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Accessibility
Small-fiber polyneuropathy (SFPN), a common underlying diagnosis in syndromes involving unexplained chronic pain and multi-system symptoms

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Background
Syndromes involving unexplained chronic widespread pain (CWP) and multi-system symptoms are common, with 1-5% prevalence for fibromyalgia alone. They more often affect females and cause disability and high costs [1-3]. Other common syndromes include chronic fatigue, seronegative Lyme, and Gulf War Illness. Fragmentary syndromes include TMJD, POTS, CRPS, irritable bowel. These syndromes are particularly devastating in children and young adults, where they interfere with education and development and disrupt entire families [4-6]. SFPN is known to cause CWP and multi-system complaints in older adults. Unlike the syndromes above, SFPN can be objectively diagnosed by measuring innervation in lower-leg skin biopsies, and autonomic functions testing (AFT) of heart rate, blood pressure and sweating [7]. SFPN has several established causes including diabetes, infections, cancer, and toxins. Many causes are diagnosable, treatable, and sometimes curable [8]. Our work suggests that unrecognized SFPN contributes to several syndromes involving CWP and multi-organ symptoms.

Materials and methods
With IRB permission, we retrospectively analyzed the medical records of 41 patients with onset of unexplained CWP and multisymptoms before age 21; most had objective testing for SFPN [9]. We also prospectively studied 27 adult patients with fibromyalgia and 30 healthy volunteers using history, examination, skin biopsies and AFT [10].

Results
Retrospective chart review identified definite (in 59%) and probable SFPN (in 17%) among the young patients with onset before age 21 [9]. We characterized the clinical features, diagnostic, and treatment options for this new early-onset SFPN. Studying children, who lacked the typical causes of late-onset SFPN, implicated autoimmune causality in most. Among patients treated with immunomodulatory therapies, pain and other symptoms improved in 2/3 [9]. Among adults with fibromyalgia, 41% of skin biopsies from subjects with fibromyalgia vs. 3% of biopsies from controls were diagnostic for SFPN, and symptom and examination scores were higher in fibromyalgia subjects than in controls (all P ≤ 0.001) [10]. All fibromyalgia patients diagnosed with SFPN then had blood tests for all known causes [8]. None had diabetes but 62% had test results consistent with dysimmunity, and some had genetic causes [10]. Other laboratories have now also linked fibromyalgia to SFPN [11-15].

Conclusions
Some patients with unexplained widespread pain and multi-system syndromes such as fibromyalgia have objectively diagnosable SFPN. SFPN can affect children and young adults, not just older adults. Multiple lines of evidence suggest that early-onset SFPN has novel causes that can be treated. The prevalence of SFPN among TMJD patients is unstudied.
Disclosures
None of the authors have any conflicts of interest.

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