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# Evidence of small-fiber neuropathy (SFN) in two patients with unexplained genital sensory loss and sensory urinary cystopathy

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## 1. Introduction

The term small-fiber neuropathy (SFN) refers to the type of polyneuropathies that preferentially damage the small unmyelinated and thinly myelinated sensory or autonomic neurons [1]. Skin biopsy to determine the epidermal nerve-fiber density (ENFD) is the most definitive method in the diagnosis of SFN, but autonomic function testing can also be useful [2]. Importantly, electromyography and surface nerve-conduction studies (EMG/NCS) do not capture the small scattered action potentials of small fibers, and thus are insensitive to small-fiber restricted neuropathies. Quantitative sensory testing is a subjective test that depends on patient volition, so it is not recommended or reimbursed for clinical use [3]. Most generalized polyneuropathies first affect the distal parts of the limbs, such as the feet. They only rarely present proximally and the diagnosis of a non-length dependent SFN is usually associated with symptoms beginning in the hands, face, or torso. Onset in the pelvic region is rare and the diagnosis can be missed. We report on two patients with an unexplained syndrome of somatic and visceral uro-genital sensory deficit with histologic

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**Authors' conflicts of interests**

All authors report no conflict of interest.

**Authors' contributions**

AbdelRazek: Study concept and design, data gathering, manuscript writing.
Chwalisz: Study concept and design, data gathering, manuscript revisions.
Oaklander: Performance of skin biopsies and data analysis, generation of photomicrograph, critical manuscript revisions.
Venna: Study supervision

evidence of SFN. All of the tests mentioned here were performed in the accredited hospital laboratories of the Massachusetts General Hospital for clinical reasons. They used standard clinical methods and interpretations.

## 2. Case 1

A previously healthy 21-year-old Caucasian man of Eastern European ancestry presented with a 2-year history of idiopathic progressive regional sensory dysfunction. He first noted reduced sensation at the tip of his penis. This gradually spread proximally to affect his whole penis, scrotum, perineum and perianal skin. He felt that his urethra and anus were numb since he could only tell that he had passed urine or stool if he was observing it visually. Sexual intercourse became less pleasurable, although he had no erectile or ejaculatory dysfunction. There were no complaints to indicate autonomic dysfunction elsewhere; as facial flushes, hypohidrosis of the extremities or compensatory hyperhidrosis of the face or trunk; orthostatic dizziness, syncope or palpitations; early satiety, dyspepsia or bowel dysfunction. He had a normal general, mental status, cranial nerve, coordination and gait examination with normal strength, reflexes, rectal tone and anal wink. His only neurological finding was decreased sensation to light touch, temperature and pinprick over the penis, and to a lesser extent over the entire scrotum and circumferentially 5 cm around the anus. Pressure on the pudendal nerves in Alcock's canal during rectal exam was not painful and showed no Tinel sign. There was preserved vibratory sensation and proprioception throughout.

## 3. Case 2

A 28-year-old Caucasian man of Northern European ancestry, healthy apart from occasional migraines, presented with penile hyperesthesia. He described this as hypersensitivity to contact with clothing or water while showering, that progressively worsened over 1–2 years to become more of a numb loss of sensation involving the penis, perineum, perianal skin and anus. He reported diminished erections and delayed ejaculation. Additionally, he reported urinary urgency and perineal pain during defecation that evolved over the same span of 1–2 years into a painless numbness in the urethra and anus similar to that described in Case 1. As with Case 1, he also had no symptoms of autonomic failure elsewhere. He had normal general and neurological exams, including mental status, cranial nerves, strength, reflexes, rectal tone and anal wink, with the exception of decreased sensation over the entire penis to light touch, pinprick and temperature, and decreased sensation to a warm stimulus distal to the ankles, on the distal fingers, in an abdominal escutcheon, over the tip of the nose, and on the vertex of the head. He had no deficit in proprioception or vibratory sensation.

## 4. Objective data

In both cases, urodynamic studies revealed a sensory cystopathy evidenced by delayed first sensation during bladder filling (at 253 mL and 163 mL respectively) and delayed desire to void (at 418 mL and 392 mL respectively). Case 2 also had an abnormally high maximum capacity (912 mL) consistent with a chronic neurogenic bladder. Both men had normal voiding parameters. Electrophysiological studies showed no evidence of lumbosacral

radiculopathy, plexopathy or large-fiber neuropathy. Sensory responses of the right and left sural and superficial peroneal and motor responses of the right and left peroneal nerve-innervated extensor digitorum brevis and tibial nerve-innervated abductor hallucis were normal. Electromyography of the iliopsoas, gluteus medius, vastus lateralis, tibialis anterior and gastrocnemius were normal. Magnetic resonance imaging (MRI) of the cervical, thoracic, lumbar spine, pelvis, and lumbar plexus were unrevealing in both cases. Case 2 had a small L5–S1 disc protrusion that minimally contacted the left L5 and S1 roots and a 9 mm S2 Tarlov cyst causing no relevant nerve compression on MRI. Case 2 also had a normal brain MRI. Autonomic testing in Case 2 revealed reduced distal-leg sweating on quantitative sweat testing, but normal blood pressure, heart rate and beat to beat variability response to Valsalva maneuver, deep breathing and tilt table tests.

In both men, microscopic examination of PGP9.5-immunolabeled thick sections from a standard 3 mm punch skin biopsy to a depth of 2 mm (Fig. 1) from the distal leg (10 cm above the lateral malleolus) showed 148 and 117 neurites/$mm^2$, corresponding to the 2nd and <1st percentile of expected values for individuals matched by age, sex and race for Case 1 and Case 2 respectively. Case 1 additionally had punch skin biopsy of the thigh (20 cm distal to the anterior superior iliac spine), which showed 68 neurites/$mm^2$, for which there is no available normative data, though clearly abnormal as it is shows less epidermal nerve-fiber density than the distal leg, thus supporting the diagnosis of a non-length dependent small-fiber neuropathy. An extensive laboratory work-up for endocrine, nutritional, infectious, rheumatologic and other inflammatory etiologies of SFN including hemoglobin A1C, serum protein electrophoeresis (SPEP), vitamin B12, erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), Sjögren's syndrome serology (SS-A, SS-B), celiac disease serology (TTG-IgG, TTG-IgA), was unrevealing [4]. Case 2 had an elevated ACE level (65), but PET-CT of chest, abdomen and pelvis was did not reveal sarcoidosis. Case 1 declined genetic testing. For Case 2, a GeneDx Hereditary Neuropathy Panel of 53 neuropathy-associated genes, including SCN9A, was positive for a variant of uncertain significance in the LRSAM1 gene, responsible for Charcot-Marie-Tooth type 2P, but it was otherwise negative.

## 5. Comments

To our knowledge, this is the first case series linking unexplained somatic and visceral uro-genital sensory dysfunction to biopsy-proven non length-dependent small-fiber neuropathy (SFN). Sensory complaints of the genital area often remain undiagnosed or are presumed to be psychogenic. Here, the similarity of the clinical presentation and the objective findings on skin biopsy, autonomic testing and urodynamic studies argue against a psychiatric explanation. Furthermore, the anatomical distribution was not consistent with pudendal neuropathy or lumbosacral radiculopathy which are often invoked in similar cases.

Our final diagnosis for these two gentleman was idiopathic non-length dependent SFN with both somatic and visceral components. It may be somewhat puzzling why these two gentlemen complained of no distal leg symptoms despite the reduced epidermal nerve-fiber density captured on skin biopsy, but we believe the non length-dependent nature of their disease, as evidenced by the lower epidermal nerve-fiber density in the thigh compared to

the distal leg in Case 1, restricted their symptoms proximally (where the extent of nerve loss distally did not pass the threshold to cause symptoms). In terms of treatment, some clinicians advocate for immunomodulatory therapy as intravenous immunoglobulin (IVIG) in cases of idiopathic SFN but we did not see evidence for aberrant immune function on laboratory testing, and thus opted not to proceed with this therapy. In other cases that show elevated immunologic markers as anti-nuclear antibody (ANA) or anti-Ro/anti-La, IVIG may be considered, but this is anecdotal.

Associated structural or medical conditions were not detected [4,5], although seronegative regional immune/inflammatory conditions remain possible. Systemic autoimmune condition as Sjögren's syndrome and celiac disease have been reported to present with a non-length dependent sensory neuropathies, but both disease serologies were negative in our cases [6,7]. Rarely, Tarlov's perineural cysts, which are incidentally encountered in ~1% of the population [8], can cause radiculopathy, but this was not the case here as evident by the absence of radicular pain and the inconsistency of the symmetric bilateral anatomical distribution with sacral root disease. Lumbar puncture was not performed in either cases. With the exception of polyradiculopathies like chronic inflammatory demyelinating polyneuropathy (CIDP), CSF analysis is of low yield for diseases of the peripheral nervous system, as is the case here.

We advocate for occult SFN to be added to the list of conditions that are important to rule out when presented with a case of unexplained regional sensory changes, as it may be hazardous to conclude a psychological etiology without a comprehensive work-up for potentially treatable neurological causes [4].

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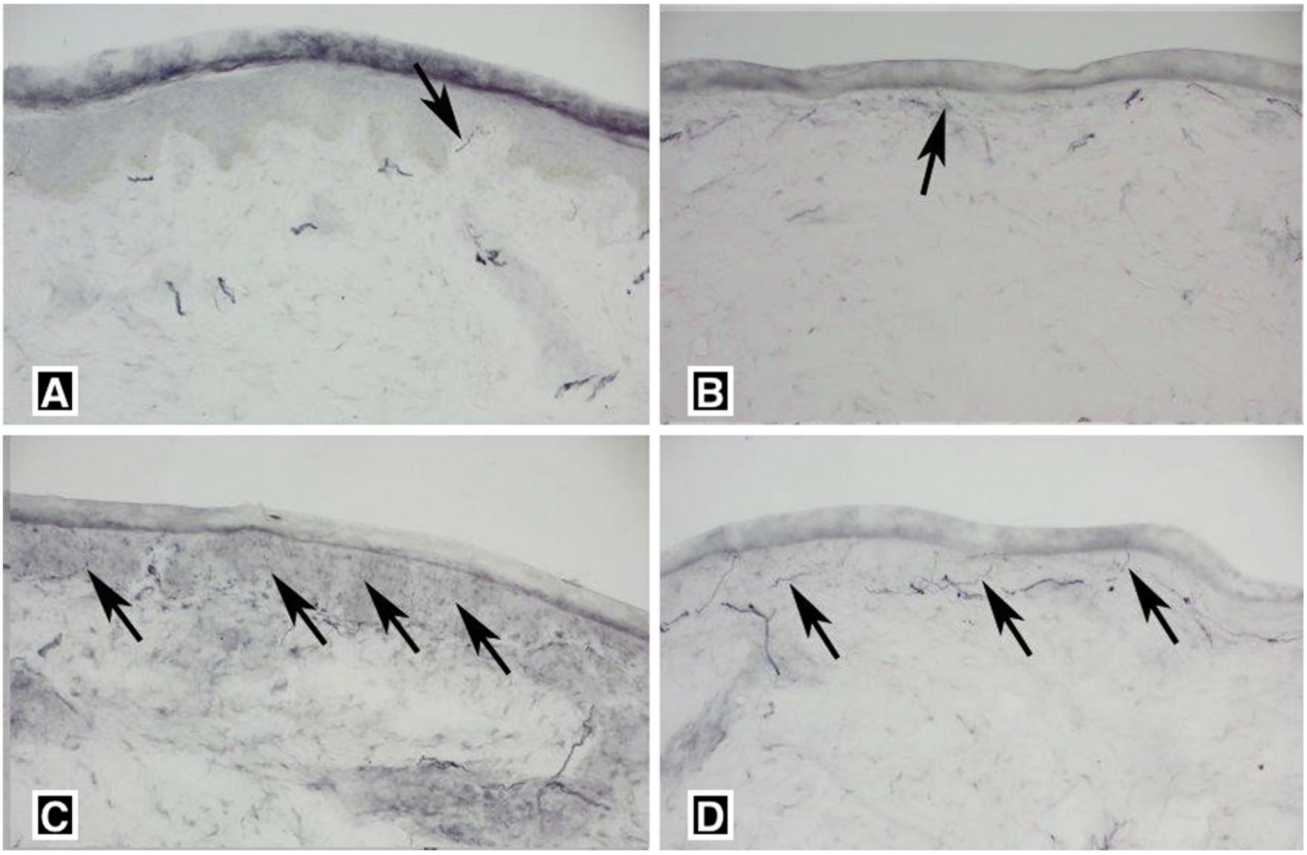


**Fig. 1.**

Microscopic examination of PGP9.5-immunolabeled thick sections from a standard 3 mm punch skin biopsy to a depth of 2 mm from the distal leg (10 cm above the lateral malleolus) in Case 1 (A) and Case 2 (B) showing reduced epidermal nerve-fiber density (ENFD) compared to age-, sex- and race-matched normal controls (C and D respectively). At the distal leg, Case 1 had 148 neurites/mm$^2$, at the 2.2 percentile compared to the laboratory's age, sex, and race matched standards. The thigh site biopsy (20 cm distal to the anterior superior iliac spine) showed worse epidermal nerve-fiber density, containing only 68 neurites/mm$^2$. Case 2 had 117 neurites/mm$^2$, less than the 1st percentile at the distal leg site.