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Scientific Advances in and Clinical Approaches to Small-Fiber Polyneuropathy
A Review

Anne Louise Oaklander, MD, PhD; Maria Nolano, MD, PhD

IMPORTANCE Small-fiber polyneuropathy involves preferential damage to the thinly myelinated A-delta fibers, unmyelinated C sensory fibers, or autonomic or trophic fibers. Although this condition is common, most patients still remain undiagnosed and untreated because of lagging medical and public awareness of research advances. Chronic bilateral neuropathic pain, fatigue, and nausea are cardinal symptoms that can cause disability and dependence, including pain medication dependence.

OBSERVATIONS Biomarker confirmation is recommended, given the nonspecificity of symptoms. The standard test involves measuring epidermal neurite density within a 3-mm protein gene product 9.5 (PGP9.5)–immunolabeled lower-leg skin biopsy. Biopsies and autonomic function testing confirm that small-fiber neuropathy not uncommonly affects otherwise healthy children and young adults, in whom it is often associated with inflammation or dysimmunity. A recent meta-analysis concluded that small-fiber neuropathy underlies 49% of illnesses labeled as fibromyalgia. Initially, patients with idiopathic small-fiber disorders should be screened by medical history and blood tests for potentially treatable causes, which are identifiable in one-third to one-half of patients. Then, secondary genetic testing is particularly important for familial and childhood cases. Treatable genetic causes include Fabry disease, transthyretin and primary systemic amyloidosis, hereditary sensory autonomic neuropathy-1, and ion-channel mutations. Immunohistopathologic evidence suggests that small-fiber dysfunction and denervation, especially of blood vessels, contributes to diverse symptoms, including postexertional malaise, postural orthostatic tachycardia, and functional gastrointestinal distress. Preliminary evidence implicates acute or chronic autoreactivity in some cases, particularly in female patients and otherwise healthy children and young adults. Different temporal patterns akin to Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy have been described; here, corticosteroids and immunoglobulins, which are often efficacious for inflammatory neuropathic conditions, are increasingly considered.

CONCLUSIONS AND RELEVANCE Because small fibers normally grow throughout life, improving contributory conditions may permit regrowth, slow progression, and prevent permanent damage. The prognosis is often hopeful for improving quality of life and sometimes for abatement or resolution, particularly in the young and otherwise healthy individuals. Examples include diabetic, infectious, toxic, genetic, and inflammatory causes. The current standard of care requires prompt diagnosis and treatment, particularly in children and young adults, to restore life trajectory. Consensus diagnostic and tracking metrics should be established to facilitate treatment trials.

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Author Affiliations: Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston (Oaklander); Department of Pathology (Neuropathology), Massachusetts General Hospital, Boston (Oaklander); Department of Neuroscience, Reproductive Sciences and Odontostomatology, University "Federico II" of Naples, Naples, Italy (Nolano); Skin Biopsy Laboratory, Department of Neurology, IRCCS, SpA SB, Telese Terme, Italy (Nolano).

Corresponding Author: Anne Louise Oaklander, MD, PhD, Massachusetts General Hospital, 275 Charles St, Warren Bldg 310, Boston, MA 02114 (aloaklander@mgh.harvard.edu).

Polyneuropathy may be the most common neurologic illness; it affects 14.8% of Americans older than 40 years.[1] This does not even include small-fiber polyneuropathy (SFN), the most common neuropathy presentation, because most patients currently remain undiagnosed. Small-fiber polyneuropathy refers to widespread preferential damage to the small-diameter somatic and autonomic unmyelinated C-fibers and/or thinly myelinated A-delta fibers. Neither surface nerve conduction studies nor electromyography testing, the universal diagnostic tests for large-fiber polyneuropathy, detect SFN. The only population-based estimate available, to our knowledge, is 52.95 affected individuals per 100 000 population in the Netherlands,[2] which yields a global SFN prevalence of 4 077 150 individuals. But because ascertainment required the identification of 2 or more symptoms by specialists plus confirmatory skin biopsies or thermal sensory thresholds and normal nerve conduction study results,[2] this represents the minimum prevalence. Some have estimated that only 10% of patients are diagnosed. Thus, global prevalence could exceed 10 million. Additionally, meta-analysis generated a 49% (95% CI, 38%-60%) prevalence of SFN in patients with fibromyalgia.[3] With fibromyalgia reportedly affecting 2% to 5% of people globally,[4] SFN could conceivably affect far more than 10 million people. Hence, there is urgency to improve awareness, diagnosis, treatment, and research.

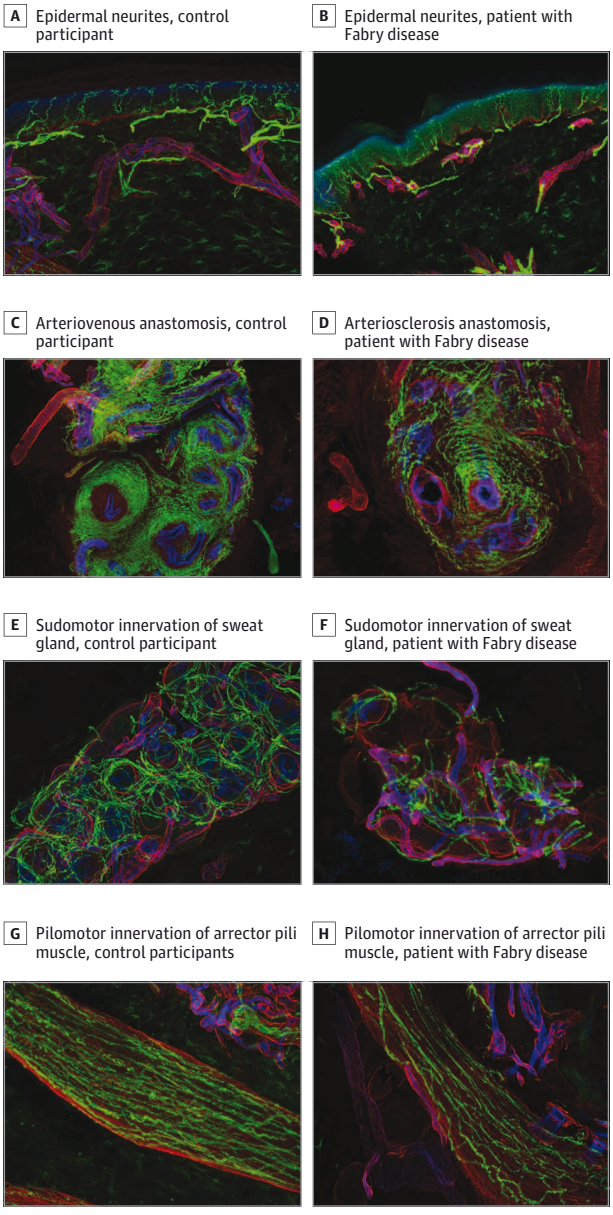
In addition to pure SFN, mixed polyneuropathies (eg, diabetes) often start as SFN, and SFN often coexists with large fiber–predominant neuropathy.[5,6] Small fibers' high surface-to-volume ratios, which is perhaps the largest among human cells, make their axons most likely to degenerate. Most small fibers are unmyelinated, precluding energy-conserving saltatory conduction and requiring panaxonal ion-channel deployment. Small fibers' enormous axonal surfaces are supported by miniscule cytoplasmic volumes that struggle to transport supplies along axons sometimes more than a meter long. Insights and treatments for SFN will likely apply to other neuropathic conditions as well.

Pathophysiology and Clinical Presentation

Small-diameter somatic and autonomic unmyelinated C-fibers and/or thinly myelinated A-delta fibers evolved to protect us from harm. They monitor for external dangers and send pain and itch signals centrally to trigger conscious and involuntary evasive maneuvers and monitor the internal physical environment to maintain homeostasis and marshal responses to injury and illness. The central nervous system integrates these exteroceptive and interoceptive inputs to improve the odds of survival. Sensory small fibers' outward signaling capacities blur classic somatosensory, motor, and autonomic distinctions. Their efferent paracrine and trophic functions (**Figure 1**) include regulating immunocytes and remodeling bone.[7] These diverse functions help explain why SFN can cause multiple symptoms (**Figure 2**). If individual patients see different specialists for each symptom, the unifying SFN diagnosis can be missed. Traditional descriptions of SFN emphasize spontaneous and stimulus-evoked distal skin pain and sensory loss, but deep aching, fatigue, postexertional malaise, and neuropathic itch (Figure 2E) are also common.[8] Postural orthostatic tachycardia syndrome (POTS), gastrointestinal complaints, and sweating complaints reflect damage to postganglionic unmyelinated autonomic small fibers.[9,10]

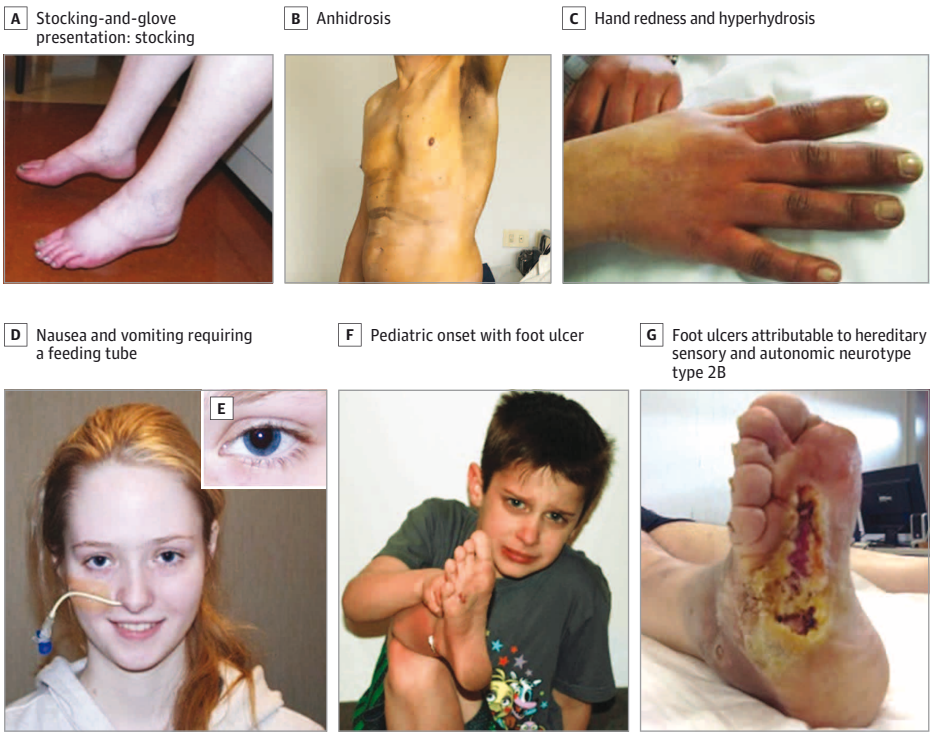
The classic erythromelalgia phenotype that Silas Weir Mitchell, MD, characterized in 1878 as swollen, red, burning feet soothed

Figure 1. Multiple Functions of Normal Cutaneous Small Fibers Reduced in a Patient With Early-Onset Small-Fiber Polyneuropathy



Multilabel fluorescent immunohistochemistry with confocal microscopy. Axons are green (PGP 9.5), basement membrane and blood vessels are red (col IV), and epidermis and endothelia are blue (Ulex europaeus agglutinin). A, C, E, and G are from the skin biopsy of a normal control (a boy aged 10 years); B, D, F, and G are from a boy with Fabry disease (aged 13 years). Images are from the standard lower-leg site, except C and D, which are from a glabrous fingertip. A and B, Epidermal neurites; B shows morphological signs of degeneration (axon thinning and beading) and regeneration (clusters within tracts of epidermal denervation) and a disordered subepidermal neural plexus. C and D, Normal abundant innervation of arteriovenous anastomoses by vasomotor fibers to maintain tonic closure, which is severely reduced in D. E and F, Sudomotor innervation of sweat glands; F shows severe axonal denervation and derangement with resultant atrophy of the sweat gland. G and H, Pilomotor innervation of arrector pili muscles; the density is moderately reduced in H.

Figure 2. Neurological Examination Findings



A, Classic stocking-and-glove erythromelalgia presentation in the distal extremities, with burning pain and neuropathic microvasculopathy causing skin redness and underlying edema. Severely affected patients often cool the affected skin to reduce C-fiber firing and pain. B, Non–length-dependent anhidrosis in a patient with small-fiber neuropathy from transthyretin amyloidosis. Thermoregulatory sweat testing results reveal residual sweating (dark staining) only in the axilla. C, Episodic hand redness, pain, and hyperhidrosis in woman with early-onset idiopathic small-fiber polyneuropathy. D and E, An adolescent with early-onset small-fiber polyneuropathy causing profound nausea, vomiting, and cachexia improved with a feeding tube (D); the same individual displays Adie pupils (E). F, A boy with biopsy-confirmed SFN attributable to *SCN9A* mutation cries from chronic neuropathic pain and demonstrates his lower-leg skin thickening and early painless foot ulcer from scratching neuropathic itch. G, A man with hereditary sensory and autonomic neuropathy type 2B from a *RAB7* mutation has severe painless foot ulcers.

by cooling (Figure 2A)[11] represents spontaneous activity of damaged sensory C-fibers that transmit unprovoked pain signals centrally while releasing vasoactive substance P and calcitonin gene-related peptide distally to cause neurogenic inflammation.[12] Some SFN symptoms are caused by neuropathic microvasculopathy as tissues become unable to increase perfusion during peak demand. For instance, chronic fatigue and reduced exertional tolerance in SFN and fibromyalgia are explicated by studies showing that in both conditions, denervated dilated arteriovenous anastomoses (Figure 1D) in skeletal muscle shunt arterial blood directly into venules, bypassing capillaries, depriving exercising myocytes, and triggering local hypoxemia.[13,14] This pathophysiologic profile reportedly identifies SFN with 90% sensitivity and 91% specificity.[14] In addition, impaired venous contractility in the legs reduces cardiac return and thus cardiac output, which worsens perfusion throughout the body. Among 229 patients with chronic fatigue attributed to preload failure, 31% had skin biopsies consistent with SFN.[15] Gastrointestinal specialists are increasingly considering neuropathic dysregulation of enteric vasculature (gastrointestinal angina) as an additional contributor, along with enteric small-fiber loss,[16] to previously unexplained postprandial nausea, vomiting, and lower dysmotility syndromes. It is possible that neuropathic dysregulation also contributes to brain symptoms of SFN, such as chronic daily headache and cognitive dysfunction.[9,17,18]

Small-fiber polyneuropathy has documented effects on the brain. The central axons of small fibers synapse in the spinal cord to trigger ascending signals or directly ascend the dorsal columns to the brainstem. Central axons also degenerate (central-peripheral distal axonopathy) with transsynaptic and network effects.[18] The C and A small-fiber nociceptors control the long-term potentiation–like pain amplification that can secondarily change in SFN (central sensitization).[19] Inactivity, pain, fatigue, deconditioning, depression, and pain medications also affect the brain.[17] Neuropsychological evaluations in patients with SFN associated with Sjögren syndrome yielded 100% with cognitive complaints, including 80% with problems in the executive domain and 70% with abnormal Wisconsin Card-Sorting Test results.[20]

Non–Length-Dependent and Patchy Presentations

One-quarter of patients with SFN do not present with classic symmetric stocking-and-glove presentations[21] (Figure 2B and D). Patchy or proximal distributions suggest targeting of sensory or auto-

Table 1. Medical Contributors to Initially Idiopathic Small-Fiber Neuropathy: Screening by History and Examination[a,b]

Cost-Effective Screening Blood Tests in the United States	Definition of Abnormal Result	Medical Condition Tested	Prevalence of Abnormal Test Result in Sample, No. (%)	% Population Prevalence of Abnormal Test Result[22]	Population or Geographic Location Studied[22]
Immune-mediated disorders					
Erythrocyte sedimentation rate	High	Inflammation or infection[9,23]	157 (28.0)	5.0	Norway
Antinuclear antibodies	≥1:160	Lupus or rheumatic disease[9]	153 (27.5)	8.9	Brazil
Complement C4	Low	Inflammation and vasculitis[9]	115 (15.7)	10.4	WHS
Complement C3	Low	Autoimmunity and vasculitis[9]	118 (11.0)	2.7	WHS
C-reactive protein	High	Injury or inflammation	95 (12.6)	7.1	WHS
Anti-Ro/Anti-Sjögren syndrome-associated antigen A	High	Sjögren syndrome[24]	98 (9.2)	0.7 and 3.9	WHS and NHANES, respectively
IgA tissue transglutaminase antibodies	High	Celiac disease[25]	109 (3.5)	0.5-1.0	United States (estimate)
Metabolic or endocrine disorders[c]					
Fasting glucose or oral glucose tolerance test	High	Diabetes	921 (7.7)	6.1[26]	The Netherlands
Thyrotropin	High	Hyperthyroidism	145 (4.1)	0.5	NHANES
Thyrotropin	Low	Hypothyroidism[27]	144 (2.1)	0.3	NHANES
Folate	Low	Folate deficiency[28]	49 (2.0)	<0.1	US residents >50 years old
Hematologic disorders[d]					
Serum protein electrophoresis or immunofixation	Variable	Monoclonal gammopathy	128 (3.9)	3.2	US residents >50 years old

Abbreviations: NHANES, National Health and Nutrition Examination Survey; WHS, World Health Survey.

[a] Additional causes of small-fiber polyneuropathy include temporally appropriate neurotoxic exposures (cancer chemotherapy [eg, with vinca, taxanes], antiretroviral HIV drugs, colchicine, vitamin B_6, metronidazole, nitrofurantoin, fluoroquinolones, and arsenic), and genetic disorders (Charcot-Marie-Tooth disease, transthyretin amyloidosis, Fabry disease, hereditary sensory and autonomic neuropathies, Ehlers-Danlos syndrome, and ion channelopathies).

[b] Infectious causes of small-fiber polyneuropathy for which no tests are included in this Table: HIV, hepatitis B and C, Lyme disease, and leprosy.

[c] Metabolic causes of small-fiber polyneuropathy for which screening blood tests are not recommended in the United States: alcohol abuse and glucose intolerance.

[d] Hematologic causes of small-fiber polyneuropathy include Waldenström macroglobulinemia and multiple myeloma.

nomic cell bodies (ganglionitis or neuronitis) rather than axonopathy. Cranial ganglionitis causes SFN symptoms, including pain and erythromelalgia, in the head and face. Most ganglionitis is inflammatory, particularly in female patients and individuals with rapid-onset cases. Small-fiber ganglia become vulnerable because they leave the protection of the central nervous system during embryogenesis to become sentinels. Their fenestrated capillaries that facilitate sampling the internal environment further expose them to infection, immunity, and toxins (**Table 1**).[29] Cerebrospinal fluid can reveal inflammatory markers, and mononuclear infiltrates and nodules of Nageotte are pathological hallmarks of cell-body degeneration.[30] Because large-fiber cell bodies are often also attacked, patients can have ataxia or reduced proprioception, hyporeflexia and abnormal nerve conduction study results, or somatosensory-evoked potentials. Magnetic resonance imaging may become useful.[31]

Sjögren syndrome and proximal diabetic radiculopathy can cause chronic non–length-dependent SFN symptoms.[32,33] Restricted ganglionitis can present without serologic markers, including in 60% of patients with Sjögren syndrome–associated SFN.[24] Ophthalmologic evaluation and lip biopsy for salivary glands help confirm suspected cases and direct therapy. Paraneoplastic painful ganglionitis is most often associated with anti-Hu amphiphysin and CV2 autoantibodies; the lung is the most common site of a malignant condition, followed by hematological and gastrointestinal tumors.[34] Thus, non–length-dependent SFN requires urgent evaluation and often disease-targeted treatment.[29]

Early Onset in Children and Healthy Young Adults

Childhood SFN is generally attributed to rare, deterministic, mendelian mutations (**Table 2**). However, affected families reveal more complex effects with wider implications. Presentation age varies from preschool, if affected neurons never form (hereditary sensory and autonomic neuropathies 3-5)[35-37] to the second and third decade, if neurons form but degenerate quickly.[38,40] Rare patients remain asymptomatic or subclinical into adulthood, unless or until axons are additionally stressed (for instance, by aging, diabetes, chemotherapy, or injury), representing variable penetrance.[38,44] Mutations are often conceptualized as loss-of-function mutations, where neural degeneration permits painless injuries, infections, and (rarely) death (Figure 2E and F) vs gain-of-function mutations, where hyperexcitable small-fiber firing triggers pain, itch, and autonomic lability. However, excess action potentials trigger deleterious ion and fluid entry and add energy demands. Together, these can cause axon degeneration and loss of function, blurring the distinction. Single-nucleotide polymorphisms (SNPs) affecting voltage-gated sodium channels (Na_v) preferentially expressed by small fibers have been linked to loss-of-function and gain-of-function SFN symptoms, but the most frequent abnormal test finding is a variant of uncertain significance (VUS). Evaluations of pathogenic significance of a VUS require integrating data on variant population prevalence, anticipated outcomes, and reported phenotypes. Clinical significance may vary in different populations and environments. A Dutch study of

Table 2. Genetic Small-Fiber Polyneuropathies

Name Inheritance	Inheritance	Pathogenesis	Pathogenic Gene(s)	Clinical Features	Age at Onset	Precision Treatments
Hereditary sensory and autonomic neuropathy IV	Autosomal recessive[35]	Lack of development	*NTRK1*	Insensitivity to pain and anhidrosis	Congenital	None
Hereditary sensory and autonomic neuropathy V	Autosomal recessive	Lack of development	*NGF-β*	Insensitivity to pain	Congenital	None
Hereditary sensory and autonomic neuropathy III (familial dysautonomia, Riley-Day Syndrome)	Autosomal recessive; almost exclusive to patients of Eastern-European Jewish ancestry[36]	Lack of development	*IKBKAP*	Tearless crying, dry mouth, diarrhea/ constipation, labile blood pressure, reduced taste, pain, and temperature	Early childhood	None
Cold-induced sweating syndrome	Autosomal recessive[37]	Abnormal maturation	*CRLF1*	Cold-induced sweating	Congenital	None
Hereditary sensory and autonomic neuropathy I	Autosomal dominant[38]	Reduced survival	*SPTLC1* and *SPTLC2*	Reduced sensitivity to touch, pain, and thermal stimuli; muscle weakness; atrophy; and distal ulcers	Subtle onset in children, teens, worsens during life	Oral *L*-serine overloading reduces neurotoxic 1-deoxysphingolipids and modestly improves adults who have been long affected.[39] Much earlier diagnosis and treatment consideration recommended.
Hereditary sensory and autonomic neuropathy IIA, B, and C	Autosomal recessive[40]	Reduced survival	*ATL1*, *ATL3*, *DNMT1*, *RAB7*, *ATSV*, *WNK1*, and *FAM134B*	Pan sensory loss and distal mutilation	Birth or early childhood	None
Fabry disease	X-linked recessive[41]	Lysosomal storage of globotriaosyl-ceramide in small-fibers and endothelial cells	*GLA*	Pain and hypohydrosis	Late childhood to early adult	Enzyme replacement agalsidase alfa (Replagal) and agalsidase beta (Fabrazyme); only Fabrazyme has been cleared by the US Food and Drug Administration.
Transthyretin amyloidosis	Autosomal dominant	Aggregation of insoluble, potentially toxic, fibrils that precipitate in tissues	Transthyretin	Pain, autonomic symptoms, carpal tunnel syndrome, and restrictive cardiomyopathy	Adults (20-80 y)	Patisiran (small, interfering RNA) and Inotersen (antisense oligonucleotide) lower transthyretin formation. Transthyretin stabilizers Tafamidis, Difluinsal, and Tolcapone inhibit release of monomers that form amyloid.
Cation channelopathy	Autosomal dominant[42,43]	Channelopa-thies; initial gain of function, with possible early or late loss of function	Nav 1.6-1.9 (*SCN* 8-11), *HCN2*, *TRPA1*, *TRPV4*, and *Piezo2*	Episodic or chronic pain, itch, sensory loss, and vasomotor and autonomic symptoms	Usually prepubertal	Trials of subtype-specific sodium-channel antagonists (Na_v 1.7 and Na_v 1.8) are in progress (ClinicalTrials.gov: NCT03339336).

Abbreviations: *ATL1*, atlastin guanosine triphosphatase 1; *ATL3*, atlastin guanosine triphosphatase 3; *ATSV*, axonal transporter of synaptic vesicles; *CRLF1*, cytokine receptor-like factor 1; *DNMT1*, DNA methyltransferase 1; *FAM134B*, family with sequence similarity 134 member B; *GLA*, α-galactosidase A gene; *HCN2*, potassium-sodium hyperpolarization-activated cyclic nucleotide-gated ion channel 2; *IKBKAP*, inhibitor of κ light-polypeptide gene enhancer in B-cells, kinase complex–associated protein; Nav, voltage-gated sodium channel; *NGF-β*, nerve growth factor–β; *NTRK1*, neurotrophic receptor tyrosine kinase 1; *Piezo2*, Piezo-type mechanosensitive ion channel component 2; *RAB7*, Ras-related protein Rab-7a; *SCN9A*, sodium voltage-gated channel subunits 8 through 11; *SPTLC1*, serine palmitoyltransferase long-chain base subunit 1; *SPTLC2*, serine palmitoyltransferase long-chain base subunit 2; *TRPA1*, transient receptor potential ankyrin 1; *TRPV4*, transient receptor potential cation channel vanilloid subfamily member 4; *WNK1*, lysine-deficient protein kinase 1.

patients with pure SFN–associated erythromelalgia symptoms with Na_v SNPs,[42] whereas a US study of patients with mixed neuropathy reported no correlations between the presence of Na_v variants and pain status.[45] The prevalence of rare Na_v SNPs also far exceeded population prevalences in the Dutch study of patients with pure SFN.[42,45] Excess Na_v firing is the electrophysiological substrate of neuropathic pain. In knock-in mice with Fabry disease, globotriaosylceramide accumulations caused gain of function of Na_v1.7 and potassium-sodium hyperpolarization–activated cyclic nucleotide-gated ion-channel 2 (HCN-2) ion channels expressed in small fibers and blood vessels, culminating in painful axonopathy. Also, Na_v variants may influence susceptibility to painful diabetic neuropathy.[41,44] Some VUS interact with other components or modulators of ion-channel complexes, and sequencing only channel exons will not detect them. Some genetic variants affect multiple fiber types. Hereditary sensory neuropathy type 1 presents in youth with distal pain, itch, and sensory loss, but weakness and muscle atrophy develop rapidly.[38] Transient receptor potential ankyrin 1 (*TRPA1*), sodium voltage–gated channel alpha subunit 9 (*SCN9A*), collagen type VI alpha 5 chain (*COL6A5*), transient receptor potential cation channel subfamily V member 4 (*TRPV4*), and Piezo-type mechanosensitive ion channel component 2 (*Piezo2*) vari-

ants have been associated with neuropathic itch.[8,43] An immune-system attack on channel complexes can mimic a genetic channelopathy.[46] Sodium-channel blockers, including carbamazepine, oxcarbazepine, and mexiletine, are attractive for treating channelopathy-associated SFN and perhaps other types as well; trials are needed.

Most early-onset SFN is not genetic but rather appears inflammatory, involving autoreactive B cells. Autoantibodies have been associated with dysautonomic SFN symptoms, including POTS,[47,48] and corticosteroid immunotherapy has effectively treated young patients with rapid-onset painful SFN.[23,49-51] The series that, to our knowledge, is largest, consisted of 41 patients with unexplained widespread pain beginning before age 21 years; objective testing identified definite SFN in 25 of 41 patients (59%) and probable SFN in 7 of 41 patients (17%).[9] Inflammatory causality was proposed when comprehensive evaluations revealed neither familial, diabetic, nor toxic causes but rather histories of other autoimmune illnesses in 14 of 41 patients (33%) and inflammatory blood-test markers in 32 of 36 (89%). Corticosteroids benefitted 67% (10 of 15 patients) and intravenous immune globulins (IVIg) benefited 5 of 8 patients (63%). Overall, 80% benefited from immunotherapy.[9] Reports of early-onset SFN after infectious exposures, particularly to human papillomavirus vaccination, suggest potential molecular mimicry.[52,53] Autoreactive SFN also affects adults but is easiest to diagnose in children and otherwise healthy young people without other risk factors.

Testing children for SFN requires age-appropriate norms. For autonomic testing, quantitative sudomotor axon reflex test norms are only established for individuals 10 years or older, and short stature blunts the sensitivity of tilt-table testing (and reduces the prevalence of POTS).[54] Skin biopsies are the best option for children currently, and preapplying local-anesthetic cream renders them painless. Biopsies are taken proportionately closer to the lateral malleolus, and a few laboratories accept 2-mm punches. Age-matched norms and statistical modeling are essential for reducing the very high rates of false-negative interpretations with adult norms. Children have 3 to 4 times more epidermal neurites, which are pruned during adolescence.[55] Children and otherwise healthy young adults are excellent participants in research because most have recent, precisely documented onsets, and their parents are motivated to advance diagnosis and treatment. Regarding treatment, because younger patients have the greatest risk of life-derailing disease trajectories, plus greatest potential for recovery,[9,56] lengthy observation or mere symptom palliation may be insufficient. Immunotherapy and/or genetic testing should be more rapidly considered. Top priorities include improving pediatrician awareness of SFN and developing age-appropriate diagnostic and tracking metrics.

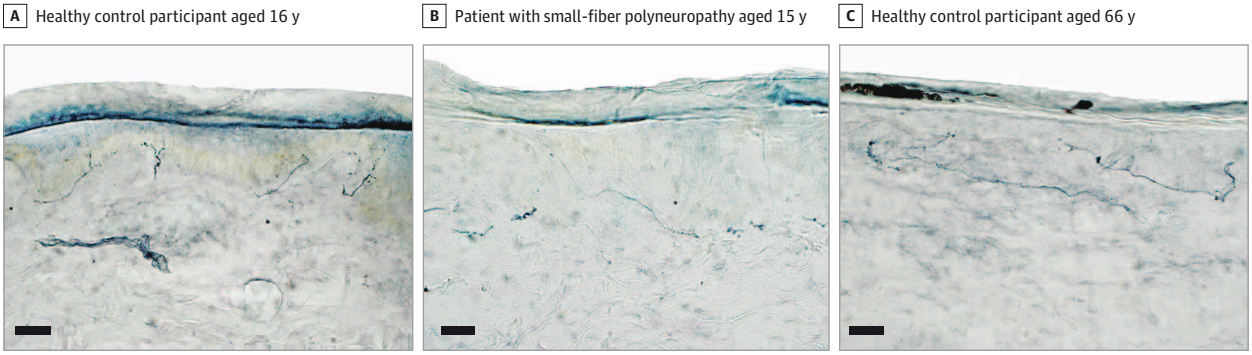
Assessment and Diagnosis

Recognition is straightforward with the classic painful-feet presentation, but experts estimate that most patients are currently undiagnosed. The lack of case definition and patient-reported and clinician-reported assessment tools hinders research as well as care. There are standardized patient-reported symptom surveys for single-cause mixed neuropathic conditions from diabetes,[57-59] sarcoidosis,[60] and specific chemotherapies,[61] and validated general questionnaires for pain and dysautonomia.[62,63] The SFN-specific Rasch-built overall disability scale and Small-Fiber Symptom Survey are comprehensive SFN symptom surveys validated for all causes.[64-66] Regarding examination findings, the Utah Early Neuropathy Scale was developed and validated for sensory-predominant diabetic polyneuropathy.[67] Insofar as we know, only the Massachusetts General Neuropathy Exam Tool (MAGNET) is validated for SFN independent of cause.[68] A recent international Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) meeting is expected to generate the first consensus research case definition of SFN and research diagnostic criteria. These will incorporate symptoms, abnormalities on neurological examination, and objective confirmation by lower-leg skin biopsy or combinations of secondary tests. Research diagnoses prioritize specificity over sensitivity, so failure to fully meet them does not preclude SFN nor should research criteria be used to justify withholding treatment or reimbursement. The impression of expert clinicians remains the clinical diagnostic standard.

Confirming Diagnosis

When symptoms are nonspecific and examination findings are muted or subjective, objective confirmation is a critical step toward effective treatment and reimbursement. However, neither standard nerve conduction study nor electromyographic test assesses small fibers. They are invisible with conventional light microscopy, and biopsying nerves for an electron microscopic examination is not often feasible. The development of minimally invasive skin biopsies revolutionized SFN diagnosis and fuels discovery of new causes and treatments, with nerve biopsies now mostly reserved for vasculitis. The Peripheral Nerve Society and American and European Academies of Neurology endorse removing 3-mm punches from 10 cm above the lateral malleolus using intradermal anesthesia. Biopsy sections are immunolabeled against panneuronal marker protein gene product (PGP9.5), which reveals small-fiber axons with light or fluorescence microscopy.[69,70] Biopsies can be performed locally and mailed to accredited laboratories for processing, and epidermal neurite density measured according to consensus standards for statistical comparison with epidermal neurite density in biopsies from healthy, demographically matched volunteers (**Figure 3**).[70,72-74] Measured epidermal neurite densities less than the fifth percentile of the anticipated normal distribution confirm SFN in patients in whom this condition is suspected. However, many laboratories use nonrepresentative or published norms, which leads to inaccurate interpretations because of variability between laboratory methods and local reference populations.[72,75,76] Insensitivity (false-negative results) is the biggest concern, not only as a result of poor norms (particularly for young patients and female patients), but also from sampling error and the fact that axons typically degenerate later than symptoms appear. Second biopsies (eg, from the thigh for non–length-dependent neuropathic conditions,[75,77-79] or from the foot[80]) add sensitivity but also cost, and there are insufficient norms to recommend routine use. Immunofluorescence (Figure 1) visualizes twice as many fibers as conventional bright-field microscopy (Figure 3) and thus requires separate norms.[81] Details about longitudinal stability and treatment responsiveness are needed for trial use. Researchers are exploring other biopsy sites and measures, such as density of sweat glands or arrector pili innervation (Figure 3), but these need more validation for clinical use.

Figure 3. Protein Gene Product 9.5–Immunolabeled Lower-Leg Skin Biopsies: Importance of Accurate Norms for Diagnostic Interpretation



This bright-field photomicrograph illustrates standard clinical processing and morphometric evaluations used most often for clinical diagnostic confirmation of small-fiber neuropathy. Skin biopsies are from 10 cm above the lateral malleolus in adults and proportionally less in children. They are cryosectioned vertically into 50-µm sections and hand-immunolabeled using monoclonal antibody targeting protein gene product–9.5, a ubiquitin hydrolase present in all axons.[71] Skilled morphometrists count the number of neurites that penetrate the dermal-epidermal junction and express epidermal neurite density per mm^2 of skin-surface area. Each patient's epidermal neurite density is statistically compared with the anticipated normal distribution calculated using within-laboratory measurements made from biopsies of screened healthy control participants. Patient with epidermal neurite densities at less than the fifth percentile of expected amounts have pathologically confirmed clinical diagnoses, and predegenerative swellings, fragmentation, or inflammatory infiltrates (not shown) can be supportive; × 40 magnification; scale bar = 100 µm. A, Screened normal, healthy, white male control patient, aged 16 years. His epidermal neurite density (356 per mm^2 of skin-surface area) was at the 58.0 percentile of the anticipated normal distribution of his age, sex, and race and provides no pathological evidence of small-fiber polyneuropathy. B, A 15.1-year-old white male patient with gastrointestinal symptoms, headache, fatigue, labile blood pressure, and postural orthostatic tachycardia syndrome (POTS) starting at age 3 years. His epidermal neurite density of 164 per mm^2 of skin-surface area is at the 1.3rd percentile of the anticipated norm by age, sex, and race, confirming the clinician's diagnosis of small-fiber polyneuropathy. Autonomic function testing results were also abnormal, antinuclear antibody test results were positive at 1:160, and a paraneoplastic panel identified autoantibodies against a voltage-gated potassium channel. C, This screened normal, healthy control participant, a 66.3-year-old white woman had 158 epidermal neurites per mm^2 of skin-surface area and was at the 37.6th percentile of anticipated normal distribution for her age, sex, and race, well within the normal range, although lower than the pathological epidermal neurite density in B.

More accessible, cheaper, and more sensitive tests would improve care. The best accepted is physiological: quantitative autonomic function testing developed at the Mayo Clinic. It includes 4 site comparisons of quantitative sudomotor axon reflex text sweating to anticipated norms,[73] which raises sensitivity toward 82% and is similar to a skin biopsy.[82-84] However, because few hospitals have the equipment, and patients must stop potentially interfering medications beforehand and travel to the laboratory, autonomic function testing is still not regularly used or validated for trials.[73] Quantitative sensory testing records only patients' subjective sensations and is not an objective diagnostic test.[85] Newer measures of sweating that are insufficiently validated for routine clinical use include the dynamic sweat test that assesses sweat gland density, distribution, and stimulated sweat production.[86,87] In vivo corneal confocal microscopy, which visualizes the exclusively C-fiber innervation of the cornea, is noninvasive and requires no preparation. It is repeatable for longitudinal tracking but not yet routine.[88] Neurophysiologic tests used mostly for research include laser-evoked and heat-evoked sensory potentials.[89]

Medical Causes and Contributors

Patients who have initially idiopathic cases of SFN (iiSFN) are first screened for cause using patient and family histories and prior test results (Table 1). Subsequent prospective blood screening identifies potential causes in 30% to 50% of patients with iiSFN.[22,26,90] Screening recommendations must integrate pretest probability of an abnormal result, test availability, cost, and diagnostic performance. Diabetes mellitus is overall the most common cause of neuropathy, but the value of screening for undiagnosed diabetes in iiSFN differs depending on its local prevalence. Prediabetes conveys far less risk and is not often causal.[22,91] Among US adults with biopsy-confirmed iiSFN, 2% had unappreciated diabetes mellitus and 22% had prediabetes, both of which were less than population prevalences (12%-14% and 37%-38%, respectively).[26] In the Netherlands, testing patients with iiSFN revealed that 71 of 921 patients (7.7%) had undiagnosed diabetes, which is of unclear significance compared with the 6% population prevalence.[26]

We discourage universal screening with low-value or futile tests, including those for heavy metals and sarcoidosis, where high serum angiotensin-converting levels had 0% positive predictive value.[22] Regarding vitamins, high B_6 levels are the major risk.[28] Universal screening for folate and B_{12} deficiencies is becoming less cost-effective in Western countries. A low folate level causes large-fiber rather than small-fiber sensory axonopathy; additionally, this deficiency is vanishing after mandated supplementation.[92] In the United States, B_{12} deficiencies are now also rare, and prevalence in patients with iiSFN does not exceed population prevalence.[22,28,90] In New England, where Lyme disease is prevalent, the prevalence of Western blot–confirmed Lyme disease was not elevated in patients with iiSFN.[22]

Secondary genetic sequencing (Table 2) is simultaneously underused in patients with a high probability of genetic causes (eg, pediatric patients, those with family history, those with highly specific phenotypes) and overused in patients with low probability of genetic causes.[93] We at least consider it in adult patients with SFN without a cause identified after primary testing and attempt it in all

children whose cases are still idiopathic, even absent a family history. The relative values of sequencing single genes, gene panels, vs initial whole-exome sequencing or whole-genome sequencing change as costs drop. Serial sequential testing delays diagnosis, whole-exome sequencing does not detect noncoding SNPs and structural effects such as gene duplications or translocations, and unbiased sequencing generates most VUS and potentially adds cost. With more genes implicated, costs dropping, and more precision treatments available (Table 2), sequencing will be performed more often, sooner, and more comprehensively, potentially enabling creation of polygenic risk scores. We and other clinicians detect Na_v variants most often in iiSFN, although their relevance is often unclear.[42,45]

Sequencing results are not final. Laboratories have limited medical information available from which to select sequences to analyze, and depth and quality of their analyses and reference comparators vary. New pathogenic variants are identified, new phenotypic correlates emerge, and some variants are later found to be spurious. Understanding of the significance of VUS in SFN-pathogenic genes changes is also evolving. Some so-called benign variants may be pathogenic in individuals with other genetic or environmental factors (ie, risk modifiers), and multiple benign variants could conceivably have combinatorial effects. Plus, we are only now appreciating that mutations in noncoding DNA can alter RNA biophysical properties in ways that influence its interactions. Initially unhelpful sequencing results may become useful later, and periodic reanalysis is a free service of many laboratories. Among 1519 patients referred to the National Institutes of Health Undiagnosed Diseases Network for advanced testing, nearly half were referred for neurological symptoms.[94] Among all diagnostic tools including imaging, whole-exome sequencing and whole-genome sequencing were most productive, providing molecular diagnoses in 74% of these patients.[94] Molecular diagnoses usually curtail further testing, can change treatments from palliative to precision-targeted to improve efficacy and safety, sometimes reduce cost, and influence reproductive planning.[94] Patients and physicians report benefit from genetic diagnoses, and the research benefits and help to other patients are incalculable.

Inflammatory and autoreactive conditions are increasingly linked to SFN, unsurprisingly, given small fibers' immune role. Their cell bodies leave the protection of the central nervous system protection during gestation to become sentinels and first responders. Sensory ganglia develop fenestrated capillaries and distal C-fiber terminal nearly contact the exterior in the superficial epidermis and mucosa. Small fibers have receptors for and release immune or inflammatory signals distally. They contact mast cells and microvessels. Neurogenic inflammation mediated by C-fibers is sometimes visible as flushing and swelling in focal or generalized small-fiber neuropathy (Figure 2A and C). Medical histories and blood test results in large studies of patients with iiSFN suggest associations with dysimmunity.[22,26,56] Among 921 Dutch patients with iiSFN, 12.9% had unspecified immunological conditions, and 6.1% had abnormal blood test results (eg, antinuclear antibodies, antineutrophil cytoplasmic antibodies, monoclonal gammopathy of undetermined significance, interleukin-2 receptor antibodies to tissue transglutaminase, and extractable nuclear antigens).[22] Among 195 US patients with biopsy-confirmed iiSFN, high erythrocyte sedimentation rate levels, high antinuclear antibodies titers, low complement C3 levels, and antibodies for Sjögren syndrome and celiac disease were each present at more than 300% of population prevalence.[22] High erythrocyte sedimentation rate and antinuclear antibodies of 1:160 titer or higher were most common, each affecting 28% of patients. These serologic markers can become false-negative or false-positive during immunotherapy, so screening should precede treatment.[22]

Primary Sjögren syndrome, the leading systemic immune condition associated with SFN, often remains undiagnosed. One-fourth to one-half of patients with all Sjögren syndrome–associated neuropathy are primarily affected by SFN.[24] The prevalence of Sjögren syndrome autoantibodies is 9% to 12% in patients with SFN,[22,74] but with nearly 60% of patients with Sjögren syndrome SFN seronegative, there may be more than 20% total prevalence of this disorder in iiSFN.[24] Patients with Sjögren syndrome and neuropathy are more likely to be seronegative than those without neuropathy.[95] Patients with Sjögren syndrome and SFN can have muted Sjögren symptoms or develop them after onset of neuropathic pain.[33] In France, more than 90% of such patients in a large study were female, and their most prevalent symptoms were burning pains (36 of 40 [90%]), numbness (35 of 40 [88%]), tingling (33 of 40 [83%]), pins and needles (29 of 40 [73%]), electric discharges (28 of 40 [70%]), and allodynia (22 of 40 [55%]). Sixty-six percent (25 of 38 patients) had vasomotor symptoms, and 47% (18 of 38 patients) sweated abnormally. Antibodies against muscarinic receptor type 3 and calponin have been reported.[96,97] Systemic lupus erythematosus, celiac disease, and psoriatic arthritis are less common associates of SFN.[25] Paraneoplastic autoimmunity can cause painful sensory ganglionitis and axonopathy, particularly anti-Hu, anti-CV2/collapsin response-mediator protein-5 (*CRMP5*), and multiple endocrine neoplasia type 2 (*MEN-2*).[98]

What about most patients with iiSFN, who do not have systemic inflammatory diagnoses?[56] Some will later receive systemic autoimmune diagnoses, and some may have ill-defined systemic predispositions toward dysimmunity, including selective immunoglobulin deficiency (SIgD).[9] In 1 study, 15 of 55 patients (28%) had IgG SIgD, 10 of 55 (18%) had IgG subclass deficiency, 8 of 55 (14%) had IgM SIgD, and 6 of 55 (11%) had IgA SIgD.[56] We and others have proposed the existence of small fiber–targeting inflammatory SFN, with acute and chronic presentations temporally resembling Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy, and preliminary evidence of episodic relapsing-remitting courses.[99] Unlike in Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy, inflammatory cells are not prominent in SFN biopsies or cerebrospinal fluid. Current evidence links autoreactive B cells using complement, with low C4 levels implicating the classic or lectin pathways.[9] Direct evidence is emerging in addition to the indirect evidence from medical histories, blood test results, and the responsiveness of some patients to corticosteroids and IVIg. Mice that were injected with sera from 3 patients with acute postinfectious SFN causing distal pain and dysautonomia developed SFN pain behaviors and small-fiber pathologic evidence of neuropathy.[100] Passive transfer of human autoantibodies to contactin-associated protein-like 2 (*CASPR2*) to mice causes pain hypersensitivity and enhanced dorsal-root ganglia cell excitability by reducing potassium-channel K_v1 function.[46] Five of 8 children with isolated iiSFN had IgM autoantibodies against trisulfated disaccharide IdoA2S-GlcNS-6S, as did 5 in a study of 22 patients with fibromyalgia, with 86% of these patients (n = 19) having SFN-

diagnostic skin biopsies.[79,101] Following examples learned from autoimmune encephalitis may enable us to identify cellular and molecular mechanisms of apparently autoimmune SFN. To do so, it is necessary to improve SFN phenotyping and conduct larger serologic studies.

Precision Treatment

Others have reviewed treatments to palliate pain and other SFN symptoms,[102,103] so we limit discussion to disease-modifying treatments that restore or preserve small-fiber function. As the benefits of eliminating or curtailing diabetes and neuropathic infectious diseases are established, we discuss emerging treatments, even though long-term benefits and cost-effectiveness are currently unknown. Most treatments for genetic SFN are very expensive, except those for hereditary sensory and autonomic neuropathy type 1. Although oral L-serine can be purchased without prescription or physician oversight, purity, dosing, and guidelines are not established, particularly for the children who are most likely to benefit.[5] Established consortia and charities that support costs of genetic testing and treatment of patients with motor-predominant genetic neuropathies (Charcot-Marie-Tooth disease) typically exclude patients with SFN, so parity for supporting patients with genetic SFN should be accelerated. Massachusetts General Hospital is developing secure internet metrics and data-sharing for such families (https://NeuropathyCommons.org). Large sets of longitudinal, real-world data would advance research and trials.

Potentially disease-modifying treatments are widely available but untrialed for inflammatory SFN, partly because of inadequate case definitions, metrics, and outcome measures. In the interim, trials for other inflammatory neuropathic conditions provide guidance. Treatment with IVIg, which is primary for Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and other autoimmune neurological conditions has the most preliminary support for off-label use in apparently immune SFN. In the first large uncontrolled study, 55 children and adults received 1 g/kg or more of IVIg every 4 weeks for 3 months or longer, and pretreatment pain severity with a mean of 6.3 (on a scale of 0 to 10) dropped to 5.2 (P = .007).[56] Three-quarters of patients and neurologists reported improvement, and 8 of 51 patients (16%) entered sustained remission, permitting IVIg withdrawal.[56] Adverse events were all as expected; these were mostly typical infusion reactions.[56] Objectively, the prevalence of autonomic function testing diagnostic for SFN dropped from 31 of 35 patients (89%) before treatment to 20 of 35 patients (57%).[9] Treatment with IVIg is reportedly helpful for sarcoidosis-associated SFN,[104] and a randomized clinical trial for idiopathic SFN is underway in the Netherlands (NCT02637700).[105] Smaller reports offer preliminary evidence of efficacy and safety of corticosteroids for acute presentations of apparently inflammatory SFN, particularly in young patients at lower risk of complications.[23,49] In a small case series of young patients, 10 of 15 patients (67%) receiving corticosteroid treatment had sustained improvement in symptoms and quantitative autonomic function testing with only 1 significant adverse event, which was cataract development.[9] In addition to the absence of untreated control participants, potential confounders included nonspecific benefits for pain, activity, and mood. Oral corticosteroids are globally available, inexpensive, and often the only immunotherapy available, so trials with them should be prioritized.

Conclusions

Small-fiber neuropathy has unappreciated symptoms, and undiagnosed cases appear common, particularly in the fibromyalgia syndrome. Presentations can vary from entirely somatic to entirely autonomic, but most patients have mixed symptoms. Skin biopsy is currently the best established test for objective confirmation of diagnosis. Because small-fiber axons grow throughout life, definitive diagnosis and treatment can lay the foundation for axonal and functional recovery. The young, otherwise healthy, and recently ill should be rapidly diagnosed and optimally treated to preserve life trajectory. Careful evaluation and screening identifies medical causes for almost half of patients whose cases are initially unknown, including seronegative Sjögren syndrome and rare genetic contributors. Multiple factors convey risk of SFN, so in all patients, it is important to manage potential secondary contributors and encourage better axonal perfusion and nutrition. Otherwise healthy children and young adults can develop acute or chronic SFN, apparently often from B-cell autoreactivity and only rarely from genetic causes. These cases, along with non–length-dependent presentations that are typically autoimmune and rarely paraneoplastic, are increasingly treatable, so they require urgent evaluation. Developing and validating simpler diagnostic and tracking metrics is a much-needed precursor for clinical trials. Most importantly, the rapid pace of discovery requires better education of clinicians and the public to improve medical care today.

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