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EDITORIAL OPEN ACCESS

Post-COVID Small Fiber Neuropathy, Implications of Innate Immunity, and Challenges on IVIG Therapy

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Introduction

Small fiber neuropathy (SFN) is frequently seen in patients with long COVID, even several weeks after infection, causing significant disability because of painful paresthesias, dysautonomia, and postural orthostatic tachycardia syndrome. Like in "apparently autoimmune SFN," IVIg is also rather liberally considered in post-COVID SFN, although no specific cellular or humoral SFN-related autoimmunities have been observed or explored. Anti-TS-HDS and anti-FGFR-3 antibodies, seen in 20%–50% of SFN cases, are nonspecific to justify using IVIg, especially after the 2 negative controlled trials. A retrospective study in post-COVID SFN patients with dysautonomia has now shown symptom resolution or improvement in all 9 patients treated with IVIg, even 17 months after acute COVID. Although uncontrolled and retrospective with subjectively assessed clinical benefits, the noted improvement in all treated patients provides the stimulus to examine the immunopathologic reasoning of why IVIg can be a justifiable treatment option in some patients with SFN. Important new evidence indicates that in autoimmune SFN with diabetes type 1, innate skin IBA1+ activated macrophages, Langerhans cells, dendritic cells, and NK cells are implicated in clinical symptomatology with proinflammatory cytokines and peptidergic proteins sensitizing skin nociceptors on intradermal nerve fibers. These data are highly relevant to post-COVID SFN where abundant cytokines activate innate immune cells initiating neurogenic inflammation. Accordingly, there is a need to explore innate immunity factors in serum and skin biopsies of patients with post-COVID SFN not only to justify a controlled IVIg trial but also to define criteria for identifying other "apparently autoimmune" SFN subsets.

RELATED ARTICLE

Case-Control Study of Individuals With Small Fiber Neuropathy After COVID-19

Page e200244

Post-COVID SFN: Symptoms and Assessment of Evidence for the Use of IVIg

Patients with long-COVID experience several neurologic symptoms weeks or months after even mild infection, characterized by a complexity of overlapping systemic, neuromuscular, musculoskeletal, and neuropsychiatric symptomatology.[1,2] Within this wide spectrum of symptoms, several patients predominantly present with SFN, manifested with episodic or continuous painful tingling paresthesias in several areas of distal or proximal extremities (according to whether SFN is length-dependent or independent), the abdomen, the thorax, or the face, often associated with dysautonomia, neurovascular dysregulation, and postural orthostatic tachycardia syndrome.[3-6] Post-COVID SFN is very distressing to patients who do not adequately respond to symptomatic therapies because it affects quality of life leading often to physical inactivity, muscle fatigue, or mild weakness due to deconditioning.

The cause of post-COVID SFN is unknown, but several factors have been hypothesized including viral infection of nerves, muscles, and sensory ganglia; post-viral inflammatory and autoimmunity processes; or even a functional neurologic-spectrum disorder.[1,2,5,6] Although there is no evidence of persistent nerve inflammation or nerve autoimmunity, many patients are

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treated with IVIg with mixed results,[5,6] generating concerns among neurologists and patients alike as to why IVIg is justified or why it is not liberally prescribed.

In this issue, McAlpine et al.[7] describe a retrospective chart review of 16 patients with long-COVID with various SFN symptoms that started a median 2.5-week period after COVID; 9 patients with persistent SFN/dysautonomic symptomatology (5 length-dependent and 4 length-independent) were treated with IVIG after a 17-month median time from acute COVID. Over the first 6 months, all 9 patients improved: 6 with total resolution and 3 with substantial improvements of all neuropathic symptoms of allodynia, paresthesias, numbness, postexertional malaise, neurovascular dysregulation, and dysautonomia. Although no specific autoimmunity features were identified (only 2 treated patients had the nonspecific IgM TS-HDS-ab), the authors hypothesized that IVIg was effective by exerting an "anti-inflammatory modulation of auto-reactive B cells and dysimmunity, allowing damaged, unmyelinated small nerve fibers to regenerate,"[7] a hypothesis also proposed for the category of apparently autoimmune SFN,[8] but never documented in SFN due to any cause.

Despite the subjective assessment of response to IVIg and a known 30%–40% placebo effect in all controlled neuropathy trials,[9] the most interesting but surprising message of this study is the observation that the whole wide spectrum of SFN symptomatology resolved in *all treated patients* even after initiating IVIg therapy 17 months from COVID. Because the use of IVIg in SFN is highly controversial,[10-12] still being pursued despite 2 negative controlled trials,[13,14] there is a need to highlight which SFN immunopathology is IVIg targeting, how efficacy is assessed, and why a control trial is justified. For the post-COVID SFN, this is highly concerning to neurologists who have no data to justify using IVIg and to patients who are frustrated that a possibly effective therapy is denied.

Exploring Immunopathogenesis of Post-COVID SFN

In SFN, there is preferential dysfunction of the thinly Aδ-myelinated and unmyelinated C-skin fibers in conjunction with postganglionic unmyelinated autonomic small fibers[8]; its cause is, however, unknown. Despite various hypothetical assumptions of autoimmunity,[8,10-12] there have not been any immunopathologic studies on cellular or humoral immunity markers in the skin biopsies or evidence of activated T and B cells; 2 SFN-associated antibodies, the IgM anti-TS-HDS and the IgG anti-FGFR-3,[10-12] variably seen in 20%–50% of patients, are nonspecific and nonpathogenic in affecting nerve fiber density or exerting axonal and ganglionic cytotoxicity. As highlighted in a negative controlled IVIg trial,[14,15] 18 individuals, referred with the diagnosis of SFN by biopsy and positive anti-TS-HDS or anti-FGFR-3 antibodies, were excluded during screening because they had no evidence of neuropathy on repeated skin biopsy while 3 patients were positive for both autoantibodies, raising concerns that SFN is often misdiagnosed and the associated antibodies are epiphenomena.[14,15]

The Overlooked Role of Innate Immunity in SFN

Except for rare, acute-onset, length-independent conditions with special antibody markers discussed later, the absence of pathogenic antibodies or inflammation does not necessarily exclude the possibility of an autoimmune process in selected SFN subsets centered on innate rather than adaptive immunity; this is an overlooked but novel possibility because innate immune cells play a key role in initiating and maintaining neuropathic pain, being the first line of immunosurveillance and activation of neurogenic inflammation.[16] In neuropathic pain modulation, proinflammatory cytokines, such as IL-1b, TNF, IL-6, IL-15, IL-17, or IL-18, or the anti-inflammatory IL-4, IL-10, and TGF-b are either predominantly algesic or analgesic while in chronic pain, there is often an imbalance between these mediators released by activated immune cells.[16]

The role of innate immunity has now become clear in 2 important studies on SFN with diabetes type 1 where 2 immune cells, the dermal IBA1$^+$ macrophages and epidermal Langerhans cells (CD207$^+$), correlate with intraepidermal nerve fiber density and neuropathic symptom severity suggesting that a reduction in these macrophages plays a role in development and progression of autoimmune-induced SFN.[17] There is also increased number of dendritic cells and activated macrophages secreting proinflammatory cytokines, which, along with increased peptidergic (calcitonin gene-related peptide [CGRP] and substance P [SP]) proteins on the intradermal nerve fibers, can sensitize skin nociceptors.[18] In post-COVID SFN, innate immune factors are even more prominent, including NK cells, dendritic cells, activated macrophages (tissue-resident or circulation-derived), and cytokines which can trigger immune-mediated injury.[19] Of direct relevance, patients with post-COVID with SFN symptomatology have reduced corneal small nerve fiber density with migration and accumulation of dendritic cells in the targeted small nerve fibers, strongly suggesting an innate immune-mediated inflammatory process.[20] Collectively, innate immunity, rather than hypothetical adaptive immunity, is likely the main culprit not only in post-COVID SFN but also in other "apparently autoimmune" SFN.

Abnormal Innate Immunity in "Apparently Autoimmune SFN"

The concept of "apparently autoimmune SFN" was based on Oaklander's observation that among hundreds of idiopathic SFN cases, close to 20% occurred in a setting of another autoimmune disease, such as Sjogren syndrome, systemic lupus erythematosus, or sarcoidosis.[8,21] Labeling them "apparently autoimmune" was based on the rationale that other secondary autoimmune diseases, such as thyroiditis, vitiligo, and pernicious anemia, are commonly seen in patients with primary autoimmunities, a hypothesis that justified the use of

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immunotherapeutics and supported by their response to IVIg, a very satisfying observation in treating a subset of previously untreatable idiopathic SFN.[21,22] The co-occurrence of an "idiopathic" SFN, however, in a patient with underlying autoimmunity does not necessarily imply that this is also autoimmune without exploring immunopathology on skin biopsies or immune factors targeting nerve-specific antigens; it does not also explain why in such autoimmune settings, SFN did not respond to immunotherapies these patients invariably received for their primary immune disease. It is more likely, therefore, that cytokines, activated macrophages, or other innate immune factors related to primary autoimmunity have been sensitizing skin nociceptors resulting in SFN symptomatology and neuropathic pain. The fibromyalgia, commonly seen in many connective tissue diseases, may also be in many cases due to SFN based on skin biopsies.[23] Collectively, the concept of "apparently autoimmune SFN" seen in connective tissue diseases[8,21,22] is probably best explained by activated innate immune players that remain unaffected by the immunotherapies received for their primary autoimmunity.

Acute-Onset SFN and Autoimmune Pain Syndromes

In contrast to common SFN, there are rare but distinct, often acute-onset, non–length-dependent SFN with patchy proximal distribution of painful dysesthesias related to dysfunction of sensory ganglionic or autonomic neurons, due to inflammatory ganglionitis or neuronitis rather than axonopathies,[24] resembling GBS. A rare subset of such patients may be associated with pathogenic antibodies directed against channels and receptors involved in somatosensory synapses, ganglionic cell antigens, or nodal/paranodal proteins,[16] comprising a distinct subcategory of autoimmune pain syndromes with antibodies against LGI1, CASPR, AMPA, glycine receptors, or water channels,[16] although it is uncertain whether these antibodies have a causative role in pain induction. Ongoing search for other antibodies with proteomics and bioinformatics in such patients with SFN[25] may prove informative. The anti-Plexin-D1 antibodies, detected in less than 13% of patients with SFN, may also have the potential to drive neuropathic pain by binding to DRG sections.[26]

The Need to Search for Innate Immunity Factors in Post-COVID SFN and Justify IVIg Trials

Accordingly, skin biopsy immunopathology will very likely identify autoimmune SFN subsets and justify trials with IVIg to suppress cytokine-activated macrophages and dendritic cells,[9] highly relevant to post-COVID SFN where cytokines are abundant and IVIg seems promising.[7] Prioritizing a study in post-COVID SFN would not only offer the potential for relief to many patients suffering from long-COVID but will rapidly advance the field of "apparently autoimmune SFN" and pain autoimmunity. Immunopathologic correlations of skin innate immunity players, quantifying CD68-positive–activated macrophages, expression of key cytokines on endothelial cells, Langerhans's cells, and fibroblasts, will provide sufficient scientific basis to conduct IVIG trials ending the ongoing controversy.[27] In contrast to other autoimmune neuropathies responding to IVIG, SFN is an ideal subset to also explore the mechanism of IVIG's efficacy based on easily performed immunopathology on skin biopsies, as done with muscle biopsies in dermatomyositis.[9] Collectively, controlled trials with IVIg would not only be important for patients with post-COVID SFN but also informative to the field if efficacy is based on objectively quantifying pain, allodynia, paresthesias, and dysautonomia.

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