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Review

Small fiber neuropathy: Diagnosis, causes, and treatment

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ABSTRACT

Small fiber neuropathy, which affects the sensory Aδ and C fibers, is now a major diagnostic and therapeutic challenge. Nearly 7% of the general population have chronic neuropathic pain responsible for severe quality-of-life impairments. Awareness must therefore be raised among clinicians of the somatosensory and autonomic symptoms that can reveal small fiber neuropathy, appropriate diagnostic investigations, most common causes, and best treatment options for each patient profile. To help achieve this goal, the present review article discusses the clinical presentation of neuropathic pain and paresthesia and/or autonomic dysfunction due to involvement of nerves supplying exocrine glands and smooth muscle; normal findings from standard electrophysiological investigations; most informative diagnostic tests (epidermal nerve fiber density in a skin biopsy, laser-evoked potentials, heat- and cold-detection thresholds, electrochemical skin conductance); main causes, which consist chiefly of metabolic diseases (diabetes mellitus, glucose intolerance), dysimmunity syndromes (Sjögren's syndrome, sarcoidosis, monoclonal gammopathy), and genetic abnormalities (familial amyloidosis due to a transthyretin mutation, Fabry disease, sodium channel diseases); and the available symptomatic and etiological treatments.

1. Introduction

A review of small fiber neuropathy (SFN) must start with a discussion of the functional characteristics of small nerve fibers, which consist of the myelinated Aδ fibers and unmyelinated C fibers (Table 1). Small nerve fibers convey temperature and pain sensation after mechanical or thermal stimulation of the skin. In addition, C fibers are involved in autonomic function. SFN affects the Aδ and C fibers and can therefore present not only as disorders of temperature and pain sensation, but also as autonomic disorders whose considerable diversity reflects that of C-fiber function [1].

Since the early 1980s, increasing attention has been directed to SFN, often described as a pain disorder, and on the management of chronic pain. Chronic pain affects nearly 30% of adults and exhibits neuropathic features in 7% [2]. In SFN, the presentation of chronic and diffuse pain accompanied with a variety of protean symptoms often suggests a psychosomatic disorder or fibromyalgia. These diagnostic wanderings lead patients to visit multiple physicians, who may prescribe numerous investigations and inappropriate symptomatic medications. The result is a major impairment in quality of life for the patient [3] and failure to identify the causal abnormality. In this setting, detecting SFN restores a useful dynamic by allowing appropriate etiological investigations and therapeutic measures that may improve the symptoms or slow the progression of the disease.

This article reviews the diagnosis, most common causes, and therapeutic management of SFN.

2. Clinical clues to the diagnosis

2.1. Pain and paresthesia

Chronic pain is often the first symptom to suggest SFN. The pain is frequently described as functional. Pain duration is longer than 6 months and may reach several years. A careful analysis of the pain features indicates neuropathic pain, thereby suggesting SFN. This analysis can be facilitated by the routine use of the 10-item DN4 questionnaire (Table 2). A score of 4 or more has 83% sensitivity and 90% specificity for neuropathic pain [4].

The next step consists in a medical history and physical examination to identify somatosensory and autonomic symptoms. Somatosensory symptoms may include pain sensations (pain, burning sensations, shooting pain) and paresthesia or dysesthesia (pruritus, pins and needles, stabbing pain, tingling, numbing, cold or crushing sensations). A symptom that strongly suggests SFN and should therefore be sought routinely is allodynia (pain in the feet caused by the sheets, socks, or weight bearing, silk shirt syndrome) [5].

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Table 1
The main types of sensory nerve fibers with their characteristics.

Type of sensory fiber	Myelin	Diameter (μm)	Conduction velocity (m/s)	Sensory information conveyed	Nerve conduction studies (electroneuromyography)
A-α	Myelinated	13–20	8–120	Proprioception	Yes (H reflex)
A-β	Myelinated	6–12	30–70	Discriminative sensitivity to mechanical stimuli (touch, vibration)	Yes (sensory nerve conduction)
A-δ[a]	Myelinated	1–5	5–40	Sensitivity to cold and pain ("rapid" pain, pinprick)	No
C[a]	Not myelinated	0.3–1.5	0.5–2	Sensitivity to heat and pain ("slow" pain, burning sensations)	No

[a] Small fiber neuropathy involves only the Aδ and C fibers, which cannot be assessed using standard electrophysiological techniques.

Table 2
The DN4 questionnaire.

Interview of the patient
Question 1: does the pain have one or more of the following characteristics?
1. Burning
2. Painful cold
3. Electric shocks
Question 2: is the pain associated with one or more of the following symptoms in the same area?
1. Tingling
2. Pins and needles
3. Numbness
4. Itching
Examination of the patient
Question 3: is the pain located in an area where the physical evaluation shows one of more of the following:
1. Touch hypoesthesia
2. Pinprick hypoesthesia
Question 4: is the pain caused or increased by
1. Brushing

This questionnaire is designed for the diagnosis of neuropathic pain. Each "yes" answer is scored 1 point and each "no" answer 0 points. The score can range from 0 to 10 and scores of 4 or more have 83% sensitivity and 90% specificity for neuropathic pain [4].

Table 3
Symptoms suggesting small fiber neuropathy (SFN).

Sensory symptoms
Pain (burning sensations, tingling, painful cold sensation, shooting pain, pins and needles. . .)
Allodynia in response to rubbing
Hypoesthesia to heat, cold, and pinprick
Hyperalgesia
Symptoms of dysautonomia
Dyshidrosis (hypo/anhidrosis, hyperhidrosis)
Impairments in vasomotricity or thermoregulation (hot flashes, erythermalgia)
Gastrointestinal symptoms (gastroparesis, diarrhea, constipation, intestinal pseudoobstruction)
Disorders of micturition (urinary incontinence or retention), erectile dysfunction
Ocular or oral sicca syndrome
Visual impairments: disorders of accommodation with blurred vision, photophobia, impaired near vision, tonically dilated Adie's pupil by ophthalmological examination
Orthostatic hypotension
Cardiac arrhythmias: premature atrial or ventricular beats, sinus bradycardia or tachycardia

These symptoms may be located at the lower or upper limbs or at all four limbs, with or without a length-dependent distribution [6]. Pain in the torso, face, tongue (glossodynia), or scalp has also been reported. The manifestations may predominate at the hands and feet, with erythermalgia or erythromelalgia, which must be distinguished from Raynaud's phenomenon. Finally, restless leg syndrome may be the presenting manifestation of SFN.

2.2. Autonomic manifestations

The autonomic manifestations are due to the involvement of C fibers in the exocrine glands (salivary, lachrymal, and sweat glands) or smooth muscle (in the blood vessels, gastrointestinal tract, bladder, and iris) (Table 3).

2.2.1. Involvement of the exocrine glands

The main exocrine manifestations are as follows:

- sweat glands: decreased, absent, or increased sweat production;
- salivary glands: decreased, absent, or increased saliva production;
- lachrymal glands: decreased or increased tear production.

2.2.2. Involvement of internal-organ smooth muscle

Involvement of the gastrointestinal tract manifests as chronic constipation, chronic diarrhea, or an alternation of both. Patients may experience chronic intestinal pseudoobstruction, colonic inertia, anorectal symptoms (dyschezia, fecal incontinence), or gastroparesis. At the bladder, SFN may result in pain, which may be triggered by micturition, dysuria, or urinary incontinence. The cardiovascular manifestations consist of blood pressure variations (orthostatic hypotension due to decreased sympathetic tone, sometimes with episodes of high blood pressure), palpitations that may indicate premature atrial or ventricular beats and, more rarely, sinus bradycardia. Other common symptoms include hot flashes with or without increased sweating, acrocyanosis, and Raynaud's phenomenon. Finally, the visual manifestations of SFN consist of impaired accommodation with photophobia and poor near vision responsible for difficulty reading. The ophthalmological assessment may show a tonically dilated Adie's pupil.

3. Diagnostic investigations for small fiber neuropathy (SFN)

Emphasis is placed here on the neurophysiological, histological, and morphological investigations most often obtained in clinical practice to characterize the involvement of the small nerve fibers.

3.1. Electrophysiological investigations

Standard electrophysiological tests cannot detect abnormalities of nerve fibers less than 7–10 μm in diameter. Thus, normal electromyography and nerve conduction test results do not rule out SFN.

Specific electrophysiological tests, however, can provide information on the small nerve fibers. They include laser-evoked potentials (LEPs), temperature-detection threshold measurement, and tests of autonomic function [7].

3.1.1. Laser-evoked potentials (LEPs)

LEPs investigate the Aδ fibers, and perhaps the C fibers, peripherally and the spinothalamic tract centrally. The responses to laser

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