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Review

COVID-19 and upper limb compression neuropathies: a review

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Abstract. *Background and aim:* COVID-19 may be asymptomatic or have a typical presentation with fever, cough, anosmia, lymphocytopenia. In some cases, it occurs with a "chimeric" presentation, with more subtle and ambiguous symptoms which may be initially misdiagnosed and are referred to in long covid conditions. A possible central and peripheral nervous system involvement has been recognized. We review the literature about the association between upper limb compressive neuropathies and SARS-CoV-2 infection. The purpose of this paper is to try to demonstrate a correlation between SARS-CoV-2 infection and canalicular syndromes of the upper limb. Although the respiratory manifestations of COVID-19 have been widely studied, there is emerging evidence suggesting potential associations between COVID-19 and various other health conditions. *Methods:* During November and October 2023, we carried out a systematic review to identify all scientific publications discussing the relationship between COVID-19 infection and compressive neuropathies of the upper limb. We followed PRISMA guidelines and searched in the PubMed database. We selected 24 articles. After a screening process, we keep 6 articles complying with inclusion criteria. *Results:* We found 24 patients who had developed canaliculopathies of the upper limb after COVID-19. The papers examined in this review did not hypothesize a clear pathological pathway, but rather examined a multifactorial one. Both SARS-CoV-2 infection and vaccination have been reported as possible causes of compression neuropathies. *Conclusions:* Nowadays, the world literature is not clear regarding the etiology of the association between upper limb compressive neuropathies and COVID-19. We conclude a causal relation may exist and needs to be further investigated. (www.actabiomedica.it)

Key words: COVID-19, canaliculopathies, upper limb compression neuropathies

Introduction

Since 2020, global health has had to face an important and challenging pandemic caused by Sars-CoV-2 infection, with acute-onset problems but also long-term sequelae. So, CoronaVirus Disease (COVID-19) has been the most important topics of medical research these two past years.

Several case reports and case series have been published associating SARS-CoV-2 with peripheral nervous system dysfunction. In most cases, olfactory and gustatory dysfunctions have been reported, as well as paralysis of the cranial nerves, especially of the VII one (1). Furthermore, a relationship with Guillain-Barrè syndrome has also been hypothesized (2).

The aim of this review is to establish any correlation between SARS-CoV-2 infection and upper limb compressive neuropathies providing a summary of studies investigating this association.

Materials and method

In November 2023 we carried out a systematic review to identify all scientific publications discussing the relationship between SARS-CoV-2 infection and compressive neuropathies of the upper limb. We followed PRISMA guidelines and searched in the PubMed database and in the Cochrane database as keywords ("COVID" or "Sars-cov-2") AND ("carpal tunnel syndrome" or "cubital tunnel syndrome" or "ulnar tunnel syndrome" or "compressive neuropathy"). We selected 20 articles, and we added 4 more due to research on other websites. After a screening process, we keep 6 articles complying with inclusion criteria. Before making data analysis, we submitted our review for registration to the National Institute for Health and Care Research (NIHR), but the PROSPERO program does not accept COVID-19 review studies.

Figure 1 shows the "PRISMA" flow chart.

We included prospective, observational, or experimental studies on the correlation between SARS-CoV-2 infection and vaccination and Cubital tunnel syndrome (CBTS) or carpal tunnel syndrome (CTS). Non-English language studies, papers discussing the correlation between COVID-19 and tarsal tunnel syndrome, and studies lacking objective outcome data were excluded. The six selected studies comprehended 3 case reports, and 3 case series.

Results

This literature review includes 6 studies with 21 patients, for a total of 18 carpal tunnel syndromes and 6 cubital tunnel syndromes. The aforementioned compression syndromes were new onset, except 6 CTS which were a worsening of an already present syndrome (3). Six patients were admitted to the Intensive Care Unit (ICU), and two vaccinated patients did not require hospitalization. The possible hospitalization of 13 patients is unknown, but three died due to COVID-19 (3).

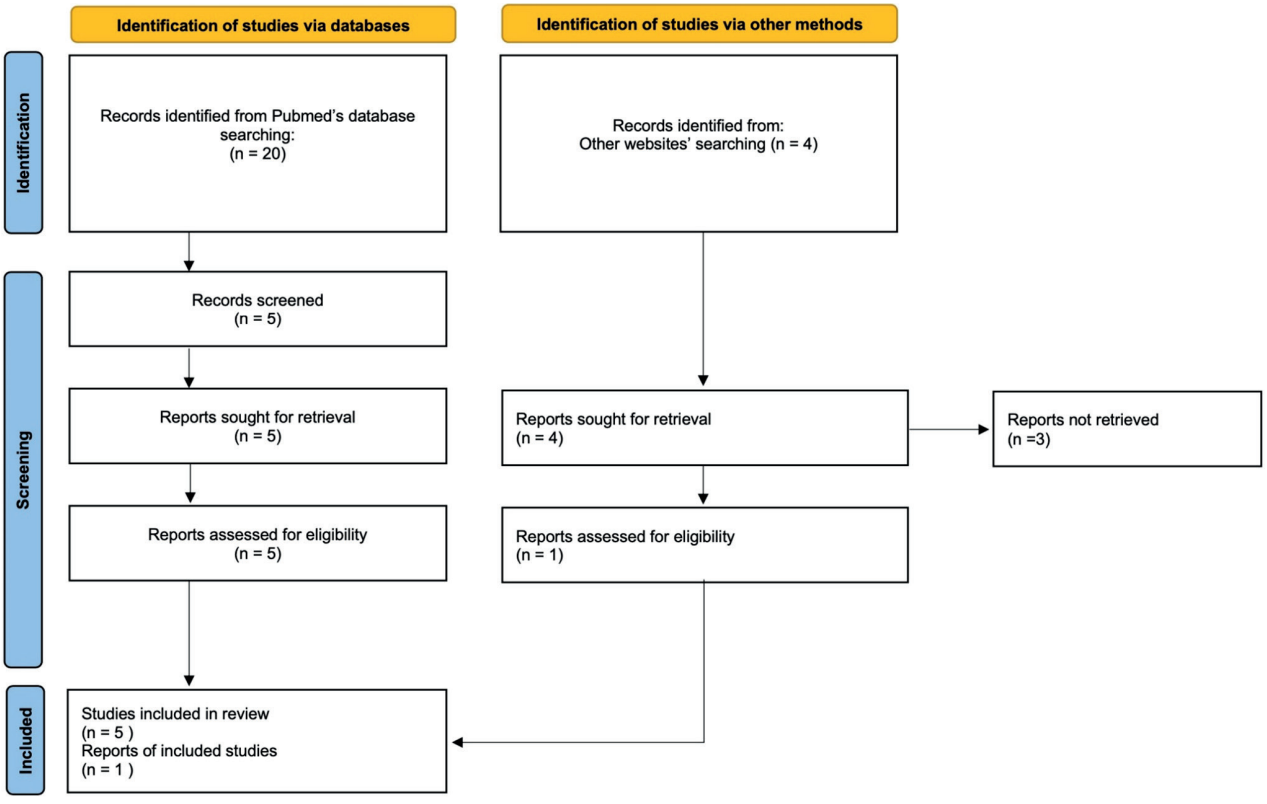

Figure 1. PRISMA Flow Chart.

In one patient, the CBTS appeared after vaccination with Spikevax® received one week before on the ipsilateral arm (4); while in another, a bilateral CTS was noted after vaccination with AZD1222 (5).

In the remaining cases, the onset or worsening nerve compression symptoms followed SARS-CoV-2 infection.

In nineteen patients the symptomatology improved after decompressive surgery, in one after oral therapy with Glìalia (Ultramicronized PEA 400 mg plus ultramicronized luteolin 40 mg) (6).

In three patients, Roncati and his group performed a histopathological examination on the tissue collected during decompressive surgery and found a myxoid degeneration of small collateral nerves without relevant inflammatory infiltrate both in the patients with Sarscov2 infection and in the vaccinated patient (4,7). Furthermore, in patients with COVID-19, Roncati et al. highlighted the absence of SARS-CoV-2 nucleoprotein at immunohistochemistry test for S100 (4).

Table 1 shows demographic data and nationality of studies included in this review.

Discussion

COVID-19 has required an enormous effort from the healthcare system in recent years to combat not only acute symptoms but also long-term sequelae. The typical presentation included fever, cough, anosmia, lymphocytopenia (8,9), but it is now well-recognized that COVID-19 also affects both the central and peripheral nervous system, causing neurological symptoms in more than 30% of patients (10,11).

The correlation between SARS-CoV-2 and upper extremity's compressive neuropathy is little studied in the literature, but the authors of the studies included in this review have highlighted a possible association. There is no evidence to confirm the pathophysiological mechanism that determines peripheral neuropathy of the upper limbs' nerves, but probably it is multifactorial.

SARS-CoV-2 can infect human cells due to Angiotensin-Converting Enzyme 2 (ACE2) receptors, which are present in many tissues, such as the lungs, heart, blood vessels, intestines, kidney, nervous system, and also synovium (12–14). Therefore, the virus can damage directly both synovial and nervous tissues.

The synovial tissue is present at the level of the osteofibrous tunnels, such as carpal or cubital tunnels. In a normal clinical condition, its function is to diminish friction between the tendon and the structures all around. It has been hypothesized in the literature that synovium may be the direct target of SARS-CoV-2 or it can be indirectly affected through immunocomplexes deposition (15,16).

Furthermore, the synovial tissue can be an indirect target of the virus through a type III hypersensitivity reaction with immunocomplexes deposition or through an autoimmune reaction due to cross-reactivity between viral antigens and synoviocytes (5,7). The synovial damage can cause reactive arthritis, associated by several authors with COVID-19 (17–19), with chronic irritation and thickening of synovial sheaths and subsequent compression of the nerves at the level of the osteofibrous tunnels (7).

The nervous tissue, however, can be damaged not only by direct damage due to viral neurotropism but also by the position of the patient while intubated. During the ICU stay, the patient is pronated to improve ventilation. Pronation determines a forced position of the upper limb with elbow flexion beyond 90°, pronation of the forearm, and abducted shoulder beyond 90° compressing especially the cubital tunnel with an increase in pressure and stretch on the ulnar nerve at this level, which may undergo ischemia or axonal damage (6,12,20).

Sayegh et al. (21) proposed prone positioning during the ICU stay as the predominant cause. Neill (22), on the other hand, has an opposite opinion, highlighting how only around 50% of pronated patients have developed neuropathies in the upper limb, attributing greater weight to direct viral damage.

Furthermore, COVID-19 is a systemic disease that in severe cases can lead to a cytokine storm and a hypercoagulable state with microthrombosis (6,12).

The acute and chronic inflammatory state due to proinflammatory cytokines contributes to nerve damage (3). It is known that the patient who survives COVID-19 and SIRS can manifest critical illness polyneuropathy (CIP), a generalized neuropathy that affects the extremities in critically ill patients immobilized for a long time (23–31).

Moreover, in literature, many studies have described the effect of interleukins, especially IL-2, on peripheral

Table 1. Demographic data and nationality of studies.

Author (first listed), Year	Study Design	N. of patient	Geographic Location	Covid infection / Vaccination	ICU admission	N. of Carpal Tunnel Syndrome	N. of Cubital tunnel Syndrome	Comorbidities	Therapy	Intraoperative or histological finding	Outcomes
De Vitis R., 2023 (3)	Case series	13	Italy	Infection	Not detected	13 (7 new onsets, 6 worsening)	-	Hypertension 7 Diabetes 1 Glaucoma 1 benign prostatic hypertrophy 1	Decompressive surgery	-	Clinical improvement 10 Death 3
Roncati L., 2021 (4)	Case series	2	Italy	Infection	Yes (2/2)	2	2	Sporadic hyperglycemic peaks 1 Low level of vitamin D 1	Decompressive surgery	Myxoid degeneration	Clinical improvement 4
Roncati L., 2022 (5)	Case report	1	Italy	Vaccination	no	-	1	Intolerant to salicylates and local anesthetics	Decompressive surgery	myxoid degeneration	-
Roncati L., 2023 (6)	Case report	1	Italy	Infection	yes	1	-	Chronic obstructive pulmonary disease, diabetes, chronic renal failure Crohn's disease	Decompressive surgery + Oral therapy with ultra micronized PEA and luteolin	-	Clinical improvement after oral therapy
Terhoeve C., 2021 (7)	Case series	3	USA	Infection	Yes (3/3)	-	3	Obstructive sleep apnea 1 Hypertension 3 Obesity 2 Idiopathic cardiomyopathy 1 Gout 1	Decompressive surgery	Flexor carpi ulnaris atrophied and pale 1 Ulnar nerve adherent to the floor 1	Clinical improvement 3
Tullie S., 2022 (8)	Case report	1	UK	Vaccination	no	2	-		Decompressive surgery	Swallen MN bulging through the transverse carpal ligament	Clinical improvement 2

nerves as a provoking factor of distress (32–34) and its important role in COVID-19 pathogenesis (35).

Due to the endothelial damage of SARS-CoV-2, instead, microthrombosi could cause a microangiopathy of the vasa nervorum, reducing nerve perfusion with a hypoxic state (12).

With the histological study, Roncati's group has certified the nervous damage on the one hand by describing the myxoid degeneration, on the other by attributing it to an indirect effect of viral infection due to the absence of SARS-CoV-2 antigens on immunohistochemistry test (4,7). Moreover, De Vitis et al. (3) suggest that a sudden neurological pain worsening in patients affected by CTS could be an early signal of SARS-CoV-2 infection and recognizing it can lead to quicker and better management of the patient's illness. Therefore, our review of the present literature suggests a correlation between SARS-CoV-2 and upper limb compressive neuropathies with a multifactorial etiology: the direct damage of the SARS-CoV-2 virus towards the nervous and synovial tissue, the immune-mediated damage on nerves and synovium, the pressure on the osteo-fibrous channels due to the prone position, the hypoperfusion caused by the microangiopathy, the pro-inflammatory effect of the cytokine storm are all factors that can contribute to the onset or worsening of carpal tunnel and cubital tunnel syndromes in genetically predisposed patients.

Conclusion

Nowadays, the world literature is not clear regarding the etiology of the association between upper limb compressive neuropathies and COVID-19. Nevertheless, our review allows us to hypothesize the multifactorial etiology of ulnar and median nerves suffering after SARS-CoV-2 infection detected in several cases.

In order to validate this hypothesis further well-designed studies are required.

Ethics: Not applicable as review of literature.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: Study Design: RA, LR; Collection of Data: FD, CM, MB; Data analysis/interpretation: FD, CM, RA, LR; Writing of the manuscript: FD, CM, MB. All authors have read and approved the final version of the manuscript, ensuring that questions related to the accuracy and integrity of any part of the work were appropriately analyzed and discussed.

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