SMALL FIBER neuropathy (SFN), a type of peripheral neuropathy (PN), is a fairly common chronic condition that can develop at any age, with the disease most prevalent in the elderly. While its prevalence is unknown, an estimated 15 million to 20 million people in the U.S. over age 40 have some type of PN. To date, there is no cure for SFN, and very few treatments are effective in reversing the neuropathy. Recently, there is a growing interest in using intravenous immune globulin (IVIG) due to some small reports showing positive results.

What Is SFN?
Smaller fibers result from damage to the small unmyelinated peripheral nerve fibers found in the skin, peripheral nerves and internal organs. Therefore, the symptoms vary depending on which small nerve fibers are affected. In the skin and peripheral nerves, symptoms can cause sensory disruption, including severe pain, burning, tingling and numbness, that can lead to functional impairment, including problems walking, stairclimbing, use of upper extremities and other interference with activities of daily living. Symptoms usually begin subtly with sensory disturbances in the feet and move upward in a stocking distribution. Eventually, the upper extremities may become affected as the neuropathy advances with sensory disturbances in the hands, moving upward in a glove-like manner.

When small fibers of internal organs are affected, dysfunction with the autonomic nervous system can occur. The autonomic nervous system controls organs and systems that are self-regulated such as digestion, heart rate and blood pressure. People with SFN who have autonomic disturbances can experience severe gastrointestinal (GI) problems, including nausea and vomiting, and unexpected drops in blood pressure and heart rate that can lead to fainting.

Causes of SFN
SFN is believed to be associated with many medical and autoimmune conditions; however, prediabetes and diabetes are most often the causes. Indeed, it is believed almost half of diabetics suffer from some form of SFN.

An underlying cause of SFN can be identified more than 50 percent of the time. While there are many different causes (Table 1), prediabetes and diabetes make up approximately 30 percent of known cases. In many cases, the cause is idiopathic (unknown). 3

Diagnosing SFN
As with any neuropathy, an electromyography, or EMG, (used to measure muscle activity) and nerve conduction studies (measuring speed and strength of nerve impulses) are routine. Because these nerve fibers are so small, the abnormalities cannot be seen on nerve conduction studies. The preferred method of diagnosis is a skin biopsy that measures small nerve fiber density. Autonomic dysfunction is tested by assessing heart rate, blood pressure, breathing and GI function in response to activities such as positional changes and deep breathing. Blood is also analyzed to look for diseases that are associated with SFN. Another aid to diagnosis is quantitative sensory testing, which assesses damage to the small nerve endings and detects thermal sensation, pain and vibration.

TREATING SFN
Treatment for SFN includes treating the underlying cause if known. For example, if the cause is diabetes, maintaining proper blood sugar through diet, exercise and insulin therapy is essential. Treatment also includes simultaneously managing symptoms that arise from SFN. Pain is one of the more challenging symptoms to manage. It can begin with a feeling like sand in the shoe, cold or pins and needles. But, it can increase to burning or shooting that can be brought on by touch or temperature change. Pain is managed with anticonvulsants, antidepressants, in some cases opioids, and nonpharmacologic treatments. However, few studies show efficacy of pain management in SFN, which can be very challenging for physicians and frustrating for patients, especially when the cause is unknown.
Many patients never experience complete relief.

IVIG treatment is being prescribed by some physicians when the cause is suspected to be autoimmune. In a study conducted by the Mayo Clinic in which patients with chronic GI dysmotility and a positive antinuclear antibody test were treated with IVIG, 74 percent showed improvement in GI function in both subjective reporting and objective testing. IVIG has also been successfully used to treat ataxic sensory neuropathy associated with Sjögren’s syndrome. Some case studies of IVIG in people with Sjögren’s who have SFN showed a reduction in painful symptoms.

Some practitioners believe there is an immune response that could be a cause of some cases of idiopathic SFN. To assess this, a clinical trial is currently taking place in the Netherlands in which researchers are looking at the efficacy of IVIG. The currently recruiting randomized, double-blind, placebo-controlled study is testing four courses of treatment, three weeks apart, compared with a placebo, to alleviate pain.

Most recently, a small study was conducted to assess the safety and efficacy of “apparently autoimmune small fiber polyneuropathy (aaSFPN). The researchers hypothesized that small-fiber-targeting autoimmune diseases akin to Guillain-Barré and chronic inflammatory demyelinating polyneuropathy, for which IVIG is often prescribed off-label, could be a cause of aaSFPN. The study included 55 patients with aaSFPN in whom 27 patients had systemic autoimmune disorders, 20 percent had prior organ-specific autoimmune illness and 80 percent had abnormal blood-test markers of autoimmunity — but none had diabetes or other known cause of neuropathy. After being treated with IVIG for an average of 28 months, 77 percent of patients responded to treatment, with pain dropping on average from 6.3 to 5.2 on a 10-point scale. Their internal organ function also improved. The researchers concluded the study provides proof-of-concept evidence that IVIG is safe and effective for rigorously selected SFN patients with autoimmune causality, providing rationale for more trials.

While these small studies and case reports show some efficacy of IVIG in treating SFN, there is little data overall to support treatment, which makes it very difficult for this therapy to be covered by insurance. Some plans refuse to cover IVIG treatment due to lack of evidence; however, some will consider a short course of treatment to assess response after the prescribing physician completes a peer-to-peer review with a physician at the insurance company.

Outlook

SFN remains a confounding disease with its cause understood in only 50 percent of cases. There is no cure, and few treatments are effective in reducing its severely painful symptoms. It’s hoped that research will make greater inroads into both understanding more about the disease and finding treatments such as IVIG that can provide patients some relief.

“Small fiber neuropathy is a devastating condition that is frequently unrecognized or misdiagnosed,” said Roy Freeman, MD, director of the Center for Autonomic and Peripheral Nerve Disorders at Beth Israel Deaconess Medical Center in Boston. “There are no approved symptomatic or disease-modifying treatments. There is an urgent need for randomized, blinded, placebo-controlled trials to treat the clinical features of this disorder.”

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References