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Small fiber neuropathy and autoimmune diseases*

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Small fiber neuropathy can be described as a dysfunction of the nerve fibers of the smallest diameter (A delta and C types), which are widely present in the skin, mucous membranes and internal organs. Among the causes of small fiber neuropathy various autoimmune and immune-mediated diseases have been recognized, including Sjogren's syndrome, celiac disease, systemic lupus erythematosus, fibromyalgia, diabetes mellitus type I and sarcoidosis. This article addresses clinical features, diagnostic methods and treatment options of small fiber neuropathy. Sensory symptoms and autonomic dysfunction are the most common clinical manifestations. There are several validated questionnaires for the small fiber neuropathy, but the "gold standard" for the diagnosis is a skin biopsy followed by an immunofluorescence or immunohistochemical analysis to assess the density of small nerve fibers in the epidermis of the skin. Besides symptomatic treatment, pathogenetic therapy of autoimmune/inflammatory subtype of small fiber neuropathy should be considered.

Keywords: autoimmune diseases, small fiber neuropathy, allodynia, paresthesia, pain, dysautonomia, postural orthostatic tachycardia syndrome, pain management.

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Introduction

Small fiber neuropathy (SFN) is a disorder that can be described as damage of the nerve fibers of the smallest diameter (A delta and C types), which are widely present in the skin, mucous membranes and internal organs. The clinical picture may contain pain syndrome and severe dysautonomia, decreasing the quality of life and making differential diagnosis difficult [1; 2]. A recent study showed that the incidence of SFN in Europe is 12 new cases per 100,000 people per year [3], but this issue requires further studies. The generally accepted clinical protocols are lacking, likewise, the skin biopsy as a diagnostic "golden standard" is complex and expensive, and awareness about this complication is low, making differential diagnosis of SFN very difficult.

The autoimmune genesis of small fiber neuropathy

SFN considered being a complication of various autoimmune diseases, such as Sjogren's syndrome, celiac disease, systemic lupus erythematosus, fibromyalgia and sarcoidosis [2; 3]. The nerve fiber damage, in this case, is possibly a result of systemic cytokine-mediated alteration. In autoimmune neuropathies, an increase in the concentration of cytokines, such as IL 1β, IL-6, IL-8 and TNFα is described. Sensory small neural fibers may secret pro- and anti-inflammatory neuropeptides themselves. Patients with the length-dependent pattern of SFN (similar to other polyneuropathies) have a corresponding distribution of the tissue pro-inflammatory cytokine concentrations, higher — in the biopsies of the distal parts of the extremities and lower — in the proximal areas. It was also shown that inhibition of TNFα and the use of intravenous immunoglobulins reduce the clinical manifestations of SFN in some rheumatological diseases. In addition, antibodies to components of the nervous tissue may be detected, e.g., antibodies to potassium channels or to nicotinic receptors, that can also be the evidence of its immune-mediated origin [4; 5].

Clinical features and diagnostics of small fibers neuropathy

The most common clinical manifestations include sensory dysfunction, mainly changes in pain and temperature sensitivity and dysautonomia, manifested in the dysfunction of exocrine glands (sweat, lacrimal and salivary) and smooth muscles (in the vessels, gastrointestinal tract, urinary bladder, and iris) [1].

The most typical sensory dysfunction is a constant burning pain without a sharp increase, in some cases, it can occur only after skin irritation. Pain is not an obligatory symptom and can be both a leading clinical manifestation and completely absent. In other cases, allodynia (perception of tactile stimuli as painful), burning sensation, decreased pain and temperature sensitivity, paresthesia, mostly in the distal extremities, and restless legs syndrome, predominantly in the night time are described [1; 2].

Discussing the autonomic symptoms, sweating, dry mucous membranes, changes in skin color, dysfunctions of the gastrointestinal tract motility and genitourinary system are noted. If sweating in the distal parts of the limbs is impaired, patients may complain of hyperhidrosis in the proximal regions that occur compensatory to maintain thermoregulation. Dysfunction of the distal autonomic vasomotor regulation can lead to a change in the color of the skin. Often there is a dysfunction of the cardiovascular system, e.g.,

impaired regulation of blood pressure, orthostatic arterial hypotension, and the occurrence of arrhythmias, as well as gastroparesis, impaired intestinal motility and urogenital functions [3].

Validated questionnaires and histological verification of the diagnosis are used to detect SFN. The most generally accepted is the "Small Fiber Neuropathy Screening List" (SFN-SL). Also, the "Small fiber neuropathy — symptoms inventory questionnaire" (SFN-SIQ), the "Rasch-built overall disability scale" (SFN-RODS), the "Douleur Neuropathique 4 questionnaire" (DN4) are used for diagnosing neuropathic pain etiology, as well as "The Autonomic Symptom Profile and the Composite Autonomic Symptom Score-31" (COMPASS-31) for assessing autonomic symptoms could be applied. The "gold standard" for instrumental diagnostics of the SFN is a skin biopsy followed by immunofluorescence or immunohistochemical analysis to assess the density of small nerve fibers in the epidermis of the skin [1–4].

Treatment of small fiber neuropathy associated with autoimmune diseases

The main classes of drugs for the treatment of neuropathic pain include tricyclic antidepressants, serotonin reuptake inhibitors, and anticonvulsants. In the case of high intensity of the pain syndrome, the use of opioid analgesics is possible. Local anesthetics such as lidocaine or capsaicin are recommended if the patient has complaints of burning pain [4; 5].

Recently, new classes of drugs for the treatment of neuropathies have appeared. The use of intravenous immunoglobulins is a well-known method for the autoimmune diseas treatment and sometimes may be recommended for the correction of the SFN symptoms in these diseases. Antagonists of TNF alpha as Infliximab and Adalimumab have shown their effectiveness against neuroinflammation and may be beneficial for the patients with SFN, though this therapy needs further research [1; 5].

Conclusion

SFN has been widely studied in recent decades and is commonly described in patients with various autoimmune diseases, such as systemic lupus erythematosus, fibromyalgia, Sjogren's syndrome, diabetes mellitus type I and sarcoidosis. Its symptoms, including sensory and autonomic dysfunction, can significantly impair the quality of life and worsen the prognosis of the underlying disease. Diagnosis of this complication seems difficult due to the fact that the symptoms of the SFN are quite nonspecific and systemic in nature; its diagnostic tools include validated scales and a skin biopsy with immunofluorescent or immunohistochemical analysis, which requires appropriate qualifications of specialists, significant time and financial costs. SFN requires further study, using both clinical and morphological methods to improve the quality of life and the quality of treatment for patients with autoimmune diseases.

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