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

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Abstract

Objectives

To report a case-control study of new-onset small fiber neuropathy (SFN) after COVID-19 with invasive cardiopulmonary exercise testing (iCPET). SFN is a critical objective finding in long COVID and amenable to treatment.

Methods

A retrospective chart review was conducted on patients seen in the NeuroCOVID Clinic at Yale who developed new-onset SFN after a documented COVID-19 illness. We collected demographics, symptoms, skin biopsy, iCPET testing, treatments, and clinical response to treatment or no intervention.

Results

Sixteen patients were diagnosed with SFN on skin biopsy (median age 47, 75% female, 75% White). 92% of patients reported postexertional malaise characteristic of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and 7 patients underwent iCPET, which demonstrated neurovascular dysregulation and dysautonomia consistent with ME/CFS. Nine patients underwent treatment with IVIG, and 7 were not treated with IVIG. The IVIG group experienced significant clinical response in their neuropathic symptoms (9/9) compared with those who did not receive IVIG (3/7; $p = 0.02$).

Discussion

Here, we present preliminary evidence that after COVID-19, SFN is responsive to treatment with IVIG and linked with neurovascular dysregulation and dysautonomia on iCPET. A larger clinical trial is indicated to further demonstrate the clinical utility of IVIG in treating postinfectious SFN.

Classification of Evidence

This study provides Class III evidence. It is a retrospective cohort study.

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Page e200248

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Background

Patients with long COVID-19 frequently present with neuropathic symptoms including exertional intolerance, numbness, paresthesias, allodynia, and autonomic dysfunction consistent with small fiber neuropathy (SFN). Preliminary evidence suggests that SFN may be a key pathologic finding in long COVID.[1-3] Many patients with long COVID also have overlapping symptomatology with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and/or postural orthostatic tachycardia syndrome (POTS). Before the pandemic, ME/CFS and POTS have been linked to SFN.[4,5] It is hypothesized that the inflammatory immune response during a viral illness may lead to immune dysregulation (dysimmunity) and damage to small fiber nerves.[1] Invasive cardiopulmonary exercise testing involves a right heart catheterization followed by exercise and monitoring the physiologic response. It is a valuable test to demonstrate the pathophysiology characteristic in ME/CFS. We report 16 patients of 482 patients seen in the NeuroCOVID Clinic

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who developed post-COVID SFN and their outcomes with immunotherapy along with a subset who underwent invasive cardiopulmonary exercise test (iCPET).

Methods

A retrospective chart review was conducted on patients seen in the NeuroCOVID Clinic at Yale who developed new-onset SFN after a documented COVID-19 illness. We collected demographics, symptoms, skin biopsy, iCPET testing, treatments, and clinical response to treatment. Patients diagnosed with ME/CFS met 2015 Institute of Medicine diagnostic criteria. The sensory neuropathy autoantibody testing was completed by the Neuromuscular Clinical Laboratory at Washington University at St. Louis. Inclusion criteria included diagnosis of long COVID based on the World Health Organization definition, no prior neuropathy diagnosis, negative electrodiagnostic testing, negative laboratory testing for other causes, and positive punch skin biopsy for SFN (defined as reduced Nerve Fiber Density (NFD) on bright field immunohistochemistry by Corinthian Reference Lab). Exclusion criteria included symptom onset after the vaccine, diagnosis of a functional neurologic disorder, and diagnosis of neuropathy from any cause. Skin biopsy was performed unilaterally on the foot and thigh. Protocols for iCPET have been described.[6,7] A standard right heart catheterization was first performed, and patients underwent a maximum, incremental, upright CPET on a cycle ergometer as ventilation, pulmonary gas exchange, and hemodynamics were continuously measured. Arterial and mixed-venous blood gases were measured every minute and cardiac output calculated by using the direct Fick principle. Group comparisons were made using Fisher exact tests or nonparametric unpaired Mann-Whitney tests. We received IRB approval, and consent was waived.

Results

Nine patients with SFN received treatment with IVIG (median age [interquartile range (IQR)], 48 years [40–62]; 7 [78%] female; 7 [78%] White individuals; 2 [22%] Black individuals). Seven control patients either opted out of treatment or were unable to obtain insurance approval (median age [IQR], 46 years [42–52]; 5 [72%] female; 5 [72%] White individuals; 1 [14%] Black individual; 1 [14%] Hispanic individual). The median onset of neuropathic symptoms after the first day of the COVID-19 illness included numbness, paresthesias, and allodynia and was similar between groups (IVIG: 2 weeks, C: 3 weeks; p = 0.77). The majority of patients had a mild COVID-19 illness. There was no difference between the groups in terms of type of SFN (p = 0.63), diabetes diagnosis (p = 0.21), hospitalization during acute COVID-19 (p = 0.63), and time to biopsy after COVID-19 illness (p = 0.11). The presence of SFN was associated with a constellation of dysautonomia symptoms, including orthostasis, altered sweating, and labile heart rate. Two control patients reported gastrointestinal motility issues and frequent urinary tract infections. Patients in both groups had comorbid ME/CFS (IVIG: 8 [89%]; C: 6 [86%]), POTS (IVIG: 3 [33%]; C: 3 [43%]) and/or another autoimmune disease (IVIG: 2 [22%; C: 2 [29%]). Laboratory testing was done after COVID-19 and before the skin biopsy. C-reactive protein (CRP) was elevated in both groups (IVIG: 5.6 mg/L [1.3–10.3]; C: 2.3 [1.8–12.8]; p = 0.61). Ten patients underwent sensory neuropathy autoantibody testing: 3 were positive for IgM trisulfated heparin disaccharide (TS-HDS) and 3 were positive for IgG fibroblast growth factor receptor 3 (FGFR3). Demographic and clinical characteristics of both groups are reported in the Table.

Seven patients (44%) who presented with postexertional malaise and autonomic symptoms underwent a clinical invasive cardiopulmonary exercise test (iCPET). All 7 patients demonstrated abnormal testing with evidence of neurovascular dysregulation and dysautonomia consistent with a diagnosis of ME/CFS. Findings included depressed aerobic capacity, elevated peak mixed venous oxygen saturation, depressed arterial-venous oxygen content difference, and low biventricular filling pressures.

Nine patients received IVIG for a median of 10 months [IQR 3–19] (Table). Because of long clinic wait times, diagnostic delays, and delays in insurance authorization, patients had SFN neuropathic symptoms for a median of 17 months IQR [7–23 months] between their COVID-19 illness and first IVIG infusion. During this time, all patients were trialed on gabapentin, pregabalin, and/or duloxetine without resolution of neuropathic symptoms. One patient received a 10-day course of prednisone with temporary improvement. The IVIG dosing was 2g/kg split over 3 days for the first infusion then 2g/kg split over 2 days every 3 weeks thereafter.

Over the first 6 months of therapy, all patients experience either resolution (6 [66%]) or improvement (3 [33%]) in their clinical neuropathic symptoms compared with the control group (2 [29%]; p = 0.001). We defined improvement as lessening in the extent of skin with neuropathic symptoms (allodynia, paresthesias, and numbness), intensity of neuropathic symptoms, and/or severity of functional impairment. Once patients reached a therapeutic response, the time between infusions was gradually spaced out. Four patients who experience resolution were able to wean off IVIG. Two patients who experienced resolution and 3 patients who experienced improvement reported the return of neuropathic symptoms during weaning before their next infusion. This group remains on IVIG at the time of publication, and we plan to reattempt weaning in the future. Notably, who experienced improvement, but not resolution, had a diagnosis of diabetes.

Discussion

SFN should be considered in the differential for patients who present with neuropathic symptoms and autonomic

Table Comparison of Patients Treated With IVIG to Control Group of Patients Who Did Not Receive IVIG

	IVIG group Median (IQR), n (%) n = 9	Control group Median (IQR), n (%) n = 7	*p* Value
Age	48 (40–62)	46 (42–52)	0.94
Female sex	7 (78)	5 (72)	0.99
Race/ethnicity			0.75
Black	2 (22)	1 (14)	
White	7 (78)	5 (72)	
Hispanic	0 (0)	1 (14)	
Hospitalized for COVID-19	4 (44)	2 (29)	0.63
Symptom onset after COVID-19 (wk)	2 (2–3)	3 (2–7)	0.77
Time to biopsy after COVID-19 (mo)	11 (3–16)	17 (13–23)	0.11
Preexisting neuropathic symptoms	1 (6)	0 (0)	0.99
Diabetes	3 (33)	0 (0)	0.21
Type of SFN			0.63
Length dependent	5 (56)	5 (71)	
Nonlength dependent	4 (44)	2 (29)	
CPET testing	4 (44)	3 (43)	
Comorbid diagnoses			
POTS	3 (33)	3 (43)	0.99
ME/CFS	8 (89)	6 (86)	0.99
Other autoimmune disease	2 (22)	2 (29)	0.99
Autonomic symptoms			
Orthostasis	8 (89)	6 (86)	0.99
Altered sweating	6 (67)	4 (80)	0.99
Heart rate lability	7 (78)	4 (80)	0.99
Exertional fatigue	7 (78)	6 (100)	0.49
GI/bladder dysfunction	0 (0)	2 (33)	0.14
Laboratory testing			
Positive ANA	1 (14)	3 (43)	0.56
ANA titer	1:80	1:80 (1:40–1:100)	
Hemoglobin A1c (normal <5.7)	5.8 (5–7.4)	5.8 (5.5–5.9)	0.83
ESR (normal 0–20 mm/h)	21 (16–29)	12 (10–27)	0.19
CRP (normal <1.0 mg/L)	5.6 (1.3–10.3)	2.3 (1.8–12.8)	0.61
IgG FGFR3 positive; normal titer (<6,000)	0/5	3/5 6,000 (6,000–6,800)	
Negative result	5/5	2/5	
IgM TS-HDS positive; normal titer (<6,000)	2/5 35,500 (14,000–57,000)	1/5 23,000	
Negative result	3/5	4/5	
Time to IVIG after COVID-19 (mo)	17 (7–23)	—	

Continued

Table Comparison of Patients Treated With IVIG to Control Group of Patients Who Did Not Receive IVIG *(continued)*

	IVIG group Median (IQR), n (%) n = 9	Control group Median (IQR), n (%) n = 7	*p* Value
Length of IVIG treatment (mo)	10 (3–19)	—	
Clinical response	**To IVG**	**To no treatment**	0.001[a]
Resolved	6 (67)	2 (29)	
Improvement	3 (33)	0 (0)	
Unchanged or worse	0 (0)	5 (71)	

Abbreviations: IQR = interquartile range; ME/CFS = myalgic encephalomyelitis/chronic fatigue syndrome; POTS = postural orthostatic tachycardia syndrome; SFN = small fiber neuropathy.
Improvement is defined as lessening in the extent of skin with neuropathic symptoms (allodynia, paresthesias, and numbness), intensity of neuropathic symptoms, and/or severity of functional impairment. Laboratory testing was done after acute COVID-19 illness and before skin biopsy for all patients. The antibody panel included testing for IgM GD1b, IgG GM1, IgG and IgM sulfatide, IgM MAG, IgM Histone H3, IgM GD1a, IgG Hu, and IgG CRMP-5. All patients tested were negative for these additional antibodies. The 3 patients with positive autoantibodies in the control group experienced unchanged or worsening symptoms. It is important to note that this study was not able to adequately assess pos-exertional malaise given it was not formally assessed.

dysfunction after COVID-19. SFN neuropathic symptoms commonly include distal, symmetric burning pain, allodynia, impaired temperature sensation, paresthesias, and numbness. SFN autonomic symptoms include abnormal sweating, skin discoloration, cool extremities, dysautonomia, and bladder and bowel issues. Electrodiagnostic testing is negative in SFN, but a skin punch biopsy, which looks for a reduction in small nerve fiber density, will support the diagnosis. Autoantibody testing may include TS-HDS and FGFR3, which have been linked with SFN and dysautonomia, but the clinical relevance is still under debate.[8] The most common causes of SFN should also be evaluated for, including diabetes, HIV, autoimmune diseases such as Sjogren, SLE, celiac, and sarcoidosis, and toxic exposures such as alcohol and chemotherapy.

SFN has been linked to both ME/CFS and POTS, and we provide further evidence here.[4,9] ME/CFS is often accompanied by cognitive impairment, orthostatic intolerance, and poor sleep. It is hypothesized that neurovascular dysregulation from damaged small nerve fibers contributes to exercise intolerance demonstrate on iCPET by mechanisms related to inadequate cardiac preload and impaired systemic oxygen extraction. Dysregulated microvascular tone of perivascular myocytes reduces venoconstriction, leading to impaired venous return and low cardiac preload. SFN results in inappropriate dilation of cutaneous arteriovenous shunts and shunting of oxygenated blood away from exercising muscles, resulting in impaired peripheral oxygen utilization.[5]

We provide evidence supporting SFN after COVID-19 has an underlying autoreactive and dysimmune etiology. We demonstrate that the time of onset is within 6 weeks of a viral illness, persistently elevated CRP, a significant response to immunotherapy, female predominance, presence of comorbid autoimmune disease, presence of autoantibodies, and wearing-off phenomenon with return of neuropathic symptoms between treatments. The suspected pathophysiology of SFN includes autoreactive B-cell–mediated damage, molecular mimicry, and/or dysimmunity.[10-14] IVIG has numerous mechanisms of action including neutralizing autoantibodies, reduce complement-mediated inflammation, and providing anti-inflammatory modulation of cellular immunity and endothelial inflammation.[14,15] We support that IVIG treats the postviral SFN through multiple mechanisms, including anti-inflammatory modulation of autoreactive B cells and dysimmunity, allowing damaged, unmyelinated small nerve fibers to regenerate.[1,10] There are limitations and potential bias given the cohort was selected from a single NeuroCOVID Clinic. Conditioning to IVIG is a concern and should be closely evaluated for in future studies. A large clinical trial is indicated to confirm the utility of IVIG and determine length of therapy in treating post-infectious SFN.

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Appendix *(continued)*

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