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REVIEW ARTICLE

Small-fiber neuropathy definition, diagnosis, and treatment

Natalia Y. Basantsova[1,2,3] · Anna A. Starshinova[1] · Amir Dori[4,5] · Yulia S. Zinchenko[1,3] · Piotr K. Yablonskiy[1,3] · Yehuda Shoenfeld[1,5,6]

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Abstract

In the last 30 years, improvement of diagnostic methods enabled routine evaluation of small A-delta and C nerve fibers impairment, which results with the clinical condition known as a small-fiber neuropathy (SFN). This syndrome develops as a result of metabolic, toxic, immune-mediated, or genetic factors. The main clinical features include neuropathic pain and autonomic disturbance, which are occasionally disclaimed due to outstanding fatigue, daily performance decline, anxiety, and depression. As clinical, neurological, nerve conduction, and electromyography studies are commonly normal, diagnosis often depends on the finding of decreased intra-epidermal density of nerve fibers, per skin biopsy. This review highlights the etiology, clinical, diagnostic aspects, and SFN treatment.

Keywords Small-fiber neuropathy · Neuropathic pain · Autoimmune diseases · Sarcoidosis

Introduction

Small-fiber neuropathy (SFN) is defined as a structural abnormality of small nerve fibers with the degeneration of the distal terminations of nerve endings [1]. The study of small-fiber neuropathy (SFN) became possible less than three decades ago with the development of skin biopsy techniques, which determines the density of small nerve fibers in the epidermis, detecting an abnormality in spite of often normal findings on clinical examination [1–3]. Nowadays, such patients may be considered as having SFN, a syndrome that is due to destruction of the smallest nerve fibers (myelinated type A-delta and unmyelinated C), that can be detected by skin biopsy, but not by routine electrophysiological studies. This syndrome is characterized by development of sensory and autonomic complaints that often significantly affect quality of life [3, 4].

The incidence of SFN in the general population is currently unknown. A recent Dutch study reported 12 new cases per 100,000 people per year, with a prevalence of approximately 53 patients per 100,000, that call for investigation with large-scale international studies [2].

The etiology of small-fiber neuropathy

The most common cause of SFN, like that of large fiber polyneuropathy, is commonly thought to be type 2 diabetes mellitus and glucose intolerance, observed in 30–50% of cases. Often these are associated with a metabolic syndrome and dyslipidemia [1, 5, 6]. However, a recent evaluation showed that abnormalities in glucose and triglycerides are uncommon in SFN patients in comparison to the general population, disclaiming their leading role in this syndrome [5]. In contrast, markers of inflammation such as elevated erythrocyte sedimentation rate and C-reactive protein levels, reduced complement, and markers of autoimmune disorders were more

✉ Anna A. Starshinova
starshinova_777@mail.ru

1 Laboratory of the Mosaic of Autoimmunity, Federal State Budget Educational Institution of Higher Education "St. Petersburg State University", University Emb., 7-9, Saint-Petersburg, Russia 199034

2 Department of Faculty Therapy, Federal State Budget Educational Institution of Higher Education "St. Petersburg State University", University Emb., 7-9, Saint-Petersburg, Russia 199034

3 Ministry of Health of Russian Federation, Federal State Budgetary Institution "St. Petersburg Research Institute of Phthisiopulmonology", St. Petersburg, Russia

4 Department of Neurology, Talpiot Medical Leadership Program, Chaim Sheba Medical Center, 52621 Tel Ha Shomer, Israel

5 Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

6 Zabludowicz Center for Autoimmune Diseases, Chaim Sheba Medical Center, 52621 Tel Ha Shomer, Israel

common in SFN patients, suggesting that inflammation or autoimmunity may be a main cause for its development [1, 2].

In most cases, combined lesions of both large and small nerve fibers may occur, either rather simultaneously or gradually, with the initial SFN development and the subsequent progression of large nerve damage. Some diseases can lead to the rather rapid development of the large fiber polyneuropathy (diabetes mellitus, alcoholic neuropathy), while others are characterized by the predominance of the isolated small or mixed nerve damage (sarcoidosis, Sjogren's syndrome, celiac disease) [7, 8].

Indeed, SFN often occurs in immune-mediated disorders, such as Sjogren's syndrome, celiac disease, systemic lupus erythematosus, and paraneoplastic syndromes [4, 5]. In sarcoidosis, up to 86% of patients present with typical SFN symptoms, considered to be of systemic cytokine-mediated nature rather than of granulomas occurrence [7]. Inhibition of TNF-α was shown to reduce the clinical manifestations of SFN in sarcoidosis suggesting a benefit by immunomodulation in SFN patients with associated immune disorder. Similarly, SFN patients with autoimmune disorders or laboratory evidence for autoimmunity showed symptomatic and laboratory improvement with intravenous immunoglobulin treatment [4].

Infectious disease could also lead to SFN development. The closest relationship is described in HIV infection, whereas hepatitis C as an etiologic factor is described only sporadically in single observations or in small groups of patients. In rare cases, the damage of small fibers is observed in Lyme disease and leprosy [1]. The presence of this complication in tuberculosis is often raised with concern but requires dedicated studies [9].

A number of toxic causes can contribute to the development of the SFN. In addition to chemotherapy, drugs such as metronidazole [10], nitrofurantoin [11], linezolid [12], bortezomib [13], statins [6], and inhibitors of tumor necrosis factor alpha (TNF-α) [14] should be used with caution in patients with predisposition to the development of the large and small nerve fibers damage. Cases of severe polyneuropathy in alcohol and thallium poisoning, mostly affecting the large fibers, are regularly described in the literature [1, 4].

Genetic cause for developing SFN includes hereditary/familial amyloid neuropathies, which is now a treatable disorder [15].

Complaints for paroxysmal neuropathic pain and erythromelalgia may be presented by patients with mutations in sodium channels (SCN9A/NaV1.7, SCN10A/NaV1.8, SCN11A/NaV1.9,). Dysfunction of the SCN9A has been described in inherited erythromelalgia (IEM), paroxysmal extreme pain disorder (PEPD), and SFN, with a large variability between genotypes and phenotypes. Levine et al. noted that such patients should be studied separately, since their neurological symptoms may be associated not with a decrease in the density of nerve fibers, but with a high excitability of the spinal ganglia. The neuropathic pain in this case may be explained with the impairment of the sodium channels in sympathetic autonomic neurons with the altered functioning of the sodium–calcium exchanger, leading to increased intracellular calcium concentrations [16, 17].

SFN is described in patients with Fabry [18], Pompe [19], and Ehlers-Danlos disease [20].

The evaluation of a patient with SFN therefore requires attention to an increasing number of etiological factors. Despite the improvement of diagnostic capabilities, up to 50% of SFN cases remain idiopathic [21, 22].

Clinical features of small-fiber neuropathy

SFN symptoms arise due to disruption, dysfunction, or hyperexcitability of small diameter fibers. Delta fibers conduct mechanical and thermal pain impulses at the speed of 5–40 m/s, which provide sensation of sharp and rapid pain. C-fiber conducts mechanical, chemical, and thermal impulses at much lower speed of 0.5–2 m/s, with a dull, diffuse pain sensation. The distal axon of the C-fibers not only transmits pain but also releases electrical and paracrine signals that support the homeostasis of tissues, modulating the tissue responses to injury or threat [1–3, 7, 23].

Symptoms of sensory disturbance most commonly manifest symmetrically and bilaterally in the lower extremities, subsequently spreading from distal to proximal segments, with a length-dependent pattern typical to a polyneuropathy. In contrast, widespread or patchy, i.e., non-length-dependent neuropathic symptoms are thought to represent a sensory ganglionopathy or single/multiple mononeuropathy [22, 24–26].

Clinical symptoms of SFN may manifest as isolated sensory disturbances, isolated autonomic disorders, and mixed conditions. SFN can manifest in a constant burning pain, which in some cases is induced only by skin stimulation. However, it is important to note that symptoms may span from a severe pain syndrome to a complete absence of pain [4, 16, 27].

Sensory symptoms in SFN often include paresthesia (tingling or pricking "pins and needles" sensation), numbness (reduced pain and temperature sensitivity), allodynia (perception of tactile stimuli as painful), and burning pain predominantly in the distal parts of the limbs. Restless legs syndrome which disrupts night sleep may be due to neuropathic pain or burning sensation in the legs. Patients with neuropathies can experience a number of negative symptoms. It should be mentioned that the feeling of numbness does not typically occur in SFN and often indicate the current damage of the larger nerve fibers [5, 25, 28].

The most common autonomic symptoms are sweating disturbance, mainly absence in the distal extremities, dry mouth, discoloration of the skin, and decreased motility of the gastrointestinal tract and the urinary system. If sweating is disturbed

in the distal parts of the limbs, patients may complain of hyperhidrosis in the proximal areas, which appears compensatory to maintain thermoregulation. Disturbance of the distal autonomic vasomotor regulation can lead to a discoloration of the skin. The skin in the affected area can appear as dry, shiny, or atrophic [3, 5, 25, 28].

In sarcoidosis, SFN features more typically include a non-length-dependent distribution of the common sensory symptoms. When muscle or joint pain predominate, these patients are often diagnosed with fibromyalgia. However, as more than 40% of these patients have reduced intra-epidermal nerve fiber density (IENFD) [29], small-fiber neuropathy or early mild sensory polyneuropathy is likely the cause of pain in fibromyalgia syndrome at least in a portion of patients [25, 30, 31]. Voortman et al. noted a 90% incidence of the chronic fatigue among patients with sarcoidosis. Most likely, its pathogenesis consists of several causes, including immune-mediated factors, psychological symptoms (depressive syndrome, sleep disorders), and direct damage to the nerve fibers, and may also occur due to the implementation of the steroid therapy [32].

Diagnostics of small-fiber neuropathy

A detailed collection of symptom history evolvement is the key to identification of SNF and its possible etiology. Use of validated scales is recommended to assess the severity and intensity of symptoms for treatment response interpretation on follow-up evaluation.

Pain intensity and its response to treatment are assessed by the visual analogue scale (VAS) [2, 4]. The commonly used questionnaire for detecting SFN in sarcoidosis is the Small Fiber Neuropathy Screening List (SFN-SL) scale. It consists of two parts of 8–13 questions. The first part assesses the incidence of symptoms, and the second focuses on their intensity. Each symptom is rated from 0 to 4 points, a total score of more than 22 points is regarded as a moderate probability for the presence of SFN, and with a score exceeding 48 points, the probability is estimated as very high. Patients with pulmonary sarcoidosis complain of pain in the extremities as well as their chest, with coldness, hypersensitivity or tingling, muscle spasms, palpitations, impaired swallowing, digestion, and urination, in addition to common autonomic symptoms. The limitations of the questionnaire include its validation only in sarcoidosis, and absence of a skin biopsy data [1, 4, 33].

In Europe, the most commonly used scale is the "Small fiber neuropathy-symptoms inventory questionnaire" (SFN-SIQ). The main limitation of this tool is the lack of quantitative grading of symptoms, which prevents their assessment for change over time [2, 28]. Other scales include the "Rasch-built overall disability scale" (SFN-RODS, [28]), the "Douleur Neuropathique 4" (DN4) questionnaire for the diagnosis of neuropathic pain of any etiology [3, 4], and the "The Autonomic Symptom Profile and the Composite Autonomic Symptom Score-31" (COMPASS-31) for autonomic symptom evaluation [33].

During the bedside neurological testing, visual signs of impaired autonomic functions (e.g., discoloration of the skin, sites of dystrophy) should be taken into account. Response to heat, cold, and pain evoked by pinprick, as well as tactile and deep sensitivity, should be studied. Altered reactions to stimuli should be recorded (e.g., painful sensations in response to tactile stimuli (allodinia), heat sensations in response to cold stimui) as well as pathological aftersensations. Negative symptoms, such as numbness or decreased vibration sensitivity, can also be recorded, suggesting damage to the larger nerve fibers [7].

Standard scales for neurological examination, such as for example the Utah Early Neuropathy Scale (UENS), are developed for the SFN diagnostic. The scale was designed to assess the least pronounced, initial manifestations of neuropathy. UENS was validated to detect early SFN in patients with prediabetes or diabetes, and has been shown to have a sensitivity of 92% and an inter-rater reliability of 94%, requiring only a number 2 (13/4 in.) safety pin and a 128-Hz tuning fork [7, 34].

The diagnosis of SFN may remain clinical but commonly employs supporting laboratory evidence.

As standard electromyography is not suitable for a representative evaluation of the SFN, though this procedure should be performed to exclude the large nerve fiber damage [1–3, 8]. The "gold standard" for instrumental investigation of SFN is a skin biopsy followed by indirect immunofluorescence (IF) or immunohistochemical (IHC) analysis to assess the density of small nerve fibers in the epidermis of the skin [28]. The technique of skin biopsy was first developed at the Karolinska Institute (Wang et al) [29] and was subsequently standardized at the University of Minnesota (Kennedy et al) [31] and Johns Hopkins University (MacCarthy et al) [35, 36] that gave rise to a new direction in neurology diagnostic. This technique employs antibodies to the protein gene product 9.5 (PGP 9.5), a neuronal form of the ubiquitin carboxyl-terminal hydroxylase transported by the slow component of axonal transport. The European Federation of Neurological Communities recommended a skin biopsy with staining of PGP 9.5 as a grade A recommendation [37].

Only two side effects were noted: minor bacterial inflammation in the wound, which can be treated with antibiotics admission, and bleeding that does not require suturing. Specificity and sensitivity of the method range from 88 to 92% [36].

It is possible to perform a punch skin biopsy (3 mm in diameter) in various areas of the body: the foreleg (10 cm proximal to the lateral malleolus), the thigh (20 cm distal to the iliac crest), and the shoulder. Taking a biopsy performed

preferentially on the body side with more prominent clinical symptoms [21, 27, 28]. Skin biopsies taken from the foreleg have high positive predictive value but lower negative predictive value. A biopsy from the thigh is sometimes required to specify the diagnosis and estimate the density of epidermal nerve fibers in the proximal-distal direction [23].

Skin biopsy technique includes the following steps:

1. Cleaning and sterilization with a chlorhexidine 0.5% solution
2. Skin anesthesia with 1% lidocaine injection, Fig. 1b
3. Three-millimeter skin punctate, Fig. 1c
4. Dissecting the deep part of the biopsy tissue with a scalpel
5. Fixation of the tissue in Zamboni solution (4% paraformaldehyde and picric acid)
6. Bandage application on the wound, Fig. 1d

The patient is instructed to remove the bandage after 12 h. Healing occurs within 7–10 days [35].

The tissue is subsequently frozen and free floating 50 μm sections are produced. When carrying out IF analysis with PGP 9.5 antibodies, the density of nerve fibers is assessed, as well as the overall morphological structure of the skin slice, the morphology of subepidermal plexuses, and the innervation of sweat glands. Advantages of the method include representativeness and reproducibility, and, unlike nerve biopsy, this method does not lead to the development of sensory disturbances at the site of biopsy sampling [37, 38].

The disadvantages of the study include high costs and the inaccessibility of appropriate equipment for many clinics, which limits routine screening studies. The density of small fibers is highly affected by quality of primary PGP 9.5 antibody and fixation density. In addition to these technical limitations, gender, age, weight, body mass index (BMI), and race affect the density of small nerve fibers in the skin, and the role of these factors requires further study [36, 37].

In addition to the IF, SFN diagnostics can be performed also using the bright-field immunohistochemistry (BFI). Nolano et al., matching the two methods, performed the study of 55 healthy subjects and 63 patients with probable SFN. Two biopsies of the skin of the thigh were taken in parallel that revealed good correlation of the two methods ($r = 0.81$) with the 2:1 ratio for the number of counted fibers. Diagnosis of SFN differed in only 6.7% of cases, with immunofluorescence, as expected, which was slightly a more sensitive method compared to BFI [39].

Reducing the density of small nerve fibers should be interpreted with other clinical and instrumental data. Nerve compression or polyneuropathy of large fibers development can lead to the decline of the density of small nerve fibers [9].

Skin biopsy allows to specify both the somatosensory and autonomic nerve fiber conditions. The result interpretation starts with measuring the length of the section and counting

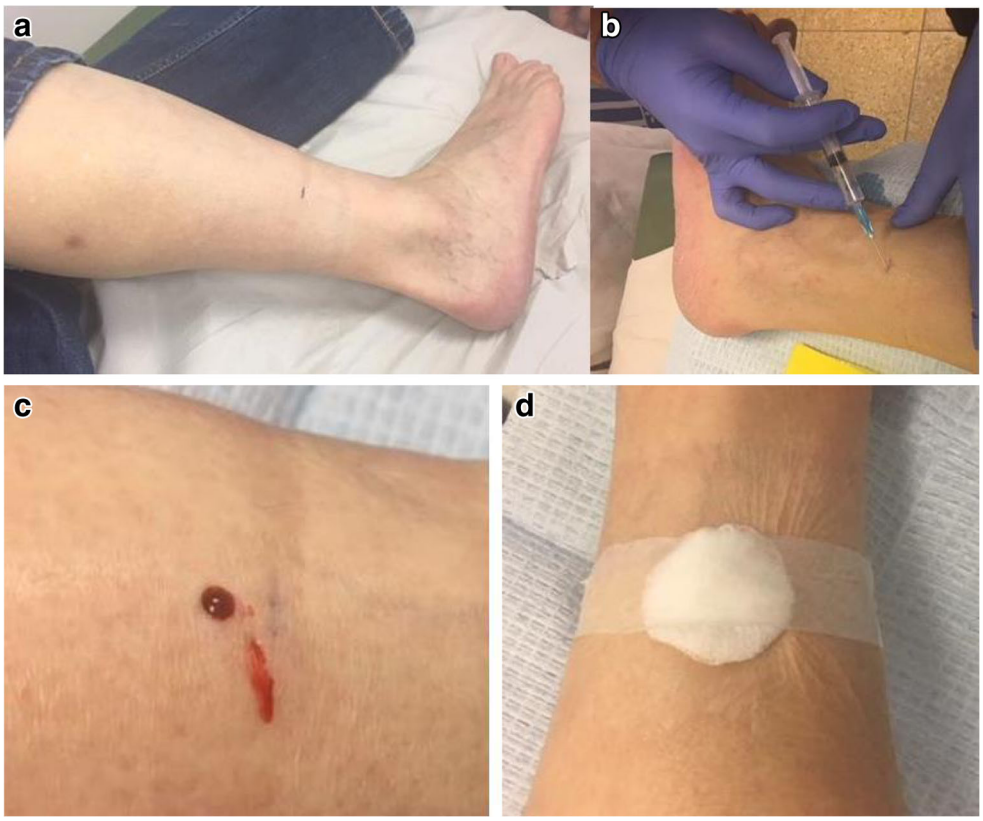

Fig. 1 Stages of skin biopsy. (**a**) The location of the puncture, 10 cm proximal to the lateral malleolus, is marked. (**b**) Anesthesia with lidocaine solution. (**c**) Three-millimeter punch biopsy. (**d**) Application of a bandage

the number of the nerve fibers, then the density of the nerve fibers in 1 mm is calculated, and comparison with age- and gender-matched normative values is performed [40]. The innervation of the sweat glands and quantification of axonal swellings can also be evaluated. With the development of pronounced pain syndrome, significantly higher swelling ratios (swellings per intraepidermal nerve fiber or per nerve fiber length density) compared to the controls can be observed, which can predict the further development of SFN and a decrease in the number of nerve fibers. The study of Langerhans cells is not usually included in the standard protocol for the skin biopsy description; however, there is evidence that the number of that cells can significantly increase in SFN with severe inflammatory and pain syndrome, especially in case of diabetes mellitus. The presence of inflammatory cells such as macrophages and increased concentrations of pro-inflammatory cytokines can also be important [22].

Other methods for verification of SFN that have not been widely accepted, but recommended for diagnosis, include quantitative sensory testing, laser evoked potentials, and confocal microscopy of the cornea and some others.

Quantitative sudomotor axon reflex testing (QSART) determines sweating in four areas of the body: the forearm, proximal leg, distal leg and foot, and assessing the function of postganglionic cholinergic non-myelinated C-fibers by ionophoresis of acetylcholine. The test results are described in sweating volumes in nanoliters per minute, taking into account age and gender norms. The overall sensitivity of the method is estimated at an average of 59 to 80% [3, 28]. This test is often used to validate SFN questionnaires instead of counting the density of nerve fibers but is currently recommended mainly as an additional diagnostic method.

Povitera et al. in 2010 announced the method of dynamic sweat testing, which makes possible to evaluate sweat gland density, distribution of active glands, and sweat rate. This distinguishes it from most of the currently used tests that have limited use: They either evaluate sweating of the whole body, or only from one small area per unit of time, or quantification from a fixed time after stimulation. The authors applied the method to diagnose diabetic neuropathy and consider it suitable for early diagnosis of the disease [41].

Quantitative sensory testing (QST) was designed to objectify subjective sensations. QST is performed by measuring thermal, cold, and pain signals by non-invasive tests in a quiet office while maintaining a constant comfortable temperature. Vibration, cold, heat, and pain sensitivity are repeatedly studied in selected areas of the body. The overall sensitivity of the method is 65–80%, and the specificity is 37–94% [4], but its limitations include subjectivity of sensory symptoms and lack of specificity to peripheral nervous system diseases, and therefore recommended only as an additional diagnostic method [3, 42].

One of the promising electrophysiological tests for verification of SFN is a heat evoked potential stimulator (CHEPS), which is based on evoking potentials from the scalp. Normal values, reliability, and clinical applicability of CHEPs in SFN were established by Atherton et al. (2008) and Lagenburg et al. (2015) whereby the tool may be recommended as an additional method for the SFN diagnostics [43, 44].

Laser evoked potentials tests the function of A-delta and possibly C-type fibers in peripheral tissues. The response to laser stimulation is a reproducible and measurable for estimating SFN with a sensitivity of 70–80%, but like QST is not specific to the peripheral nervous system [1, 3].

Microneurography is a neurophysiological test for recording nerve impulses from C-nociceptors and sympathetic nerve fibers in patients while walking that allows to study the functional characteristics of the sensory system, including neuropathic pain. At the same time, the test has technical difficulties; method is time consuming and has not yet been validated for the study of SFN [40].

Confocal corneal microscopy is a non-invasive method for evaluating the density of small C-fibers originated from the trigeminal nerve in the cornea of the eye, which is reduced in SFN. Automatic analysis and standardized evaluation criteria make the method suitable for diagnosing SFN. The four main characteristics—corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD), corneal nerve fiber length (CNFL), and corneal nerve fiber tortuosity (CNFT)—can be evaluated by the program CCmetrics. The diagnostic sensitivity and specificity of this technique in diabetic polyneuropathy are 91% and 93%, respectively. It correlates well with skin biopsy results but is currently recommended only as an additional diagnostic method [1–3, 42, 45, 46].

Thus, in contrast to multiple ancillary testing to verify the diagnosis of the SFN, the increasingly used method to objectively support the presence of SFN is a skin biopsy followed by an indirect immunofluorescence or IHC using PGP 9.5 antibody to detect small diameter fiber lesions in the epidermis.

Devigili et al. in 2008 proposed the following diagnostic criteria for SFN (at least two of the following examinations should be abnormal): (1) clinical signs of SFN (pinprick and thermal sensory loss and/or allodynia and/or hyperalgesia), which distribution is consistent with peripheral neuropathy (length or non-length dependent manner); (2) abnormal warm and/or cooling threshold at the foot assessed by quantitative sensory testing (QST); and (3) reduced IENFD at the distal leg. The presence of clear clinical criteria significantly simplifies the evaluation of the diagnosis. However, these particular criteria may be found difficult to apply. QST and skin biopsy with IF may not be available in the majority of medical centers; at the same time, QST is also a subjective method of SFN evaluation [47].

Treatment of small-fiber neuropathy

Symptomatic treatment of pain mainly employs tricyclic antidepressants, serotonin, and norepinephrine reuptake inhibitors and anticonvulsants. In the case of a high intensity of pain, opioid analgesics may be used but may worsen gastrointestinal motility [1, 10]. For focal burning pain sensation, the use of local anesthetics such as lidocaine or capsaicin is prescribed. Lidocaine, which blocks the pain impulses in nerve fibers, is especially recommended for patients with neuropathic pain with mutations in sodium channels. Capsaicin interacts with the type 1 vanilloid receptors (TRPV1), leading to destruction of nerve fibers in the skin for 3 weeks, followed by recovery, which results in a temporary decrease in pain [48, 49].

In cases with evidence for autoimmunity treatment with immunomodulatory drugs such as corticosteroids may show benefit. Intravenous immunoglobulin (IVIG) was reported to reduce pain and paresthesia in immune-mediated diseases SFN, especially in Sjogren's syndrome and systemic lupus erythematosus. Particularly in sarcoidosis-associated small-fiber neuropathy, IVIG was reported beneficial in treating symptoms [48, 50, 51]. Additionally, sarcoidosis patients responded well to anti-TNF treatment [51]. Studies employing a novel treatment with ARA290, an erythropoietin derivative, which is a potential treatment for SFN in sarcoidosis, are currently in progress. Dietary deficiencies, toxic substances, and genetic manipulations are treatments that target these specific etiologies when identified. This includes vitamin B complex and copper loss, alcohol and chemotherapy toxicity, or transthyretin amyloid accumulation due to transthyretin-gene mutations.

Conclusion

The study of SFN opens up new perspectives for the diagnosis of neurological disorders. The pathogenesis includes a wide range of immune-mediated, metabolic, hereditary, and genetic diseases. Evaluation of asymptomatic decline in the density of intraepidermal nerve fibers in patients with neurodegenerative diseases raises new questions about the origin and development of the peripheral nervous system disorders.

In the study of SFN, clinician should pay attention to the disturbance of pain and temperature sensitivity, as well as a variety of autonomic disorders of the skin and internal organs. It is important to note that in isolated lesions of small fibers, the vibratory and muscular-joint senses remain completely intact.

Validation scales, such as the SFN-SL, SFN-SIQ, SFN-RODS, and DN4 questionnaires, can significantly assist the physician in the SFN evaluation. The practical approach for diagnosing this type of neuropathy is a skin biopsy followed by an indirect immunofluorescence or IHC with anti-PGP 9.5 antibody, counting the density of intraepidermal nerve fibers. However, there are a number of additional methods for evaluating neuropathy with lower sensitivity and specificity.

Treatment of SFN focuses initially on identification of the etiology and preventing further damage. Dietary deficiencies should be corrected, toxic compounds or drugs withdrawn, and immune disorders appropriately treated. Symptomatic control of neuropathic pain includes antidepressants, anticonvulsants, and in some cases opioid analgesics. Local anesthetics may also be used.

The lack of information about the natural history of SFN and the characteristics of its manifestation in various diseases requires further study using modern clinical and morphological methods of diagnosis, which can contribute to a significant improvement in the quality of medical care and quality of life.

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