Small Fiber Neuropathy in Sarcoidosis

Subjects: Clinical Neurology

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Sarcoidosis (SC) is a granulomatous disease of an unknown origin. The most common SC-related neurological complication is a small fiber neuropathy (SFN) that is often considered to be the result of chronic inflammation and remains significantly understudied.

sarcoidosis autoimmune inflammation polyneuropathy small fiber neuropathy autoimmunity

1. Introduction

In patients with sarcoidosis, the development of systemic inflammation and internal organ dysfunction are observed, which significantly reduces quality of life and worsens patient prognosis. One of the most common complications is considered to be small fiber neuropathy (SFN), a condition that remains significantly understudied [1][2][3][4]. Quite often, patients with lung sarcoidosis complain of a number of non-specific symptoms, such as weakness, sleep disorders, etc., which can significantly affect the patient's quality of life, even in the absence of significant deviations from the pulmonary system.

The development of SFN is considered to be the result of cytokine-mediated inflammation, which is typical for various autoimmune diseases, including sarcoidosis [5][6][7][8]. Small nerve fiber damage is also observed in systemic lupus erythematosus, Sjogren's syndrome, and fibromyalgia [9][10]. Considering the significant role of genetic predisposition and the possible provocative role of exogenous triggers in the development of this complication, SFN in patients with sarcoidosis can be considered as a part of the autoimmune/inflammatory syndrome that is induced by adjuvants (ASIA) [11]. Several proven cases SFN have also been observed in patients suffering from the bacterial inflammation, e.g., Lyme disease and leprosy [1][2][3][4].

The prevalence of sarcoidosis varies throughout the world. In Japan, there is 1 case per 100,000 people, while in Scandinavian countries, the prevalence of sarcoidosis is as much as 63 cases per 100,000 people. In the Russian Federation, sarcoidosis is described to have a prevalence of 22 to 47 cases per 100,000 people, depending on the region [12][13][14][15]. The prevalence of SFN may also vary because it not only presents with neuropathic pains and paresthesias, but also with various symptoms of autonomic dysfunction, which may not be recognized as a neurologic complication [16][17][18][19][20].

Currently, there are no generally accepted criteria for the diagnosis of SFN. The presence of a small nerve fiber dysfunction in a patient is mainly based on clinical criteria, such as a neurological examination and validated scales

(the small fiber neuropathy screening list, for example) [19][21][22][23]. In addition, electroneuromyography can be performed to ensure that limited damage is induced in large nerve fibers. The “gold standard” for diagnostics is the immunofluorescence or immunohistochemistry of a skin biopsy that allows the density of the intraepidermal nerve fibers to be calculated. This technique requires special training and equipment and is time consuming [24][25][26][27][28][29][30]. A preliminary clinical diagnosis of SFN in patients with sarcoidosis is important due to the low awareness of healthcare practitioners about this complication as well as to determine a quick assessment for neuropathic signs and to increase the performance of skin biopsies in diagnosing his condition.

2. Current Insights

In this study, complaints that are typical for the small fiber neuropathy were described in 60% of the patients with sarcoidosis. Small fiber neuropathy can manifest with a wide range of symptoms, including autonomic and sensory dysfunction. The most common clinical manifestations that were observed in our study in the patients with sarcoidosis were impaired cardiovascular regulation (36% of cases), e.g., the development of palpitations and dizziness. In 32% of cases, patients noted pain in the chest or limbs, which was often accompanied by allodynia, a subjective perception of tactile touch as pain. In some cases, this can result in sleep disturbances due to the pain sensations that are caused by bed linen touching the skin. Another symptom that is often noted by patients with sarcoidosis is blurred vision, which is described in 20% of cases. A physician needs to clarify whether these visual impairments are transient or permanent in nature in order to determine a differential diagnosis of ophthalmic pathology. In the neuropathy of small fibers, blurred vision is transient, arising while overworking or during physical exertion. Gastrointestinal tract disorders are less commonly reported with patients with sarcoidosis. In 12% of the cases, the patients complained of impaired intestinal motility, with the development of both diarrhea and constipation, which occurred simultaneously with the onset of sarcoidosis. This also includes subjective complaints of swallowing dysfunction, which is associated with both impaired muscle innervation and with the progression of mouth dryness.

While a negative, statistically significant correlation between the IEND and SFN-SL scores was described in both groups (Spearman coefficient, $r = -0.3508$, $p = 0.0102$, and $r = -0.7382$, $p = 0.0064$), a decrease in the density of the small nerve fibers in patients with pulmonary sarcoidosis was more prominent.

Thus, the neuropathy of small fibers seems to be a widespread pathology that results in the development of multiple organ dysfunction. Disorders in small fiber neuropathy, along with the typical complaints of patients with lung sarcoidosis, such as cough and shortness of breath, can significantly contribute to a decrease in the quality of life. At the same time, when focusing on the main complaints as well as on instrumental and laboratory deviations, clinicians often do not attach the necessary importance to the manifestations of SFN. It is necessary to identify the main causes that are responsible for a patient’s quality of life deteriorating in order to determine a treatment strategy and to improve the prognosis of the patient’s disease [31][32].

Given the low awareness of both medical specialists and patients about the development of this complication and the difficulties that are involved in its diagnosis, further study into this issue is required.

In patients with pulmonary sarcoidosis, small fiber neuropathy may develop as a result of systemic immune-mediated inflammation. The validated questionnaires and histologic verification of the diagnosis help to establish the severity of the neuropathy of small fibers to determine the prognosis and to plan the treatment strategy.

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