

Small fiber neuropathy – how to start, where to go?

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ABSTRACT - Small fiber neuropathy (SFN) is a type of sensory neuropathy which selectively affects small diameter somatic and autonomic nerve fibers. Diagnosis is challenging, given that clinical picture can be difficult to interpret. Patients typically present with painful paresthesias and/or signs of autonomic dysfunction. In SFN, neuropathic pain was shown to be a frequent and early symptom, so it is considered as a reliable marker of this neuropathy. The diagnosis of SFN relies on clinical features combined with abnormal quantification of intraepidermal nerve fiber density (IENFD) and/or deficit in temperature threshold on quantitative sensory testing (QST). SFN is associated with various systemic diseases, among which diabetes was found to be the most common one. This knowledge urges a detailed diagnostic work-up of every patient presenting with SFN because new understanding of the SFN etiology could help narrow the proportion of idiopathic SFN patients, which is still large. Most recent discoveries of several novel mutations to sodium channels in patients with idiopathic SFN could help in this area, as well as in the development of specific treatment options. For now, the treatment of SFN is very complex. Causative therapy is advised whenever possible and symptomatic treatment should follow newest guidelines on the management of neuropathic pain in general.

Key words: small fiber neuropathy, neuropathic pain, skin biopsy, quantitative sensory testing

INTRODUCTION

Small fiber neuropathy (SFN) is a type of sensory neuropathy characterized by painful paresthesias or signs of autonomic dysfunction. SFN is associated with various metabolic, infectious, inflammatory and genetic diseases, but in the majority of cases the cause is idiopathic. The incidence and prevalence of SFN is unknown (1). SFN affects

both small somatic and autonomic fibers. Affected fibers are small myelinated A δ fibers and small unmyelinated C fibers, the sensory function of which includes thermal perception and nociception (2,3). A δ myelinated fibers are the main afferents for cold

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perception, and they are also involved in cutaneous nociception. Unmyelinated C fibers play a role in warm perception and only a minor role in cold thermoperception (2). Small fibers are also involved in a number of autonomic and enteric functions (3).

Over the last decade, SFN and its diagnosis has become of great interest, especially since the introduction of quantification of intraepidermal nerve fiber density (IENFD) in skin biopsies (1,4). Various studies have proposed different definitions for SFN (1,2,5). According to recent findings, the diagnosis of SFN relies on clinical features combined with abnormal quantification of IENFD and/or deficit in temperature threshold testing (1). The diagnosis of SFN should be graded as possible, probable or definite (6). Possible SFN requires presence of length-dependent symptoms and/or clinical signs of small fiber damage. Probable SFN requires presence of length-dependent symptoms, clinical signs of small fiber damage and normal sural nerve conduction study (NCS). Definite SFN includes length-dependent symptoms, clinical signs of small fiber damage, normal sural NCS and altered IENFD at the ankle and/or abnormal quantitative sensory testing (QST) thermal thresholds at the foot (6). These criteria were originally proposed for diabetic SFN, but they should be applied in each patient irrespective of the underlying cause (6).

PATHOGENESIS AND ETIOLOGY

Specific etiology of SFN is mostly unknown. In some cases, SFN is part of an underlying systemic disease, including different metabolic, immune-mediated, genetic or infectious diseases. It can also be a consequence of the intake of drugs or toxins (6,7).

Diabetes and impaired glucose tolerance (IGT) stand out as the most common from the metabolic group of diseases (2,6,8). The majority of older patients with SFN have prediabetes or diabetes, while IGT was found to be frequent in cases of idiopathic SFN, with a prevalence of 34%-35.6% (2,9,8). In patients with diabetes, various tests assessing sudomotor dysfunction showed good predictive value for detecting SFN. This is very important, considering that these tests are noninvasive and that sudomotor dysfunction is one of the early signs of SFN in diabetic patients (8,10). Some patients with diabetes may experience an acute painful SFN called insulin neuritis, which is associated with rapid glycemic control (3,6). In a long-term follow-

up Oslo study, SFN was found as a major manifestation in type 1 diabetes. This study showed that small fiber damage was even more prevalent than large fiber neuropathy, which was explained by greater sensitivity of small nerve fibers to metabolic changes, such as changes in blood glucose level (11). Considering that sensory small fibers are predominantly involved in diabetic neuropathy, it is advisable to understand its pathophysiology because a connection to understanding SFN in other systemic diseases could also be found (9).

The pathophysiology of diabetic neuropathy is multifactorial, with hyperglycemia being the central factor. There are three main metabolic effects of hyperglycemia on nerve function, including activation of the polyol pathway, formation of advanced glycosylation end products (AGEs) and changes in the metabolism of essential amino acids. Hyperglycemia increases the activity of polyol pathway, which leads to the accumulation of sorbitol and fructose in the peripheral nerve axons. This causes osmotic influx of water and cell edema, which in turn damages Ranvier's nodes and nerve conduction velocity. Accumulation of sorbitol also causes diminution of myo-inositol and taurine concentration, which interferes with the activity of Na⁺-K⁺-ATPase and causes more pronounced cell edema. Finally, excessive activation of the polyol pathway results in a decrease of reduced nicotinamide adenine dinucleotide phosphatase (NADPH) and oxidized nicotinamide adenine dinucleotide (NAD⁺), which leads to decreased synthesis of reduced glutathione and nitric oxide causing in the end massive oxidative stress. Disorder of amino acid metabolism causes changes in nerve membrane structure, microvascular abnormalities and changes in nerve excitability, while lipid peroxidation reduces nerve conduction velocity. Nonenzymatic glycosylation produces AGEs, which cause microvascular damage, glycation of tubulin, other neurofilaments and myelin. Macrophages cause glycosylated myelin phagocytosis and cause demyelination. This damages the structure of nerve fibers and Schwann cells. In addition, AGEs contribute to oxidative stress by creating free radicals (12). Oxidative stress stands out as the main factor in the pathogenesis of diabetic neuropathy and a growing body of evidence implicates its importance in different diseases causing SFN (7,13-19). Effects of hyperglycemia on nerve function are shown in Fig. 1. There is a large overlap between diabetes and metabolic syndrome. Patients with diabetes and metabolic syndrome appear to have twice the risk of developing SFN compared to those with diabe-

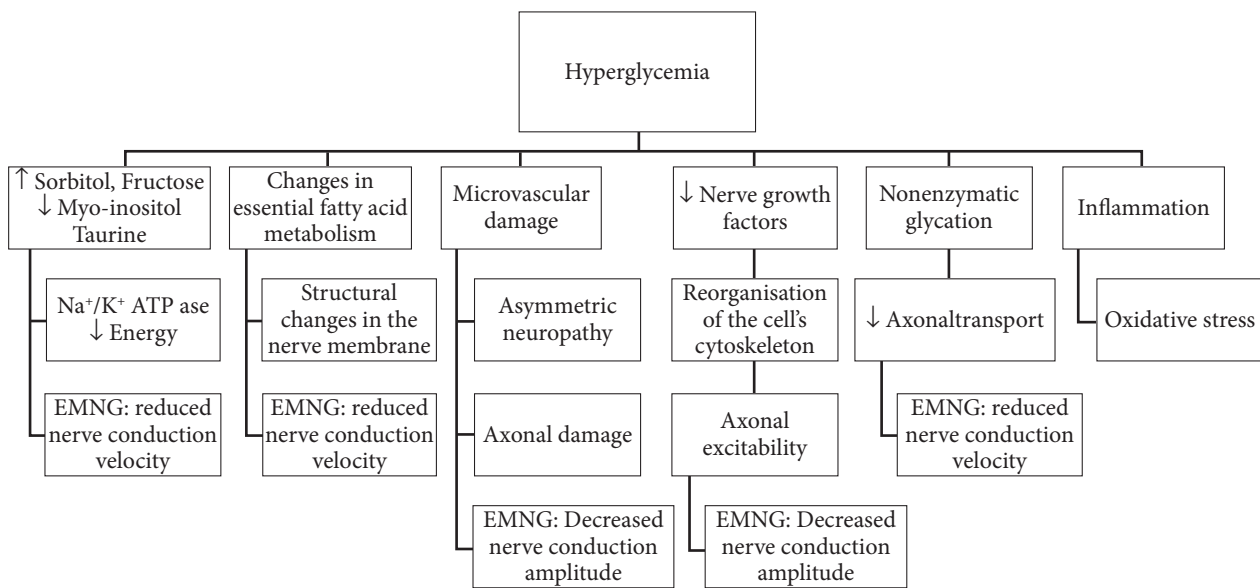


Fig. 1. Effects of hyperglycemia on nerve function.

tes alone. All factors of metabolic syndrome (hyperlipidemia, hypertension, obesity, abnormal glucose metabolism and insulin resistance) convey an increased risk of developing SFN. Studies suggest that hyperlipidemia is the single largest contributor to the development of neuropathy, especially elevated serum triglycerides (>800 mg/dL) (2,3). Other less common metabolic diseases associated with SFN include hypothyroidism and vitamin B12 deficiency (5,6,20).

Different immune-mediated diseases are connected with SFN, but the underlying mechanism is not entirely explained. Supporting data mainly relate to good therapeutic response to immunoglobulin or immune-suppressant treatments (6,7,21). Several pharmacological and physiological studies give support to an immune-mediated role, considering that proinflammatory cytokines are involved in the generation and maintenance of neuropathic pain (7) (22-24). Small nerve fibers were found to be more vulnerable to ischemia than large diameter nerve fibers, so damage to small fibers due to ischemia was suggested in patients with vasculitis (7,25,26). Decreased antioxidant defense capacity was found in patients with sarcoidosis (7,19). Other immune-mediated diseases associated with SFN include Sjögren's syndrome, celiac disease, systemic lupus erythematosus (SLE), rheumatoid arthritis, inflammatory bowel diseases, paraneoplastic syndrome, monoclonal gammopathy and complex regional pain syndrome type 1 (2,6). Among genetic diseases, SFN was found in hereditary sensory autonomic neuropathy (HSAN) type IV, Fabry's disease, familial amyloidosis, hemochromato-

sis and familial burning feet syndrome (6). Most recent studies found gain-of-function mutations in sodium channels Na(V)1.7 and Na(V)1.8 in some SFN patients (27,28). SCN9A-gene variants (single amino acid substitutions) were found in ~30% of a cohort of idiopathic SFN patients, producing gain-of-function changes in sodium channel Na(V)1.7, which is preferentially expressed in small diameter peripheral axons (27). Na(V)1.8 mutations were found more recently in patients with idiopathic SFN (28). Both mutations cause hyperexcitability of small dorsal root ganglion (DRG) neurons and development of specific treatment in these patients seems a logical target for future studies (27,28).

Different infectious diseases and drugs are involved in the development of SFN, such as HIV, hepatitis C, influenza and usage of antiretroviral drugs, metronidazole, bortezomib, statins, nitrofurantoin, flecainide and linezolid (6). Chronic alcohol abuse in early stages causes predominantly SFN (2,6).

Despite the association of SFN with various acquired and genetic conditions, in a substantial proportion of patients (25% to 90%), the cause of SFN remains unknown (2,5-7). Progression of SFN is usually slow and spontaneous remission is rare (6,29). Over time, in some patients pure SFN can evolve to large fiber sensory neuropathy (2,6).

CLINICAL FEATURES

Symptoms of SFN can vary widely in severity and mostly have gradual onset (3). In most patients,

Table 1. Differences in clinical picture and electrodiagnostic findings in small vs. large fiber neuropathy

Type of neuropathy	Symptoms	Clinical signs	Electrodiagnostic findings
Large fiber neuropathy	<ul style="list-style-type: none"> - painful cramps and fasciculations - muscle atrophy - numbness without pain - tingling - weakness 	<ul style="list-style-type: none"> - diminished deep tendon reflexes - reduced vibratory and position sense - muscle weakness 	EMNG-abnormal: <ul style="list-style-type: none"> - slowed motor and sensory conduction velocities - reduced motor and sensory action potentials and denervation
Small fiber neuropathy	<ul style="list-style-type: none"> - <i>Positive</i>: burning feet, tingling, prickling, shooting pain or aching, allodynia, cramps - <i>Negative</i>: numbness, 'tightness', 'coldness' - <i>Autonomic</i>: increased/ decreased sweating, facial flushing, skin discoloration, dry eyes and mouth, presyncope/syncope, nausea, vomiting, diarrhea, constipation, difficulty with urinary frequency, erectile dysfunction, changes in skin temperature 	<ul style="list-style-type: none"> - reduction in thermal and pain sensitivity - normal strength, proprioception and tendon reflexes - mostly normal vibratory sensation and light touch 	EMNG-normal <ul style="list-style-type: none"> - QST-abnormal: decreased temperature sensitivity

SFN starts distally in a length-dependent fashion, resulting in the loss of function in stocking distribution in lower extremities (3,6). A glove-like sensory loss in upper extremities appears when the condition is more advanced (3). In some cases, diffuse and asymmetric symptoms were described (6). Patients typically present with positive sensory symptoms and burning feet is the most common complaint reported. Other sensory symptoms include tingling, prickling, shooting pain or aching, while allodynia and cramps occur less often. Cramps usually affect calf muscles and may mislead clinicians to think of other diagnosis, such as metabolic disorders or drug side effects (7). However, it is important to think of SFN in these cases because a recent study revealed that 60% of patients with muscle cramps, who lacked neuropathic complaints, actually had SFN (29). Damage to small fibers frequently causes neuropathic pain, which occurs as an early symptom in SFN (5,9). Quality of pain may differ from spontaneous pain to thermally evoked pain and/or allodynia. It is commonly worse at rest and during the night (6). Negative symptoms of SFN include numbness, „tightness“ and „coldness“ (2,3,6). Regarding autonomic symptoms, patients may have increased or decreased sweating, facial flushing, skin discoloration, dry eyes and mouth, postural hypotension, presyncope or syncope, nausea, vomiting, diarrhea, constipation, difficulty with urinary frequency, nocturia, erectile dysfunction (occurs in up to 40% of males) and changes in skin temperature (2,3). Generally, patients experience sensory symp-

toms far more often than autonomic symptoms. If autonomic dysfunction is present, vascular deregulation in lower limbs is more frequent than cardiovascular autonomic impairment (2,5,6). Patients can sometimes present with late-onset restless legs syndrome (RLS). It is important to evaluate this type of patients for SFN, especially if they do not have positive family history of RLS (2,6,30). SFN has also been suggested in patients with focal burning pain and burning mouth syndrome (6).

Neurological examination of patients with SFN reveals normal to marginally pathological findings (31). There is a reduction in thermal and pain sensitivity in association with normal strength, proprioception and tendon reflexes. Light touch and vibratory sensation are mostly normal. Associated skin changes may include cracked, dry or shiny skin (2,3). Diagnosis of SFN is challenging, as the clinical picture can be difficult to interpret (32). Considering differential diagnosis, other conditions that may mimic SFN include venous insufficiency, spinal stenosis, myelopathy and psychosomatic disturbances (3). Distinguishing small from large fiber neuropathy is also important; the most common symptoms, clinical and electrodiagnostic findings are shown in Table 1.

DIAGNOSING SMALL FIBER NEUROPATHY

The new attitude towards SFN is that it should be considered as a complication of an underlying sys-

temic disease. Therefore, for all patients with SFN a detailed diagnostic work-up should be done (6). Frequently associated diseases like prediabetes and diabetes indicate the need of oral glucose tolerance test, fasting glucose and glycosylated hemoglobin tests (3,6). Next, testing for different autoimmune diseases like Sjögren's syndrome, sarcoidosis, SLE and celiac disease should be considered (6,7). Suspicion of amyloidosis rises in patients with dysautonomia and cardiac or liver involvement (6). In view of the most recent discovery of several novel mutations to sodium channels, screening of SCN9A gene should be considered, especially in patients with positive family history of SFN (6,33). Finally, neuropathic pain was shown to be a reliable marker of SFN (1). Considering that pain is a subjective phenomenon which patients are not always capable to describe properly, the use of different screening tools in clinical practice for identifying neuropathic pain is useful and important. One of the widely used screening tools for neuropathic pain is the PainDETECT questionnaire. This is a self-administered questionnaire that consists of nine items; 7 questions relate to the intensity of sensory symptoms and 2 questions relate to pain pattern and to radiation of pain to other parts of the body. PainDETECT was validated in a multicenter study in Germany, its sensitivity and specificity being rated as 85% and 80%, respectively (34). According to the final score on the questionnaire, pain is classified as nociceptive, unclear or neuropathic. Another efficient screening tool is the Total Neuropathy Score (TNS), which estimates subjective and objective aspects of peripheral nerve fiber function, as well as characteristics and duration of patient symptoms. This makes it one of the most capacious tools for clinical assessment of neuropathies (35). TNS analyzes sensory, motor and autonomic symptoms, pin and vibration sensibility, strength, tendon reflexes, QST vibration and thermal threshold, and NCS of sural and peroneal nerve (36).

There is only one validated tool designed specifically for assessing symptoms of SFN, the 13-item Small Fiber Neuropathy and Symptoms Inventory Questionnaire (SFN-SIQ) (1,6). This questionnaire assesses the presence of several SFN specific sensory and autonomic symptoms and each item is scored on a 4-point Likert scale (1). SFN-SIQ was used for screening of patients with sarcoidosis and genetic sodium-channel associated SFN (6).

Patient medical history and clinical examination findings pose suspicion of SFN, but for confirmation of the diagnosis further neurophysiologic tests

are needed. NCS, QST and skin biopsy are sorted out today as the most relevant diagnostic tests (1,6,37).

ELECTROMYONEUROGRAPHY

Clinical electromyoneurography is a diagnostic method that helps objectify damage to the peripheral nervous system. It consists of electromyography (EMG) and NCS. Considering that EMG and NCS are used to assess the integrity of larger myelinated sensory and motor fibers, they are generally normal in patients with pure SFN (3,6,7). Older patients are an exception because they may sometimes lack sural response in NCS, but they can still be diagnosed with SFN (2).

QUANTITATIVE SENSORY TESTING

Quantitative sensory testing is an important tool in assessing the function of small as well as large sensory fibers (2,7). Small caliber fibers are assessed by measuring temperature thresholds and heat pain thresholds, whereas large caliber fibers are assessed by measuring vibration thresholds (7).

Two general schemes are used in QST: the method of levels and the method of limits. Delivered thermal stimuli consist of a ramp of ascending (warm) and descending (cool) thermal energy delivered through a thermode (7). In the method of levels, the patient receives standardized stimuli and has to signal whether a specific level is detected. This method is also referred to as a „forced choice“ algorithm. This method takes longer to complete, which makes it susceptible to errors from decreased attention by the patient. Consequently, reliability of the results can come in question. In the method of limits, the patient receives stimuli the intensity of which increases or decreases over time at a predefined speed. The patient has to indicate as soon as he starts or stops detecting the stimuli (12,38). The same stimuli are repeated 3-5 times and the threshold is calculated statistically (12). Physical properties of the stimuli must be standardized, including the area of application, intensity, duration and rate of stimulus application (39). Quality reference values must be available and patients must be tested in the appropriate environment. Many studies confirm the efficacy of QST in diagnosing SFN, and its sensitivity ranges from 60% to 85% (2). Limitations of QST are the following: testing is subjective, patient must be concen-

trated and cooperative, which may lead to difficulties during testing in conditions of cognitive impairment, and abnormalities in either the central or peripheral nervous system can result in the same deficit on the test. There are different equipment types among laboratories and due to a relatively broad range of normality of small fiber function, some patients with SFN may be undetected (2,3). QST is useful in detecting SFN, but it needs to be used in a clinical context and along with other diagnostic tests (6).

SKIN BIOPSY

Skin biopsy is considered to be the most accurate method to diagnose SFN (1,4,5,37). It has higher diagnostic accuracy compared with clinical features and QST results (1). The sensitivity (74%-90%) and specificity (64%-90%) are high across many studies (37). Skin biopsy confirms reduction of the IENFD in SFN and biopsy should be taken 10 cm above the lateral malleolus, within the sural nerve territory (6). Normative reference values for IENFD at the distal leg based on the 5th percentile cut-off adjusted *per* age decade and sex are available for bright-field immunohistochemistry (6,40).

OTHER DIAGNOSTIC TESTS

The following diagnostic tests were found useful in some studies, but most of them are still not implemented in broad clinical use. This includes various tests of sudomotor function, with the exception of quantitative sudomotor axon reflex test (QSART), cardiovascular reflex testing, current perception threshold testing (CPT), sural nerve biopsy, laser-evoked potentials, contact heat-evoked potential stimulators (CHEPs), microneurographic C-fiber recordings, laser Doppler flowmetry (LDF), metaiodobenzylguanidine (¹²³I-MIBG) scintigraphy, blister biopsy and corneal confocal microscopy (2,6,7). Results of corneal confocal microscopy showed high correlation with skin biopsy results in SFN patients (6). Considering that this is a noninvasive technique, further research is advisable to implement it in everyday clinical practice. A recent study has pointed out that assessment of autonomic function of small fibers is not included in the official diagnostic procedures for SFN (41). QSART provides a quantitative, validated assessment of postganglionic sudomotor function and studies have suggested that it is frequently abnormal in patients with SFN. Therefore, implementation of QSART in the diagnosis could enhance the diagnostic criteria for SFN (41).

THERAPY

Treatment of SFN is very complex because there is limited evidence for specific therapy (3). Causative therapy, depending on the underlying disease, should be given whenever possible. This usually includes antidiabetic drugs, steroids, immunosuppressants or intravenous immunoglobulin (IVIG) treatment (6). If there is no specific identifiable cause found, therapy is usually focused on treating neuropathic pain, for which updated guidelines are available (2,6,7,42,43). As first line treatment, tricyclic antidepressants (TCA), gabapentin, pregabalin and selective norepinephrine and serotonin reuptake inhibitors (SNRI) are recommended. Tramadol is recommended as second line therapy, with the exception of patients with predominant coexisting non-neuropathic pain and those with exacerbations of pain, where it can be given as a first line therapeutic option. Strong opioids are recommended as third line therapy because of their addiction potential and misuse (43).

It is important to note that most clinical studies examined drugs in the treatment of different neuropathic pain syndromes, and not specifically pain secondary to SFN (3,6). This represents a challenge in developing SFN treatment recommendations because most of the studies focused on SFN included a limited number of patients without long term follow up. For example, Ho *et al.* showed that both gabapentin and tramadol were found to be effective in the treatment of SFN in comparison with placebo (44). Hong *et al.* describe a case of type 2 diabetic peripheral small fiber neuropathic pain successfully treated with whole body vibration therapy, after a failed trial of conventional drugs and interventional pain management (45). Wakasugi *et al.* describe a patient with Sjögren's syndrome who developed SFN and was treated with IVIG therapy, which proved immediately and extremely effective (46). Hedstrom's study indicated that topical application of GFR α /RET receptor signaling modulators may be a unique therapy for SFN (47). Considering that SFN has an overall severe impact on the quality of life, future studies are warranted to determine the best possible treatment (1).

CONCLUSION

Small fiber neuropathy is a relatively common disorder, which is often underdiagnosed and undertreated. Suspicion of SFN is based on medical history and neurological examination. Standard electrophysiological tests such as EMG and NCS are

normal, so the diagnosis can only be confirmed with additional diagnostic work-up, such as QST and IENFD. Neuropathic pain was shown to be a frequent and early symptom of SFN. Due to commonly associated metabolic, immune-mediated and genetic diseases, it is important to do adequate diagnostic work-up when dealing with painful neuropathy. Early diagnosis is crucial because it can lead to prompt initiation of causative or symptomatic treatment. Future studies are needed to find best treatment possibilities and to determine the pathophysiology of SFN. The answer to the question from the title could be: "Start with detailed neurologic examination and go to the site where SFN has begun".

LITERATURE SEARCH STRATEGY

We conducted a review of the original papers and review articles indexed in Current Contents, PubMed, Medline and Google Scholar between 1982 and 2013. We used several terms individually or in combination including small fiber neuropathy, painful neuropathy, diagnostic criteria, neuropathic pain, screening tools, quantitative sensory testing, intraepidermal nerve fiber density, diabetic polyneuropathy, and idiopathic. Only articles on adult population were reviewed.

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Neuropatija tankih vlakana - kako početi, kamo ići?

SAŽETAK - Neuropatija tankih vlakana (NTV) je vrsta senzorne neuropatije koja zahvaća tanka somatska i autonomna živčana vlakna. S obzirom na to da je klinička slika ponekad atipična, postavljanje dijagnoze NTV-a je zahtjevno. Kod pacijenata su najčešće prisutne bolne parestezije i/ili znakovi autonomne disfunkcije. Neuropatska bol je česta i manifestira se vrlo rano u tijeku bolesti te se danas smatra pouzdanim biljekom NTV-a. Dijagnoza se postavlja temeljem neurološkog pregleda i patološkog nalaza na kožnoj biopsiji i/ili mjerenju praga osjeta za temperaturu na kvantitativnom senzornom testiranju (KST). NTV je povezana s različitim sistemnim bolestima, s time da se dijabetes izdvaja kao najčešća. Ova saznanja upućuju na to da je svakog pacijenta s NTV-om potrebno detaljno dijagnostički obraditi u smislu podležće bolesti, jer bi upravo novi podaci o etiologiji NTV-a mogli utjecati na smanjenje udjela pacijenata s idiopatskim NTV-om koji još uvijek zauzima značajan udio. Najnovija istraživanja otkrila su postojanje novih mutacija natrijevih kanala u pacijenata s idiopatskim oblikom, što bi u budućnosti moglo razjasniti etiologiju NTV-a te utjecati na razvoj ciljane terapije. Zasad je terapija NTV-a veoma složena. Ako je moguće, liječi se podležća bolest koja je dovela do neuropatije, dok se u ostalim slučajevima savjetuje simptomatska terapija neuropatske boli u skladu s najnovijim dostupnim smjernicama.

Ključne riječi: neuropatija tankih vlakana, neuropatska bol, kožna biopsija, kvantitativno senzorno testiranje