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NON-SYSTEMATIC REVIEW

Small Fiber Neuropathy Associated COVID-19: A Common or Uncommon Complication?

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Abstract

The spectrum of neurological manifestations of COVID-19 range from anosmia and dysgeusia to myopathy and encephalitis. With the persistence of COVID-19 pandemic and the increase of infected subjects, new acute manifestations and sequels are being discovered. Lately, a new important neurological complication has been reported: Small Fiber Neuropathy (SFN). The existing literature reports cases of dysautonomia, orthostatic intolerance, and hyperesthesia manifestations, until the moment.

Keywords

Neuromuscular, Neuropathy, SARS-CoV-2, Small fiber neuropathy

Abbreviations

ACE2: Angiotensin Converting Enzyme 2; ARDS: Acute Respiratory Distress Syndrome; POTS: Postural Orthostatic Tachycardia Syndrome; SFN: Small Fiber Neuropathy

Introduction

Several neurological manifestations are related to COVID-19 disease, with its prevalence varying from 36.4 to 57.4% in two major observational studies. According to these studies, the most frequently acute symptoms were myalgia, headache, dizziness, anosmia and dysgeusia. Acute cerebrovascular diseases, impaired consciousness and skeletal muscle injury occurred in severe cases. Less frequently, but also reported manifestations, were myopathy, dysautonomia, cerebrovascular diseases, seizures, movement disorders, encephalitis, Guillain-Barré syndrome, and optic neuritis. Besides that, neurological complications were the main cause of death [1,2]. Small Fiber Neuropathy (SFN) is a newly reported manifestation of COVID-19 with a poorly understood mechanism. Acording to the existing literature, it may present as orthoststic intolerance, hyperesthesia, hyperidrosis, and/or gut dismotility; either in the acute phase or in the post-acute one (Table 1).

Methods

We conducted a non systematic review of papers addressing small fiber neuropathy and Covid-19 disease.

Results

17 manuscripts were included.

Discussion

With the persistence of COVID-19 pandemic, and the huge number of infected subjects, new manifestations and sequels, including neurological ones, are being discovered. SARS-CoV-2 related Small fiber neuropathy (SFN), for instance have been recently reported in dysautonomia, orthostatic intolerance, and hyperesthesia manifestations [3-6]. The most accepted mechanism for neuroinvasion is the entrance of SARS-CoV-2 in Angiotensin Converting Enzyme 2 (ACE2) host cells, which are richly present in many brain regions. Since the neurological manifestations are often inconsistent with the viremia, which is frequently low, other mechanisms for virus disseminations are hypothesized, such as vesicular axonal transport and passive diffusion [7].

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Table 1: Small fiber neuropathy reported in COVID-19.

Manifestations	Authors	n (number of reported patients)
Postural Orthostatic Tachycardia Syndrome - POTS	Blitshteyn S, Whitelaw S (2021) [4]	20
	Johansson M, Ståhlberg M, Runold M, et al. [9]	3
Hyperhidrosis	Hinduja A, Moutairou A, Calvet J-H. [14]	13
	Umapathi T, Poh MQW, Fan BE, et al. [8]	1
	Krajewski PK, Szepietowski JC, Maj J [6]	2
Hyperesthesia	Harsch IA, Atudorei I, Frank K [15]	1
Gastrointestinal complications	El Moheb M, Naar L, Christensen MA, et al. [16]	68

Small fiber involvement reported in COVID-19 patients, its authors and number of patients described.

The virus binds to ACE-2 increasing angiotensin II and activating renin-angiotensin-aldosterone system. This could explain the rise in sympathetic activity (which induces hyperadrenergic crisis in Postural Orthostatic Tachycardia Syndrome - POTS) and the hypokalemia seen in COVID-19 patients [8]. Besides that, research indicates that COVID-19 infection may cross-react with autonomic ganglia and fibers and with G protein-coupled receptors, in addition to neuronal and cardiovascular ones. Many antibodies have already been found in patients with POTS, such as antibodies against Angiotensin II, acetylcholine, adrenergic, muscarine, and opioid receptors [4]. This could justify the dysfunction of the autonomic nervous system, and therefore it is hypothesized that autoimmunity is one of the main mechanisms that could cause the syndrome, although much is not yet fully understood [4,8].

POTS is the most frequent post-acute-COVID autonomic cardiovascular dysautonomia, and an important cause of disability 6-8 months after acute infection. This autonomic syndrome manifests itself in different ways, such as dizziness, postural tachycardia, orthostatic intolerance, pre-syncope and difficulty in exercising, and it is more common in women. POTS' diagnosis is made by the tilt test or a 10-minute support test, in which characteristically occurs an increase in heart rate of at least 30 bpm from the supine position to the upright position without orthostatic hypotension, in association with pre-syncope symptoms and orthostatic intolerance [4,9,10]. Lately, few studies have reported the occurrence of POTS after COVID-19 infection [9-13].

A study by Blitshteyn and Whitelaw evaluated the course of POTS and other autonomic disorders in 20 COVID-19 patients. Most of the COVID-19 diagnoses were clinically made. After the resolution of acute disease, most patients presented fatigue, postural tachycardia, and exercise intolerance. 6 had minor pulmonary and cardiac abnormalities, and 4 had inflammatory abnormalities. 15 out of 20 patients (75%) were diagnosed with POTS, 3 with neurocardiogenic syncope and 2 with orthostatic hypotension. 16 patients (80%) required pharmacology for autonomic dysfunction, and all of them required non-pharmacological therapy. An improvement in POTS was observed with the use of drugs such as beta-blockers, midodrine, fludrocortisone, and ivabradine, in addition to drugs used to treat other comorbidities, such as headache, neuropathic pain or allergies. 6-8 months after COVID infection, 85% still reported residual symptoms. Only 3 patients were able to return to work with almost complete resolution of symptoms and 5 were able to work from home within 8 months of the COVID-19 infection. Since that was a retrospective study, it is not known if more subjects had improvement or resolution of the symptoms [4].

Other manifestations of Small Fiber involvement in SARS-CoV-2 infection, such as hyperhidrosis, have been lately known. Hinduja, et al. described fifty (50) post-COVID-19 patients who visited an outpatient clinic for neurological symptoms and fatigue within 3 months from infection. 26% had sweat dysfunction, and those with sweat dysfunction were more likely to be older, to have been treated at home, used antiviral drugs, and to present at least one associated motor, sensory or autonomic symptom [14]. Furthermore, Umapathi, et al. described a COVID-19 patient treated with antiviral medication (remdesivir) who presented hyperhidrosis and associated orthostatic tachycardia, similarly to what has been pointed out in Hinduja's study, although he was 39-years-old and developed thrombotic state requiring embolectomy. Patient was asymptomatic 4 months later in the outpatient review [8].

Another intriguing and recently described manifestation is cutaneous hyperesthesia. Krajewski, et al. firstly described two patients, a man and a woman, both 40-years-old, who presented hyperesthesia during SARS-CoV-2 infection. In both cases, abnormal sensitivity of the skin was noted in the first day of symptoms, was accompanied by fever, affected mostly the abdomen and the back, and was aggravated by other kinds of touch (such as clothing). The man reported attenuation with warm baths, while the woman only had relief with diclofenac pills. They were both treated with hydroxychloroquine (200 mg twice a day), and the woman also received azithromycin. Hyperesthesia resolved in 10 days [6]. On the other hand, Harsch, et al. described a 69-years-old with moderate COVID-19

infection who presented with abdomen and legs cutaneous hyperesthesia, aggravated by any kind of touch, and which spontaneously resolved 8 days later. Other kinds of cutaneous hypersensitivity (diabetes mellitus and vitamin B12 deficiency) were discarded in this case [15].

Moreover, a cohort study comparing patients with COVID-19 induced severe acute respiratory distress syndrome (ARDS) vs. non-COVID-19 ARDS showed that the COVID-19 group developed a higher rate of gastrointestinal (GI) complications such as bowel ischemia, transaminitis, GI bleeding, pancreatitis, Ogilvie syndrome, and severe ileus. Therefore, distinct features were hypothesized for either COVID-ARDS and non-COVID-ARDS [16]. Since gut motility is small-fibers mediated, a SFN is a plausible mechanism for GI involvement in SARS-CoV-2 infection [17].

Ultimately, neurological complications of COVID-19 are always updating. SFN occurrence in COVID-19 patients remains poorly understood; however, the existing literature helps the medical community to identify these newly reported manifestations.

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Conflicts of Interest

All authors declare that there is no conflict of interest.

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