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Case report

Post COVID-19 syndrome associated with orthostatic cerebral hypoperfusion syndrome, small fiber neuropathy and benefit of immunotherapy: a case report

Peter Novak*

Autonomic Lab, Brigham and Women's Faulkner Hospital, Boston, MA, United States of America

A B S T R A C T

Coronavirus disease (COVID-19) is a novel highly contagious infectious disease caused by the coronavirus SARS-CoV2. The virus affects the human respiratory and other systems, and presents mostly as acute respiratory syndrome with fever, fatigue, dry cough, myalgia and dyspnea. The clinical manifestations vary from no symptoms to multiple organ failure. Majority of patients fully recover. Several postinfectious presumably autoimmune complications of COVID-19 affecting the brain or peripheral large nerve fibers have been reported. This report describes a post COVID-19 patient who developed chronic fatigue, orthostatic dizziness and brain fog consistent with orthostatic hypoperfusion syndrome (OCHOS), a form of orthostatic intolerance, and painful small fiber neuropathy (SFN). Initially, the patient was diagnosed with.

OCHOS (detected by the tilt test with transcranial Doppler monitoring) and SFN (confirmed by skin biopsy), and both OCHOS/SFN were attributed to Post Treatment Lyme Disease Syndrome of presumed autoimmune etiology. Patient recovered on symptomatic therapy. COVID-19 triggered exacerbation of OCHOS/SFN responded to immunotherapy with intravenous immunoglobulins. This case suggests that post COVID-19 syndrome may present as an autoimmune OCHOS/SFN and that early immunotherapy may be effective. Further studies are necessary to confirm the link between OCHOS/SFN and COVID-19 disease as well as to confirm the benefit of immunotherapy.

1. Background

Coronavirus disease (COVID-19) is a novel highly contagious infectious disease caused by the coronavirus SARS-CoV2 [1]. The virus affects the human respiratory and other systems and presents mostly as acute respiratory syndrome with fever, fatigue, dry cough, myalgia and dyspnea. The clinical manifestations vary from no symptoms to multiple organ failure. Majority of patients fully recover. The virus can invade central and peripheral nervous system [2] and cause acute neurological complications. Several postinfectious presumably autoimmune complications of COVID-19 affecting the brain or peripheral large nerve fibers have been reported [3]. This report describes a post COVID-19 patient who developed symptoms (chronic fatigue, orthostatic dizziness and brain fog) consistent with orthostatic hypoperfusion syndrome (OCHOS) [4], a form of orthostatic intolerance; and painful small fiber neuropathy (SFN) with good response to immunotherapy.

1.1. Case description

A 64-year-old woman presented with a cough and dyspnea. She has a past medical history of headaches hypothyroidism (euthyroid on liothyronine), Lyme disease, SFN and OCHOS. Four years ago she experienced a tick bite with Bull's eye rash, arthralgia and swollen lymph nodes. She was treated with oral doxycylin for three weeks. Three months later she experienced headaches, several pain syndromes, disabling fatigue, brain fog and mood lability. Her neurological evaluation including magnetic resonance imaging of the brain was unrevealing. She was treated with several antibiotics (rifampin, ceftin, cefdinir) for possible incompletely treated Lyme disease and suspected coinfections. She experienced signs and symptoms typical for SFN (distal burning sensation without weakness and normal reflexes on neurological examination) and with symptoms of cerebral hypoperfusion (dizziness, brain fog and fatigue, all predominantly of orthostatic character). She underwent standardized autonomic testing (deep breathing, Valsalva maneuver, tilt and sudomotor test) with cerebral blood flow velocity (CBFv) monitoring using transcranial Doppler. Autonomic tests showed minimal parasympathetic dysfunction on deep breathing test (mean respiratory sinus arrhythmia = 7.0, normal > 7.0). Blood pressure responses to Valsalva maneuver and tilt test were normal, which is indicative of normal adrenergic sympathetic functions. Tilt test showed reduced orthostatic CBFv in middle cerebral artery (CBFv was reduced by 21% at the 10th minute of the tilt, normal decline < 14%) while orthostatic hypotension orthostatic tachycardia and hypocapnia were absent which is consistent with OCHOS. Skin

* Corresponding author.
E-mail address: pnovak2@bwh.harvard.edu.

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biopsy showed reduced epidermal nerve fiber density (4.13 fibers/mm at distal leg, normal ≥6.06) consistent with SFN. Sudomotor testing showed reduced electrochemical skin conductance at feet (0.7 μS/kg, normal ≥1.14) and at hands 0.85 μS/kg, normal ≥1.03), which is also consistent with SFN. Workup for known causes of SFN [5] (diabetes, pre-diabetes, parkinsonism, Parkinson's disease, history of heavy alcohol use, B12 and/or folate deficiency, active thyroid disease, celiac disease, hepatitis C, cancer, chemotherapy exposure systemic autoimmune disease, medications that have been associated with SFN) was negative. The autonomic testing findings (SFN and OCHOS) were attributed to Post Treatment Lyme Disease Syndrome [6]. She improved on symptomatic and physical therapy. At her baseline, she had moderate headaches occurring in average twice per week.

She was at that baseline for about a year. Then she presented with a cough and dyspnea of suddent onset. Several days later she experienced fever, progressive worsening of dyspnea and disabling headaches. Computed tomography of chest showed viral pneumonitis. Reverse transcriptase-polymerase chain reaction was positive for SARS-CoV2 and she was treated with a five day course of hydroxychloroquine and azithromycin as she self-quarantined. Within a week of therapy, her fever and respiratory symptoms have resolved, and she was close to her preinfectious baseline. Two weeks later she experienced new symptoms such as severe leg pain with burning sensation at feet and hands, twitching and vibration feeling at her face, blurred vision, headaches, brain fog, forgetfulness, chronic fatigue, orthostatic dizziness and urinary incontinence but no weakness or dyspnea. Repeated testing for SARS-CoV2 was negative. Evaluations for common infections including influenza, respiratory syncytial virus, white cell counts and urine analysis were all negative or within normal limits. Autonomic testing could not be repeated due to COVID-19 related safety restrictions. Autoimmune mechanisms were suspected as a cause of patient's symptoms. Patient was treated with intravenous immunoglobulins (IVIG) at the dose 2 g/kg monthly for two months that was decreased to 1 g/kg monthly due to the IVIG induced headaches. Immunotherapy successfully resolved leg pain, brain fog, urinary problems and of blurred vision. Her headaches and chronic fatigue persisted but improved by about 50%.

2. Discussion

This report illustrates a case of a postinfectious autonomic syndrome likely due to autoimmune process in patient with previous COVID-19 disease. In general, postinfectious disorders include a variety of disorders developing over periods of days or weeks after viral or bacterial infections [3,7]. These disorders probably reflect altered autoimmunity caused by previous infections, although in many cases the antigens targeted by immune system are unknown. Already reported post COVID-19 complications include Guillain-Barre syndrome (GBS), acute disseminated encephalomyelitis, postinfectious brainstem encephalitis and necrotizing autoimmune myositis and they may respond to immunomodulatory therapy [2,3].

This case expands the spectrum of reported postinfectious COVID-19 complications. The presented patient has both symptoms of central (dizziness, brain fog) and peripheral (distal burning sensation) nervous system dysfunction. The patient experienced identical symptoms before when autonomic testing showed OCHOS and SFN. The same clinical presentation as in the past provides a suggestive evidence that the OCHOS and SFN were again responsible for current post COVID-19 symptoms. Unfortunately, these diagnoses could not be confirmed by repeating autonomic testing.

OCHOS is a variant of orthostatic intolerance syndrome associated with reduced orthostatic cerebral blood flow and signs of cerebral hypoperfusion without orthostatic hypotension or orthostatic tachycardia. OCHOS results from cerebral autoregulatory failure due to abnormal cerebral arteriolar vasoconstriction and immune-mediated arteriolar dysfunction was postulated as one of the possible mechanism [4]. Immune-mediated SFN secondary to viral infections has been reported [8]. Thus both OCHOS and SFN may have immune-mediated basis and theoretically, both may respond to immunotherapy. Immunotherapy with IVIG has been reported to reduce pain in immune-mediated SFN[8] while the effect of IVIG for OCHOS is unclear. The patient improved after therapy with IVIG which is consistent with autoimmune basis of her complaints [3,7].

In summary, this case describes a probable OCHOS and SFN in post-COVID disease. This reports provides an additional evidence that COVID-19 disease can trigger autoimmunity which is consistent with previous reports of several autoimmune neurological diseases including GBS in post-COVID disease, although exact mechanism how the coronavirus is triggering autoimmunity is largely unknown [3]. This case also suggests that early immunotherapy may be effective. Further studies are necessary to confirm the link between OCHOS/SFN and COVID-19 disease as well as to confirm the benefit of immunotherapy.

Declaration of Competing Interest

Dr. Novak is advisor – independent Contractor for Dysimmune Diseases Foundation. Dr. Novak received speaker's honoraria from KabaFusion and Lundbeck, he is a member of the Scientific Advisory Board of Endonovo Therapeutics. Dr. Novak received royalties from Oxford University Press.

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