber dysfunction is identified, and disease-modifying therapy can be instituted. More commonly, the treatments for small-fiber neuropathy revolve around the treatment of pain. Pharmacological therapy, surgical intervention, physical therapy, and psychological intervention are the hallmarks of symptomatic treatment of painful neuropathy. Additionally, there are several alternative approaches to the treatment of pain.

Several classes of drugs have proven track records in treating neuropathic pain but have not been studied specifically in the context of small-fiber neuropathy. Some tricyclic antidepressants (29), anticonvulsants (30), sodium channel blockers (31), and opioids (32) have all been shown efficacious in randomized controlled trials for treatment of painful neuropathy. There are several other classes of drugs that appear to have some benefit, but more rigorously structured drug trials are lacking. These drugs include topical local anesthetics (33) and other antidepressants (34).

Exercise and physical therapy are essential for preservation of function. Alternative treatments for neuropathic pain have not yet been clearly shown to provide symptomatic improvement in research studies. Acupuncture trials have not demonstrated efficacy (35).

Conclusion

Small-fiber neuropathy is an underdiagnosed condition that causes substantial distress and disability. Pain is its most common clinical feature. Although numerous challenges remain, the first steps to developing effective disease-modifying and symptomatic treatments for this disorder are defining the pathophysiology and identifying disease processes responsible for small-fiber nerve injuries.

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