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Sarcoidosis and Small-fiber Neuropathy

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Abstract Chronic pain is one of the most commonly reported symptoms among sarcoidosis patients. Not only does it significantly affect quality of life, but it also is a source of frustration for both the patient and physician because the etiology for pain often is unknown. Although patients typically complain of neuropathic-type pain, nerve conduction studies and other conventional diagnostic procedures frequently fail to reveal objective evidence of neurologic disease. However, in recent years, the growing use of specialized tests such as skin biopsy and sudomotor testing has helped to establish the diagnosis of small-fiber neuropathy as the cause of pain in these patients via objective and quantifiable means. Management of sarcoidosis small-fiber neuropathy should consist of target-directed treatment of the underlying disease and appropriate symptomatic therapy.

Keywords Small-fiber neuropathy · Pain · Sarcoidosis · Autoimmune

Introduction

Chronic pain is one of the most commonly reported symptoms among patients with sarcoidosis [1, 2], a multisystemic inflammatory disorder characterized by the presence of granulomas. Neurological complications of sarcoidosis are well described and notably include cranial neuropathies such as Bell's palsy or optic neuropathy. Neuropathic pain also is frequently reported, with one study documenting the complaint of burning feet in up to 30% of patients with sarcoidosis [3]. In nearly a third of these cases, the diagnostic evaluation revealed evidence of a small-fiber neuropathy [3]. Small-fiber neuropathy is a peripheral nerve disorder that affects thinly myelinated Aδ fibers and unmyelinated C fibers, which are involved in somatic and autonomic function [4•]. While somatic nerve fibers mediate cutaneous sensation, predominantly of pain and temperature, autonomic nerve fibers innervate sweat glands and involuntary muscles such as cardiac and smooth muscle fibers. Small-fiber neuropathy thus refers to an abnormality of one or both modalities, which results in pain and/or autonomic nerve dysfunction.

While a generalized large-fiber polyneuropathy is seen in only about 1% of patients with sarcoidosis [5, 6], sarcoidosis small-fiber neuropathy (SSFN) increasingly is being diagnosed given the more widespread recognition of the disorder and availability of special diagnostic procedures. The emergence of autonomic testing and skin biopsy for the evaluation of intraepidermal nerve fiber (IENF) density has aided physicians greatly in their ability to detect the presence of organic neuropathology in patients with sarcoidosis presenting with chronic pain and paresthesias. This is especially important in those with no objective findings on examination or who have multifocal areas of sensory disturbance in a non–length-dependent distribution. First described by Hoitsma et al. [7] in 2002, SSFN likely is much more common than previously thought and now is being considered as a potential source of pain in the evaluation of patients with sarcoidosis.

Clinical Features

Patients with SSFN usually present with prominent somatic nerve dysfunction, such as pain, numbness, burning

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dysesthesias, sheet intolerance, and vibrating or electric shock–like sensations [7, 8•]. At onset, symptoms are migratory and intermittent, but later become constant, and then slowly progress over time. Other cases may present in a subacute manner and then rapidly evolve into diffuse, generalized paresthesias. In many instances, the distribution of neuropathic pain does not follow a length-dependent pattern as is usually seen with large-fiber disease, in which the distal portion of the limbs are affected before the proximal sites; symptoms typically begin in the feet and slowly ascend to the level of the knees, at which point the hands may become affected [9, 10].

On the other hand, the symptoms of patients with SSFN may begin with numbness and burning symptoms in the feet, but they then spread quickly in a patchy, noncontiguous distribution. Patients often report unilateral flank numbness, chest tingling, thigh pain, or constant facial paresthesias; many of them describe a crawling, vibrating sensation in and around their lips. In our experience and that of others, SSFN is commonly non–length-dependent and is manifested as prominent sensory disturbances in the trunk, face, or more proximal portions of the limbs [9, 10]. In addition, the involved areas may be exquisitely tender to temperature extremes. The sensation from a momentary rush of cold air due to a light breeze or with opening a door has been reported by many patients to simulate the feeling of knives against their skin, which can be excruciatingly painful and last for minutes at a time.

Although limb strength and proprioception are unaffected in patients with SSFN, which theoretically results in preserved ambulation even with a protracted course, the diffuse pain can be so severely disabling that this in itself can limit a patient's ability to walk and perform activities of daily living. For some patients, symptoms often are worse during periods of inactivity as with prolonged sitting, standing, and lying down, while other patients report worsening of symptoms with exertion of the affected limbs. It is unsurprising that, despite having multiorgan involvement, many patients with sarcoidosis often will report small-fiber neuropathy symptoms as the most troubling from a quality-of-life standpoint.

Patients with SSFN also may experience autonomic disturbances such as changes in sweating patterns (hyperhidrosis or hypohidrosis), orthostatic intolerance, gastrointestinal dysmotility (nausea, constipation, diarrhea), secretomotor symptoms (sicca), facial and limb flushing, cardiac palpitations, sexual dysfunction, and bowel/bladder disturbances [7, 8•]. Autonomic involvement in SSFN tends to occur in combination with somatic manifestations rather than as an isolated finding. In a recent study evaluating the correlation between autonomic and somatic dysfunction, patients with SSFN who had higher scores on a self-reported autonomic symptom scale (indicating increased symptoms of autonomic dysfunction) also were found to have increased severity of pain compared to healthy control patients and patients with sarcoidosis without symptoms of small-fiber neuropathy [11]. Other studies utilizing cardiovascular autonomic function testing and 123I-MIBG (metaiodobenzylguanidine) scintigraphy have demonstrated the presence of cardiac sympathetic dysfunction in up to 50% of patients with SSFN [12, 13]. Although not as commonly seen as pain and paresthesias, autonomic nerve involvement in the setting of SSFN needs to be addressed and appropriately treated because it may result in significant complications.

Finally, fatigue is a major issue that severely impacts quality of life in patients with sarcoidosis with neuropathy as well as those without neuropathic pain [5, 14]. Although a direct cause–effect relationship between fatigue and small-fiber neuropathy has not been established yet, it also is a frequent complaint among patients with small-fiber neuropathy due to other conditions such as diabetes and hereditary causes. For patients with SSFN, the fatigue is likely multifactorial due to a combination of chronic pain, medication side effects, involvement of other organ systems, and psychosocial factors.

In many cases, the neurologic examination of patients with SSFN is normal with no abnormalities found despite patient complaints of severe neuropathic pain. However, some patients demonstrate allodynia, hyperalgesia, and sensory loss to pinprick and temperature in the affected areas. Mildly reduced vibratory sensation in the toes also is seen sometimes [4•]. Other large–nerve fiber functions such as proprioception, motor strength, and deep tendon reflexes remain unaffected. On general examination, atrophic, smooth, and shiny skin changes can be present, which also may be accompanied by discoloration and hair loss in the affected areas due to sudomotor and vasomotor dysfunction [4•]. Other abnormalities on the examination include orthostatic hypotension and varying degrees of tachycardia and bradycardia.

Pathophysiology

Much is known about the pathophysiology of sarcoidosis neuropathy affecting large nerve fibers, which is characterized by granulomatous deposition in and around the nerves, microvasculitis, and/or necrotizing vasculitic changes [6, 15]. Biopsy studies taken from distal large-fiber nerves of affected sarcoidosis patients have demonstrated the presence of noncaseating granulomas within both nerve and muscle fibers as well as macrophage infiltration of the perineurium, endoneurium, and epineurium [5, 6]. In contrast, the exact pathology of axon loss in SSFN is unknown. In one recent study evaluating the skin biopsy findings in patients with sarcoidosis, those with symptoms of small-fiber neuropathy were found to have significantly decreased IENFs as compared to patients with asymptomatic sarcoidosis and

healthy control patients [3]. This correlates with the reduced IENF density values seen on the skin biopsy of patients with small-fiber neuropathy due to other conditions.

Morphologic changes within the axon have been documented in patients with small-fiber neuropathy [16]. In particular, the finding of axon swelling (up to two to five times the diameter of normal nerve fibers) may be the pathological precursor to the loss of small nerve fibers; their presence predicts degeneration of the IENF, which correlates with pain and sensory disturbances in patients with small-fiber neuropathy [16]. The axon swelling is attributed to the accumulation of cellular debris that is a result of degeneration of the nerve cytoskeleton and transport system. Postulated mechanisms include ischemia and toxic exposure for small-fiber neuropathy due to other diseases, but have not yet been determined for sarcoidosis.

Genetics also may play a role in the development and severity of SSFN. Susceptibility to sarcoidosis has been associated with class II human leukocyte antigens, most strongly with the presence of the DQB1 allele [17]. A study by Hoitsma et al. [18] found that sarcoidosis patients with the HLA-DQB1*0602 allele were more likely to have abnormal temperature-threshold testing consistent with small-fiber neuropathy than healthy control patients. In addition, the degree of severity for overall disease progression was worse in patients with the allele than those without it [18].

Diagnostic Studies

For the patient with sarcoidosis presenting with neuropathic pain, the diagnosis of small-fiber neuropathy may be established with a variety of currently available tests. Many of the published SSFN studies utilized skin biopsy for evaluation of IENF density and quantitative sensory testing (QST), which evaluates subjective thermal-threshold testing [3, 7, 8•, 11]. Autonomic studies, which include sudomotor, tilt table, and heart rate variability to deep breathing, also have been reported to be of benefit in patients with SSFN, especially those with symptoms related to autonomic dysfunction [8•, 11–13]. Although conventional peripheral nerve studies, most notably nerve conduction studies and needle electromyogram, are designed to evaluate large nerve fibers and will not show abnormalities in the patient with pure small-fiber neuropathy, they may be considered in the diagnostic evaluation of SSFN to exclude the possibility of subclinical large-fiber involvement, which has been reported to occur in small-fiber neuropathy due to other causes [19].

Skin Biopsy

As reported in a number of studies, one of the most accurate tests (up to 88% sensitivity) that can detect the presence of small-fiber neuropathy due to sarcoidosis or any other condition is the skin biopsy [3, 4•, 19, 20•]. Its use is supported by the American Academy of Neurology (AAN) as well as the European Federation of Neurological Societies and is considered by some to be part of the gold standard for the diagnosis of small-fiber neuropathy [19, 20•, 21]. The procedure consists of a small 3-mm punch biopsy taken from the lower extremity, usually in at least two sites: the distal leg and proximal thigh. The tissue then undergoes immunostaining with an antibody to protein gene product 9.5, a panaxonal marker, and is examined under a microscope for the number of small nerve fibers seen in the epidermis. The calculated IENF densities then are compared to normative values, with a reduced number considered diagnostic for small-fiber neuropathy [22]. Although the IENF densities may be within normal limits early in the disease, morphological changes such as axonal swelling may be seen and are thought to be predictive of degeneration as discussed previously [4•, 16].

Quantitative Sensory Testing

The QST is a psychophysical test in which patients are given an objective stimulus, usually pain or thermal sensation, when evaluating for small-fiber neuropathy, and their responses then are recorded according to a rating scale that is specific for pain and temperature (cold and/or warm) thresholds with predetermined normative values. Despite the administration of technically calibrated stimuli from a QST device, the recorded response is subjective, which reduces the ability to transpose results from one laboratory to another and also decreases reproducibility [23]. In addition, the results may be affected by several external factors including patient motivation, age, and background [23]. In one study evaluating the use of QST and skin biopsy for painful small-fiber neuropathy, a diagnostic efficiency of 46.9% was seen for QST compared to 88.4% for skin biopsy [20•]. Although another study found the reproducibility of QST to be higher than that of quantitative sudomotor axon reflex testing (or QSART [discussed below]) in the setting of neuropathy related to impaired glucose tolerance, the most current AAN guidelines recommend that QST not be used in isolation as the sole indicator of peripheral nerve dysfunction, and that abnormalities should be supported by other clinical or diagnostic means [23, 24].

Autonomic Testing

Two main types of autonomic testing have been found to be helpful in sarcoidosis: sudomotor and cardiac testing. The most common type of sudomotor testing for SSFN is QSART, which evaluates the volume and rate of sweat output in the upper and lower extremities. Electrodes on the limbs record the sweat output parameters in response to stimulation of sweat glands

via acetylcholine iontophoresis. This noninvasive procedure, which is usually 30 minutes in duration, is perceived by most patients to be only mildly uncomfortable. Patients report feeling a small electrical stimulus during iontophoresis, but the test is otherwise well tolerated. With a sensitivity ranging from 62% to 72.8% in small-fiber neuropathy cases, the QSART is an objective study that is complementary to the skin biopsy [25, 26]. It may be especially helpful in patients with non–length-dependent SSFN because the arm is routinely included in the examination.

Because cardiac dysautonomia frequently is seen with sarcoidosis, specific testing of cardiovagal and adrenergic function is an essential part of the comprehensive SSFN evaluation [13]. The recorded variability in heart rate response to deep breathing and the Valsalva ratio, which is calculated from blood pressure changes in response to the Valsalva maneuver, are simple procedures that have been used to test cardiovagal function in patients with SSFN [8•, 27]. Adrenergic function is evaluated by recording incremental changes in heart rate and blood pressure in response to head-up tilt-table testing. Results are compared to normative data, with abnormalities indicative of cardiac autonomic dysfunction. Of note, primary cardiac involvement can result in abnormalities as well. However, further studies such as cardiac positron emission tomography and 123I-MIBG scintigraphy can help exclude this possibility.

In some cases, the onset of small fiber–neuropathy symptoms may precede the diagnosis of sarcoidosis by weeks to months. Although the diagnostic evaluation of sarcoidosis is beyond the scope of this article, the inclusion of potential sarcoidosis markers such as the serum angiotensin-converting enzyme (ACE) should be considered in the routine evaluation of a small-fiber neuropathy, especially those that present in a subacute, non–length-dependent manner, and are associated with systemic manifestations.

It also is important to consider other nonsarcoidosis causes of small-fiber neuropathy in patients with biopsy-proven sarcoidosis. For example, steroid-induced diabetes is a common complication of long-term steroid use that also may result in a small-fiber neuropathy in patients with sarcoidosis. An extensive evaluation to rule out comorbid conditions or complications of sarcoidosis that may result in a small-fiber neuropathy, such as thyroid dysfunction, vitamin deficiencies, or renal impairment, should be undertaken so that appropriate therapy may be instituted.

Treatment

Although the exact pathophysiology of SSFN is not yet known, the mechanism of axonal degeneration is suspected to be immune-mediated. Thus, treatment of the underlying active sarcoidosis with immunosuppressive therapy is key. However, in some cases, the symptoms of SSFN persist despite optimized treatment and resolution of other systemic manifestations. In these cases, nonconventional immune-modulating therapies may be helpful. Anecdotal reports on the use of infliximab, an anti–tumor necrosis factor-α agent, have shown a significant improvement in SSFN at doses of 3 mg/kg every 4 to 6 weeks [8•, 27]. However, the use of infliximab for treatment of systemic sarcoidosis has not been well established yet.

More recently, intravenous immunoglobulin (IVIG) was reported to be helpful in one sarcoidosis patient with large-fiber polyneuropathy [28]. Based on this finding, we reported a small series of patients with SSFN who experienced resolution of neuropathic pain after an initial loading dose of IVIG at 2 g/kg followed by tapered maintenance therapy at 0.75 g/kg every 3 weeks; since the publication of this paper, two of the patients have been able to further taper down the dose to every 8 weeks [8•]. However, all patients remained on an aggressive immune-modulating regimen that included methotrexate and/or infliximab for maintenance therapy for the sarcoidosis because IVIG was considered adjunct therapy specifically for the SSFN. Although intravenous and oral steroids have been shown to improve symptoms of large-fiber neuropathy in patients with sarcoidosis, they have not been found to be beneficial for SSFN in our experience and that of others [5, 8•, 29].

For those patients with SSFN whose symptoms are refractory to aggressive immune-modulating therapy, chronic pain management with pain medications as well as lifestyle modifications should be considered. SSFN symptoms, especially those that affect the feet and face, can be disabling and result in chronic depression, anxiety, and other mood and psychiatric disorders. Therefore, pain management should be instituted as soon as possible with the help of a multidisciplinary team. Medications typically prescribed for neuropathic pain, such as antidepressants and antiepileptics, can provide some symptomatic relief. Narcotics should be avoided if possible due to the potential risk of addiction and other adverse effects. However, its use may be considered in refractory cases when the severity of pain prevents employment or activities of daily living. For a list of commonly used medications for small-fiber neuropathy in general, please see Table 1. Finally, lifestyle modifications, which include exercise, nutrition, and mind–body therapies (eg, meditation and tai chi) may improve pain-reduction and coping skills in patients with painful neuropathy of all causes [30, 31].

Prognosis

There currently are no longitudinal studies evaluating the prognosis of SSFN because the entity has been established

Table 1 Pain medication treatment for small fiber neuropathy in sarcoidosis

Antidepressants	Dosage recommendations	Common side effects
Amitriptyline	20–150 mg	Sedation, weight gain, anticholinergic effects, sexual dysfunction, arrhythmia (side effects most prominent in amitriptyline)
Nortriptyline	20–150 mg	
Desipramine	20–200 mg	
Duloxetine	60–120 mg	
Anticonvulsants		
Gabapentin	300–3600 mg	Sedation, dizziness, peripheral edema, weight gain
Pregabalin	150–600 mg	Similar to gabapentin
Topiramate	25-400 mg	Weight loss, sedation, cognitive slowing, renal stones, paresthesias
Lamotrigine	25–400 mg	Stevens–Johnsons syndrome, rash, dizziness, nausea, sedation
Carbamazepine	200–1200 mg	Dizziness, sedation, ataxia, aplastic anemia, liver-enzyme elevation
Oxcarbazepine	600-2400 mg	Dizziness, nausea, fatigue, leukopenia
Topical anesthetics		
5% Lidocaine patch	Every 12 hrs	Local edema, burning, erythema
Capsaicin 0.75%	3 or 4 times a day	Burning
Opioids/opioid agonists		
Tramadol	50–400 mg	Sedation, dizziness, seizures, nausea, constipation
Oxycodone	10–100 mg	Sedation, constipation, nausea; potential for addiction/abuse

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only recently. In one retrospective natural history report of sarcoidosis polyneuropathy, which included both large- and small-fiber involvement, the clinical course was described to be monophasic, in which there was a discrete onset of symptoms followed by generalized worsening, plateau, and then improvement [5]. Although the improvement may have been related to treatment with steroids, no spontaneous remission was seen [5]. In our experience and that reported by Hoitsma et al. [27], those patients who do not respond to immune modulating therapy, including infliximab, steroids, and IVIG, have a progressive and disabling course with pain that is often refractory to aggressive pain medication regimens. Many patients are unable to return to work and require counseling and psychiatric care due to concomitant or subsequent development of depression. Fortunately, evolution to large-fiber nerve involvement is not common among our patients in contrast to diabetes-related neuropathy, but long-term follow-up is needed for more definitive characterization.

Conclusions

Small-fiber neuropathy is a significant complication of sarcoidosis that should be suspected in patients who present with a non–length-dependent distribution of neuropathic symptoms. Confirmation of the diagnosis may be made with skin biopsy, QSART, and cardiac autonomic testing, while the QST is considered a complementary diagnostic tool. Although immune-modulating medications and pain management are essential in the treatment of SSFN, further studies are needed to help elucidate therapy options for those patients with refractory symptoms.

Conflict of Interest No potential conflicts of interest relevant to this article were reported.

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