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# Autoimmunity may underlie newly discovered painful nerve-damage disorder

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An analysis of the medical records of patients treated at Massachusetts General Hospital (MGH) for an often-mysterious condition involving damage to small nerve fibers supports the hypothesis that some cases are caused by autoimmune disease and also identifies the first effective treatment option. This report on 55 patients diagnosed with what appears to be autoimmune small-fiber polyneuropathy (SFPN) finds that treatment with intravenous immunoglobulin, used to treat other autoimmune and inflammatory conditions, provided symptom relief and improved nerve function for most patients, allowing some to discontinue treatment.

"This is a proof-of-concept finding that dampening the body's immune system may be safe and effective for treating apparently autoimmune SFPN, a condition that most patients don't even know they have," says Anne Louise Oaklander, MD, PhD, director of the Nerve Unit in the MGH Department of Neurology and the senior author of a paper receiving advance online publication in *Therapeutic Advances in Neurological Disorders*. "This is the first treatment that has the potential to actually improve the nerve damage, not just block symptoms with drugs such as opioids that don't address its cause."

SFPN involves widespread damage to the tiny nerve fibers that carry pain signals and control internal functions such as heart rate, blood pressure and sweating. Patients often develop chronic pain, fatigue, weakness or fainting when standing, rapid heart rate or gastrointestinal problems. Common causes of SFPN include diabetes and chemotherapy-

induced nerve damage, but this paper studied some of the 30 to 50 percent in whom no cause is found when they are first evaluated, leading to a diagnosis of "idiopathic" SFPN. Studies from Oaklander's group and others have suggested that some such patients have a previously undiscovered autoimmune condition.

In a 2013 study published in *Pediatrics*, Oaklander's team reported the first evidence that SFPN commonly affects children and adolescents. While these otherwise healthy young people didn't have any medical explanation for their neuropathy, the researchers noted that many had personal or family histories of autoimmune illness or blood test evidence of immune/inflammatory activation. This and other evidence led the team to propose the existence of apparently autoimmune SFPN (aaSFPN), in which the immune system directly attacks small nerve fibers. Several other types of nerve damage, including Guillain-Barré syndrome, are caused by autoimmune attack against large nerve fibers, and systemic autoimmune disorders such as rheumatoid arthritis and lupus have been linked to SFPN, lending a solid basis to the hypothesis.

The 2013 Pediatrics study also reported that treatment with steroid drugs or immunoglobulins improved 12 of 15 treated patients. Steroids had been found helpful in a few other published cases, but since their long-term use cause significant adverse side effects, the current study focuses on the outcomes of treatment with intravenous immunoglobulin, a treatment that is FDA-approved for a wide variety of immune disorders and can be prescribed off-label for other immune conditions.

The team examined medical records for 55 patients who met their criteria for SFPN diagnosis, had no evidence of non-immune causes and who were treated at MGH with intravenous immunoglobulin at a starting dose of 2 grams per kilogram of weight every four weeks. All but four were treated for at least three months, the others discontinuing because of side effects. The team studied nine types of follow-up data, all of

which showed improvement - 74 percent of the 51 patients rated their symptoms as improved after treatment, as did 77 percent of their physicians. For 8 patients, symptoms improved so much they were able to taper off and eventually discontinue all treatment.

"This study is wildly surprising," says Oaklander. "Although not a controlled clinical trial, it is paradigm-changing because the fact that an immunomodulatory treatment was effective is the strongest evidence so far that some people have an autoimmune cause of SFPN that can be improved. This paper offers not only a new class of treatments but also further evidence of a new disease discovery. While immunotherapy isn't for everyone with SFPN, patients with idiopathic SFPN should be systematically screened for all common causes, push their physicians to identify their specific cause and discuss disease-modifying treatment options. I'd also urge insurance companies, which are reluctant to cover this expensive treatment, to be more willing to consider covering three-month trials in appropriately diagnosed patients."

An associate professor of Neurology at Harvard Medical School, Oaklander stresses that this "real-world" retrospective case study needs to be validated in a prospective, randomized clinical trial, something her team is seeking grant funding to conduct. She notes that learning more about the mechanisms behind aaSFPN and tracking outcomes of other treatments should lead to less expensive and easier to manage immunotherapies than intravenous immunoglobulin. In the meantime, patients with SFPN and their physicians can find more information, including a list of recommended blood tests, at https://NeuropathyCommons.org.

Provided by Massachusetts General Hospital