대한임상신경생리학회지 3(1):1~10, 2003 ISSN 1229-6414

세섬유 신경병증

대구가톨릭대학교 의과대학 신경과학교실

이 동 국

Small-Fiber Neuropathy

Dong Kuck Lee, M.D.

Department of Neurology, School of Medicine, Catholic University of Daegu

Small-fiber neuropathy (SFN) is a common clinical problems. The disorder is a generalized peripheral polyneuropathy that selectively involves small-diameter myelinated and unmyelinated nerve fibers. It is often idiopathic and typically presents with painful feet in patients over the age of 60. And autoimmune mechanisms are often suspected, but rarely identified. The clinical features consisted of painful dysesthesias and postganglionic sympathetic dysfunction, as well as reduced pinprick and temperature sensation. Although affected patients complain of neuropathic pain, this condition is often difficult to diagnose because of the few objective physical signs and normal nerve conduction studies. Diagnosis of SFN is made on the basis of the clinical features, normal nerve conduction studies, and abnormal specialized tests of small fiber function. These specialized studies include assessment of epidermal nerve fiber density as well as sudomotor, quantitative sensory, and cardiovagal testing. Unless an underlying disease is identified, treatment is usually directed toward alleviation of neuropathic pain.

Key Words: Small-fiber neuropathy

Painful and burning feet represent one of the most enigmatic conditions encountered by neurologists with limited diagnostic and treatment options. In the absence of systemic diseases as diabetes mellitus or local foot problems, the symptoms may be unexplained because no objective abnormalities can be found on physical examination. Unless there is associated large-diameter myelinated fiber involvement, affected patients have few or no objective physical signs such as muscle weakness, absent tendon reflexes, and loss of vibratory sense and proprioception. The results of nerve conduction studies, which primarily evaluate the function of large myelinated fibers, are also normal in the majority of patients. Therefore despite the compalint of significant neuropathic pain, this condition is often difficult to diagnose and may be mistaken for a psychiatric disorder. Burning pain has typically been attributed to neuropathies selectively involving small myelinated and unmyelinated fibers such as amyloidosis, Tangier and Fabry disease, and some cases of hereditary sensory and autonomic neuropathies. Despite the frequency of SFN, relatively little attention has been devoted to this condition.[1-4]

Fortunately, over the past 15 years, new electrophysiologic and histologic methods have led to improvement in diagnosis, and these methods are becoming more widely available. It is likely that advances in treatment will follow, as it is now easier to design SFN treatment trials that quantitate small-fiber dysfunction.[5]

I will review the major features of SFN and emphasize the newer diagnostic methods.

Address for correspondence
Dong Kuck Lee, M.D.
Department of Neurology, School of Medicine,
Catholic University of Daegu
3056-6 Daemyung 4-dong, Nam-gu, Daegu 705-718, Korea
Tel: +82-53-650-4267, Fax: +82-53-654-9786
E-mail: dklee@cataegu.ac.kr

1. Definition

Generalized peripheral neuropathies can selec-

tively affect certain types of nerve fibers. SFN is a subtype of sensory neuropathy. SFN can be defined anatomically or physiologically as a sensory neuropathy that exclusively or predominantly affects small diameter thinly myelinated and unmyelinated fibers and their functions. Small somatic or autonomic fibers, or both, may be involved. But many patients with predominantly SFN have mild, often subclinical large-fiber involvement, a practical definition allow the presence of mild large-fiber dysfunction. There is no agreement regarding the amount of large-fiber dysfunction that can coexist and still allow the diagnosis of SFN.[5-7]

The essential criterion of SFN is the predominant symptoms of dysesthesias arising in the distal limbs. For inclusion, the neurologic examination had to either be normal or show diminished small-fiber mediated functions. But, more significant indicators of large-fiber dysfunction are exclusive, including decreased proprioception at the toes, vibratory loss at or above ankles, any distal wasting or weakness, generalized areflexia, or abnormal findings on routine nerve conduction studies or needle electromyography (EMG).[1,5,6]

Therefore SFN is a sensory neuropathy manifest by paresthesias that are typically painful, along with abnormal findings of small-fiber function on at least one of the followings as neurologic examination, pathologic studies, or specialized electrodiagnostic testing.

2. Morphology and function of peripheral nerve fibers(Table 1)[8]

There is a relative abundance of small-fibers in peripheral nerves. In most somatic nerves, unmyelinated axons outnumber myelinated axons fourfold. Of the myelinated axons, 32~45% are small(<7 μm diameter). Most unmyelinated axon diameters measure 1.0~1.6 μm.[5,9]

The physiologic functions performed by small somatic fibers include warm perception which is mediated by type C unmyelinated fibers. These fibers also play a minor role in cold thermoperception. Type Aδ are small myelinated fibers that are the main afferents for cold perception, and they also play a role in cutaneous nociception.[5,10-12]

Autonomic fibers have multiple functions. Preganglionic sympathetic and parasympathetic cholinergic efferent fibers are myelinated with diameters ranging from 1.5~4.4 μm. Postganglionic fibers are unmyelinated. Nonsudomotor, postganglionic sympathetic fibers are adrenergic. Sudomotor fibers innervating sweat glands are cholinergic, postganglionic, sympathetic, and unmyelinated[8].

3. Etiology (Table 2)[8]

Unfortunately, an etiology for SFN, especially in patients over the age of 60, is rarely found. When an etiology is found, it is usually diabetes mellitus. In general, diabetic polyneuropathy have primarily a sensory disturbance. In the small-fiber type of diabetic neuropathy, the unmyeli-

Table 1. Morphology and function of peripheral nerve fibers

Morphology	Function
Large-diameter myelinated fibers	Skeletal muscle efferents(αmotoneurons) Tendon reflex afferents Vibration and proprioception afferents Some skin touch afferents
Small-diameter myelinated fibers	Preganglionic sympathetic efferents γEfferents to intrafusal spindle muscle fibers Cold sensory afferents
Small-diameter unmyelinated fibers	Warm sensory afferents Pain afferents Some skin touch afferents Autonomic efferents Sympathetic postganglionic Parasympathetic pre-and postganglionic Autonomic afferents

nated and small myelinated fibers are involved before large myelinated fibers. The neuropathy seems to progress centripetally by the involvement of longer lengths of axon associated with abortive axonal regeneration.[5,14]

And known heritable causes of such SFN include autosomal recessive hereditary sensory neuropathy, familial amyloidosis, and Fabry's disease. Known acquired causal or predisposing conditions for SFN include systemic amyloidosis, human immunodeficiency virus infection, and exposure to certain neurotoxic medications. And vasculitis also cause SFN.[2,8,15-18]

However, no specific etiology is identified for the majority of SFN encountered in clinical field. Idiopathic type is the largest category in SFN. For example, 93% of 44 patients studies by Periquet et al.[19] had SFN of unknown etiology. Most of these patients are over the age of 60 years. And they have predominantly foot symptoms. Their paresthesias are usually painful and may be accompanied by negative symptoms. Examination findings are usually normal. Symptoms often spread proximally, but small-fiber dysfunction

Table 2. Causes of small-fiber neuropathy

Common causes	
	Diabetes mellitus
	Primary systemic amyloidosis
	Idiopathic
	Hereditary
	HSAN types I, IV, and V
	Burning foot dominantly inherited sensory neuropathy
	Tangier disease (hereditary high-density-lipoprotein deficiency)
	Fabry's disease (αgalactosidase A deficiency)
Rare causes	
	Nutritional neuropathies
	AIDS
	Alcohol
	Toxins and drugs
	Monoclonal gammopathy/antisulfatide antibodies
	Hyperlipidemia
	Cancer
	Primary biliary cirrhosis

HSAN, hereditary sensory and autonomic neuropathy

Table 3. Potential causes of small-fiber neuropathy and suggested evaluation

Disorder	Evaluation
Diabetes or impaired glucose handling	2-h oral glucose tolerance test
Systemic amyloidosis	Serum and urine protein electrophoresis, consider biopsy of nerve, muscle, abdominal fat, or rectum
Alcohol	History
Sjögren's syndrome	ANA, SS-A, SS-B antibodies, Schirmer tear test, Rose-Bengal corneal staining, lip biopsy
Pharmacologic toxins, e.g.,metronidazole	History
Environmental toxins	History, specialized toxicologic studies
Acquired immunodeficiency syndrome	HIV antibody
Hyperlipidemia	Fasting lipid panel
Familial "burning feet" neuropathy	History, exclude amyloidosis
Tangier disease	Alpha (high-density) lipoproteins
Familial amyloidosis	Transthyretin gene test, biopsy of affected tissues
Fabry's disease	Alpha-galactosidase assay
Hereditary sensory neuropathies	History, examination, possible DNA study when available
Monoclonal gammopathy	Serum and urine protein electrophoresis, quantitative immunoglobulins

Table 4. Clinical symptoms of idiopathic small-fiber neuropathy in 39 patients

Descriptor	Patients affected, number
Type of burning	30
Tingling	15
Numbness	12
Aching	8
Prickling	6
Cold	5

usually remains to be the predominant findings. Therefore weakness or other large-fiber dysfunction usually does not occur. In some patients with idiopathic SFN, an inflammatory autoimmune basis has been hypothesized.[5,16,18] Kelkar et al.[7] suggest that some cases of sensory-predominant, painful, idiopathic neuropathy may be due to autoimmune vasculopathy and therefore may respond to immunotherapy.

In generally, SFN is considered as a wastebasket if physician fail to find a cause despite an adequate evaluation. The potential causes of SFN and suggested evaluation methods are as Table 3.[5]

4. Clincal features

Preferential involvement of small or large nerve fiber populations produces specific patterns of symptoms in neuropathies. Therefore the clinical manifestations of peripheral neuropathies differs considerably depending on the nerve fibers mainly involved. Most patients with peripheral neuropathies manifest clinical, electrophysiologcal, and pathological evidence of large-caliber myelinated nerve fiber involvement, including weakness, absent or diminished tendon reflexes, loss of vibration and proprioception, and abnormal nerve conduction studies. In contrast, certain neuropathies selectively involve small-diameter myelinated and unmyelinated fibers. The patients typically present with positive sensory symptoms, including tingling, burning, prickling, shooting pain, or aching(Table 4).[8] The pain is often worse at night and may interfere with sleep. Allodynia and cramps may also occurs. Although common, pain is not synonymous with small-fiber dysfunction. Pain also occurs with large-fiber disorders, perhaps related to the rate of axonal degeneration. Patients may also have negative symptoms, including numbness and tightness and coldness. Symptoms are usually distal and length-dependent, but they are sometimes patchy or diffuse.[5,10,11,18,20-24]

In autonomic symptoms, patients have increased or decreased sweating, facial flushing, skin discoloration, dry eyes and mouth, skin temperature changes, and erectile dysfunction. Symptoms of orthostatic hypotension and gastrointestinal dysmotility are uncommon except in disorders such as amyloidosis and diabetes mellitus.[4,5,22]

The clinical findings of SFN often include a reduction in thermal and pain sensitivity in association with normal strength, proprioception, and tendon reflexes. And vibration is usually normal.[19]

5. Diagnostic tests (Table 5)[5]

The investigations to be considered in a patient with probable SFN can be categorized as follows: (a) tests of peripheral nerve function, both somatic and autonomic; (b) tests for autonomic dysfunction involving other organs; and (c) investigations aimed at establishing a cause.[8]

And test of small-fiber function is important for diagnosis of SFN, follow-up the course of the neuropathy, and assess the response to treatment. When decide which tests to perform and what equipment to purchase, the following information should be borne in mind. Most tests evaluate only a single type of small-fiber. However, it is possible that in SFN, other small-fibers, such as somatic unmyelinated nociceptive afferents, may also be affected. Therefore test only one type of fibers may yield misleading results, and is analogous to do nerve conduction studies in SFN. And the capacity of a test to detect abnormality of small-fiber is influenced by the nature and design of these tests, and the range of biological variability in control subjects. So the lack of comparability of the different tests, the results of a variety of tests of different small-fiber population cannot be taken as an indication of damage to different types of nerve fibers. And as a prac-

Table 5. Advantages and disadvantages of specialized tests for small-fiber dysfunction

Method	Advantages	Disadvantages
Sympathetic skin response	Performed on routine electromyographic equipment. Simple, fast, objective.	Semiquantitative. Probably low sensitivity. Does not correlate with clinical or other features of small-fiber involvement.
Quantitative sudomotor axon reflex test (QSART)	Sensitive for small-fiber neuropathy. Objective, reproducible, allows sampling of multiple sites. Quantitative. Can be used for serial testing.	Requires special equipment. Moderately time-consuming.
Cardiovagal and adrenergic autonomic testing	Objective. Quantitative. May identify subclinical, as well as symptomatic, autonomic dysfunction.	Only moderate sensitivity for mostly subclinical autonomic dysfunction. Requires special equipment. Moderately time-consuming.
Epidermal nerve fiber analysis	Quantitative. Sensitive. Can sample multiple sites. Can be used for serial testing.	Limited availability. Histologic technique can be complicated, depending on method.
Quantitative sensory test(QST)	Evaluates different sensory receptors and small and large fibers. Can detect pain threshold. Reproducible. Can be used for serial testing.	Subjective component. Requires special equipment.

Table 6. Treatment options for neuropahtic pain in small-fiber neuropathy

Drug class	Drug example	Daily dose range	Side-effects and limitations
Anticonvulsant	Gabapentin	300 ~ 3,600 mg	Somnolence, dizziness. confusion, edema; adjust with renal failure
	Lamotrigine	25 ~ 400 mg	Rash, including Stevens-Johnson syndrome; dizziness, constipation, nausea
	Topiramate	50 ~ 400 mg	Sedation, poor concentration, weight loss, nephrolithiasis, myopia, glaucoma
Antidepressant	Amitriptyline	10 ~ 100 mg	Anticholinergic side-effects, cardiac arrythmia, weight gain
	Nortriptyline	10-100 mg	As indicated for amitriptyline, but milder
	Venlafaxine XR	150 ~ 225 mg	Nausea, anorexia, hypertension, mydriasis, sweating, dizziness, sexual dysfunction
Antiarrhythmic	Mexiletine	To 750 mg	Liver dysfunction, nausea, heartburn, arrhythmia, dizziness, tremor
Opioids	Tramadol	200 ~ 400 mg	Nausea, constipation, dizziness, seizures
	Controlled-release oxycodone	20 ~ 60 mg	Constipation, nausea, sedation; potential for abuse
Topical	Capsaicin (0.075%)	Apply locally tid or qid	Burning, initially; complicated application limiting compliance

tical issues, availability, reliability, ease of use, cost, comfort to patient, and time required to perform the test are also all factors to be considered.[8,25]

1) Nerve conduction studies

The conventional electrophysiological estimation of motor, sensory, and mixed nerve conduction velocities reflects activity in the fastest conducting, heavily myelinated nerve fibers, a small proportion of the total. The Aδ and C fibers, numerically the largest group of fibers in human cutaneous nerves, are not tested by this technique. Motor, sensory, and mixed nerve conduction studies are usually normal in SFN.[10,20] Therefore standard nerve conduction studies and needle EMG recordings are valuable to rule out subclinical large-fiber involvement. Normal results of an EMG study in the presence of clinical signs of neuropathy provide preliminary evidence of SFN.[5,8,16]

In SFN, routine nerve conduction studies are generally normal because the studies only evaluate large-fiber function. Of course, elderly patients who have no or minimal response to sural nerve stimulation can also be diagnosed as SFN. Oh et al.[26] also found evidence of axonal loss in plantar nerves by near-nerve needle recordings in patients with sensory neuropathy but have normal sural sensory responses. Therefore predominantly SFN also have some large-fiber involvement. So patients who have the clinical features of SFN with normal nerve conduction studies should be considered to have SFN until proven otherwise.[5,8] A variety of techniques can be used to assess small-diameter peripheral nerve fibers.

2) Nerve biopsy

Electron microscopy is required to perform histologic evaluation and quantification of the unmyelinated fibers. But it is difficult and time-consuming.[6,8,24] A nerve biopsy specimen seldom helps to identify the specific causes of SFN except amyloidosis or inflammatory process. Therefore sensory nerve biopsies are not commonly utilized in evaluating SFN unless amyloidosis or an inflammatory process is strongly suspected. Demyelinating processes do not exclusively affect small fibers. So distal axonal loss causes SFN.[5,7,8]

And the following features are consistent with unmyelinated fiber pathology: (1) mild proliferation of Schwann cell projections next to unmyelinated axons; (2) drop-out in the total number of unmyelinated axons, linked with increased numbers of Schwann cell bands devoid of axons; (3) early regeneration as suggested by the presence of many flat Schwann cell bands devoid of axons and associated with a normal number of unmyelinated axons; and (4) advanced regeneration as evidenced by an increased total number of unmyelinated axons and increased Schwann cell projections.[8,27]

3) Skin biopsy

Small-diameter C fibers and Aδ nerve fibers innervate the skin. Punch biopsies of the skin allow further histologic examination of these nerve fibers. After fixation of the skin tissue, the sections are stained with monoclonal antibody to neuron-specific ubiquitin hydrolase. After then nerve fibers are counted within the sections of tissue and the numbers compared with control values. This techniques represents a method for quantification of small cutaneous sensory fibers. And this method may allow for histopathologic evaluation of the response of cutaneous nerve fibers to treatment with NGFs or other compounds.[5,8,15,28]

In neuropathies affecting epidermal innervation, the most frequently reported abnormality is a reduction in nerve fiber numbers. Nerve swellings and a change in branching may occur. Excessive proximal branching suggests reinnervation. As most neuropathies are length-dependent, the fiber loss is usually worse distally. Epidermal nerve fiber loss correlates with loss of small-fibers in sural nerve biopsy specimens. In some neuropathy, epidermal nerve fiber assessment is more sensitive than sural nerve histopathology.[5,28-30]

Although this diagnostic method is very useful, a limitation is that it is available only in several academic centers. But skin biopsy itself is simple, and multiple sites can be examined easily and studied serially. And the utility of the epidermal nerve fiber density measurement was confirmed for sensory neuropathy with a diagnostic efficiency of 88%. Therefore skin biopsies may be useful to assess the spatial distribution of

involvement in peripheral nerve disease and the response to neurotrophic and other restorative therapies. However, the histologic technique is moderately complicated, and normals also should be studied to compare. In addition, it is not useful in detecting features of amyloidosis or inflammation as can be seen in peripheral nerve biopsy. Nevertheless, it is an excellent method for diagnosis of SFN.[5,31]

4) Sympathetic skin response(SSR)

The SSR is an older, widely available, inexpensive method of assessing small-fiber sudomotor function. It is a reflex change in the sweat-related skin electrical potential elicited by various unexpected, adrenergic stimuli such as electric shock to a somatic nerve. A major advantage is that it is measured on routine EMG equipment.[5,32]

Although the sensitivity of the SSR in SFN is uncertain, it is probably low. And specificity of the SSR for SFN is also low, and the responses are not easily quantitated. The respones may habituate and amplitude decline by repetitive stimulation. And there may be a limited role for the SSR in differentiating certain causes of mixed small- and large-fiber sensory neuropathy.[5]

5) Quantitative sensory testing(QST)

QST has become an important test in assessing the function of small and large sensory fiber function. It is commonly used for serial measurements in neuropathy treatment trials and for the diagnosis of SFN. Small-fibers are assessed by measuring temperature thresholds, and large-fibers by vibratory thresholds. Cooling may be a more accurate measure than warming due to a low density of warm receptors in some normals.[5,33]

The utility of QST in diagnosis of SFN was reported by Jamal et al.[10] who assessed heat, cold, and vibration thresholds in 25 patients with suspected SFN. The patients had normal nerve conduction studies. Compared to normals, all had abnormal thresholds but vibration thresholds were normal. The diagnostic sensitivities of QST in SFN range from 60~85%.[4,19]

It should also be noted that studies often reveal subclinical vibratory abnormalities in SFN, and that central nervous system sensory dysfunction can also cause an abnormal QST. Lower sensitivity may be due to technical and patient factors. Because the testing is subjective, patients must concentrate and be cooperative. And there is also a relatively broad range of normality, so some patients with small-fiber dysfunction may be undetected.

Regardless of the systems used for QST, it is important that testing is validated and standardized. Quality reference values must be available, and patients must be tested in the appropriate environment. Although the test is subjective, these safeguards help keep the sensitivity and reliability relatively high.[5,34]

6) Quantitative sudomotor axon reflex test (QSART)

The QSART evaluates postganglionic sympathetic sudomotor function. Axons in the skin are activated locally through acetylcholine iontophoresis.[35] Antidromic transmission to an axon branch point elicits action potentials that travel orthodromically to release acetylcholine from nerve terminals producing sweat. The sweat is measured at the skin surface with a sudomometer.[5]

QSART is a sensitive indicator of SFN even in patients lacking symptoms of sudomotor dysfunction. Length-dependent reductions in sweat volume can often be identified. The sensitivity of QSART in SFN is 60~80%.[4,6,20]

The test is objective, reproducible, only moderately time-consuming, and specific to peripheral nervous system dysfunction. It could be used serially to monitor disease progression or treatment responses. Tested patients must stop the medications that affect sweating, including tricyclic antidepressants.[5]

7) Microneurography

Microneurography record from very fine needles inserted into peripheral nerves. It can be used to study function in small-fiber sensory afferents and sympathetic efferents. But this method lends itself better to the study of the normal physiology of peripheral nerves than to the detection of abnormalities. And it is also invasive and time-consuming, so it is unlikely to become a routine diagnostic test of SFN.[36,37]

8) Other tests of sudomotor function

Other methods of sudomotor function include

the thermoregulatory sweat test and the Silastic skin imprint method. The thermoregulatory sweat test involves dusting a patient with an indicator powder that turns purple when moist. And the pattern of body surface covered by sweat is assessed semiquantitatively. The sensitivity of the test in SFN is high. Stewart et al.[6] reported the sensitivity of the test in SFN is 72%. It is especially useful for detecting very distal loss of sweating. But the disadvantages of the test are that it is messy, semiquatitative, and requires a special room. And is also time-consuming and may not be economically feasible for many situation.[5]

The Silastic skin imprint method is performed by applying Silastic material to stimulated skin. Sweat droplets indent the Silastic material and are counted within a certain surface area. But the sensitivity of the method is uncertain.[5,25]

9) Other autonomic tests

The sympathetic nervous system is assessed by the Valsalva maneuver and by the blood pressure response to standing or tilting. And the parasympathetic, cardiovagal axis can be assessed by measuring the heart rate variation during deep breathing and during the Valsalva maneuver.[5] In a study of 47 patients with painful, primarily SFN, 57% had abnormal cardiovagal testing.[4] And among 15 patients with SFN, 75% had asymptomatic cardiovagal dysfunction.[38]

6. Treatment (Table 6)[5]

Treatment of SFN can be categorized as primary therapy of the underlying disorder, symptomatic therapy, and therapy with experimental agents that may reverse nerve damage and promote repair of small-fibers. Approaches to primary therapies include tight control of diabetes mellitus, abstinence from alcohol, measures to correct nutritional defiencies, and removal of toxins. Therefore if the causes of SFN are not found such as diabetes mellitus, the management of SFN usually centers upon symptomatic treatment of neuropathic pain. But most of the drugs that are efficacious reduce pain sensitivity by only 20~40%. Therefore patients should understand the goal of treatment, and that pain is often not totally relieved by treatment. Useful drugs include anticonvulsants, tricyclic antidepressants, opiates, lidocaine and lidocaine-derivatives, and antiglutaminergic drugs. These drugs can be used as monotherapy or in combination. Drugs are often more effective in combination than when given singly. In particular, it is useful to combine the classic analgesics, such as acetaminophen and codeine, with carbamazepine, phenytoin, or a tricyclic antidepressant. When none of these measures effectively relieve severe pain, narcotics should be used. And treatment is started at a low dose and titrated to the maximum tolerable dose until benifit is achieved or intolerable side effects occur. And sometimes a few patients show dramatic response to intravenous immunoglobulin.[5,8,16]

7. Evolution

SFN may evolve in one of 4 ways. In the first pattern, the large-fibers become involved and give rise to a pansensory or sensorimotor neuropathy. Many SFNs due to diabetes mellitus, amyloidosis, alcohol and nutrition-related, and hereditary sensory autonomic neuropathy type I fall into this category. In the second pattern, diffuse involvement of the autonomic nervous system gives rise to widespread autonomic dysfunction. Both the first and second patterns can occur together, as is seen in some patients with diabetes mellitus and primary amyloidosis. In the third patterns, the neuropathy is restricted to the distal small-fibers. And in the fourth patterns, the neuropathy can resolve, partcularly if a toxic cause is identified and eliminated. Some patients with alcohol-related and diabetic neuropathy show improvement with treatment.[8]

Despite extremely troubling symptoms, there was no progression in half the patients, and it was slow and mild in the others. And a few patients show spontaneous remission.[16]

8. Summary

SFN results from pathologic processes causing preferential damage to small-diameter fibers of peripheral nerves. And dysesthesias are common in SFN, but clinical signs are minimal and frequently limited to reduced sensation of pinprick and temperature in the distal regions of the legs. And burning feet are common symptoms, but SFN and painful sensory neuropathy are not synonymous. The causes of SFN are relatively few, but

the most commonly diagnosed cause of SFN is diabetes mellitus. And conventional EMG studies are normal in SFN, therefore tests that specifically evaluate small nerve fibers are more valuable. And now symptomatic and specific treatment is available for SFN.[5,8,24]

9. Conclusion

In conclusion, it is reasonable to conclude that the nerve fiber diameter alone does not determine susceptibility to damage. Mixed syndromes occur frequently. Selective impairment of small-fiber subgroups in some patients is probably only the endpoint of a wide range of possible combination of affected fibers.

SFN is a common, slowly progressive neuropathy that begins in late adulthood and causes limited motor impairment. A number of investigative methods are now available for confirming the diagnosis. Based on the advantages and disadvantages as well as economic issues regarding these methods, one or a combination of these modalities can be used. In all patients with SFN, evaluation for diabetes mellitus or impaired glucose tolerance should be done. And other causes also be identified by history, physical examination and laboratory findings.

And pediatricians also should be aware of idiopathic SFN because this condition can be mistaken for a psychiatric disorder. Although unusual in childhood, it must be considered in the differential diagnosis of burning limb pain with no apparent physical or electrophysiologic abnormalities.

10. Future directions

In the future, it will be important to determine whether a marker for an autoimmune cause of idiopathic SFN can be established. A larger prospective study is needed to determine whether it is possible to identify the subgroup of patients who may have inflammatory changes and may be considered candidates for immune-modulating therapies. Therefore treatment trials with immune-modulating therapies as intravenous immunoglobulin should be considered. It is also important to determine how many middle-aged patients with burning feet have underlying causes of secondary SFN. And better treatments for neuropathic pain and small-fiber degeneration are also important problems.

REFERENCES

1. Wolfe GI, Baker NS, Amato AA, et al. Chronic cryptogenic sensory polyneuropathy. *Arch Neurol* 1999;56:540-547.
2. Wakamoto H, Hirai A, Manabe K, Hayashi M. Idiopathic small-fiber neuropathy in childhood: a diagnosis based on objective findings on punch skin biopsy specimens. *J Pediatr* 1999;135:257-260.
3. Periquet MI, Novak V, Collins MP, et al. Painful sensory neuropathy. *Neurology* 1999;53:1641-1647.
4. Novak V, Freimer ML, Kissel JT, et al. Autonomic impairment in painful neuropathy. *Neurology* 2001;56:861-868.
5. Lacomis D. Small-fiber neuropathy. *Muscle Nerve* 2002;26:173-188.
6. Stewart JD, Low PA, Fealey RD. Distal small fiber neuropathy: results of tests of sweating and autonomic cardiovascular reflexes. *Muscle Nerve* 1992;15:661-665.
7. Kelkar P, McDermott WR, Parry GJ. Sensory-predominant, painful, idiopathic neuropathy: inflammatory changes in sural nerves. *Muscle Nerve* 2002;26:413-416.
8. Giuliani MJ, Stewart JD, Low PA. Distal small-fiber neuropathy. In: Low PA. Clinical autonomic disorders. 2nd ed. New York: Lippincott-Raven. 1997;699-714.
9. Ochoa J. Recognition of unmyelinated fiber disease: morphologic criteria. *Muscle Nerve* 1987;10:375-387.
10. Jamal GA, Hansen S, Weir AI, Ballantyne JP. The neurophysiologic investigation of small fiber neuropathies. *Muscle Nerve* 1987;10:537-545.
11. Navarro X, Kennedy WR, Fries TJ. Small nerve fiber dysfunction in diabetic neuropathy. *Muscle Nerve* 1989;12:498-507.
12. Light AR, Perl ER. Peripheral sensory systems. In : Dyck PJ, Thomas PK, Griffin JW, Low PA, Poduslo JF. *Peripheral neuropathy*. 3rd ed. Vol. 1. Philadelphia: WB Saunders Company. 1993;149-165.
13. Ravitus JM. Autonomic nervous system testing. *Muscle Nerve* 1997;20:919-937.
14. Said G, Slama G, Selva J. Progressive centripetal degeneration of axons in small fibre diabetic polyneuropathy. *Brain* 1983;106:791-807.
15. McCarthy BG, Hsieh ST, Stocks A, et al. Cutaneous innervation in sensory neuropathies: evaluation by skin biopsy. *Neurology* 1995;45:1848-1855.
16. Gorson KC, Ropper AH. Idiopathic distal small fiber neuropathy. *Acta Neurol Scand* 1995;92:376-382.
17. Lacomis D, Giuliani MJ, Steen V, Powell HC. Small fiber neuropathy and vasculitis. *Arthritis Rheumatism* 1997;40:1173-1177.
18. Holland NR, Crawford TO, Hauer P, Cornblath DR, Griffin JW, McArthur JC. Small-fiber sensory neu-

ropathies: clinical course and neuropathology of idiopathic cases. *Ann Neurol* 1998;44:47-59.
19. Periquet MI, Novak V, Collins MP, et al. Painful sensory neuropathy. *Neurology* 1999;53:1641-1647.
20. Smith SJM, Ali Z, Fowler CJ. Cutaneous thermal thresholds in patients with painful burning feet. *J Neurol Neurosurg Psychiatry* 1991;54:877-881.
21. Schüller TB, Herman K, Baron R. Quantitative assessment and correlation of sympathetic, parasympathetic, and afferent small fiber function in peripheral neuropathy. *J Neurol* 2000;247:267-272.
22. Amato AA, Dumitru D. Acquired neuropathies. In: Dumitru D, Amato AA, Zwarts MJ. *Electrodiagnostic medicine.* 2nd ed. Philadelphia: Hanley & Belfus, INC. 2002;1015.
23. Dyck PJ, Lambert EH, O、Brien PC. Pain in peripheral neuropathy related to rate and kind of fiber degeneration. *Neurology* 1976;26:466-471.
24. Polydefkis M, Allen RP, Hauer P, Earley CJ, Griffin JW, McArthur JC. Subclinical sensory neuropathy in late-onset restless legs syndrome. *Neurology* 2000;55:1115-1121.
25. Le Quesne PM. Peripheral neuropathy profile in various groups of diabetics. *J Neurol Neurosurg Psychiatry* 1990; 53:558-563.
26. Oh SJ, Melo AC, Lee DK, et al. Large-fiber neuropathy in distal sensory neuropathy with normal routine nerve conduction. *Neurology* 2001;56:1570-1572.
27. Monks R, Merskey H. Psychotropic drugs. In: Wall PD, Melzack R. *Textbook of pain*. 1st ed. Edinburgh: Churchill Livingstone, 1984;526-537.
28. Holland NR, Stocks A, Hauer P, Cornblath DR, Griffin JW, McArthur JC. Intraepidermal nerve fiber density in patients with painful sensory neuropathy. *Neurology* 1997; 48:708-711.
29. Herrman DN, Griffin JW, Hauer P, Cornblath DR, McArthur JC. Epidermal nerve fiber density and sural nerve morphometry in peripheral neuropathies. *Neurology* 1999;53:1634-1640.
30. Lauria G, Holland N, Hauer P, Corhblath DR, Griffin JW, McArthur JC. Epidermal innervation : changes with aging, topographic location, and in sensory neuropathy. *J Neurol Sci* 1999;164:172-178.
31. McArthur JC, Stocks EA, Hauer P, Cornblath DR, Griffin JW. Epidermal nerve fiber density. *Arch Neurol* 1998; 55:1513-1520.
32. Sandroni P, Low PA. Autonomic peripheral neuropathies: clinical presentation, diagnosis, and treatment. *J Clin Neuromuscul Dis* 2001;2:147-157.
33. Gruener G, Dyck PJ. Quantitative sensory testing: methodology, application, and future directions. J Clin Neurophysiol 1994;11:568-583.
34. Low PA. Autonomic nervous system functions. *J Clin Neurophysiol* 1993;10:14-27.
35. Coelho T. Familial amyloid polyneuropathy: new developments in genetics and treatment. *Curr Opin Neurol* 1996; 9:355-359.
36. Mackel R. Properties of cutaneous afferents in diabetic neuropathy. *Brain* 1989;112:1359-1376.
37. Mackenzie RA. A micro-electrode study of peripheral neuropathy in man. *J Neurol Sci* 1977;34:157-174.
38. Tobin K, Giuliani MJ, Lacomis D. Comparision of different modalities for detection of small-fiber neuropathy. *Clin Neurophysiol* 1999;110:1909-1912.