

# PERIPHERAL NEUROLOGICAL COMPLICATIONS DURING COVID-19 PANDEMIC. SHORT REVIEW.

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## Abstract

Covid-19 disruption has led to a dramatic loss of patients infected with SarsCov2 agent. With a well reviewed vulnerability for the respiratory and cardiovascular systems, studies have expressed concern also for the neurological system. Lately, a number of cases regarding manifestations of central nervous- and peripheral nervous system have been reported, raising awareness of the high prevalence of prolonged neurological symptoms.

Although affecting a smaller number of patients in comparison to central nervous system, the peripheral nervous system disorders have impacted the quality of patients's life to a great extent. Infection with SarsCov2 has been connected with the development of several disorders like Guillain -Barre syndrome, or affection of cranial nerves with anosmia and dysgeusia being the most encountered. Furthermore, exacerbation of symptoms involving already established disorders like CIDP and Myasthenia Gravis have also been revealed. Nonetheless, neurological complications following vaccination against SarsCov2 infection can not be omitted.

Key-words: COVID-19 pandemic, peripheral neurological complications

## 1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiological agent responsible for Coronavirus Disease 19 (COVID-19). On clinical

evaluation, this disease mainly presented pulmonary and cardiovascular complications. The central nervous system (CNS) complications can also be present (like encephalopathy, stroke, seizures, meningoencephalitis, and acute disseminated encephalomyelitis). These manifestations are especially prevalent in elderly patients, due to their increased risk to develop neurological events [1].

Lately, literature has drawn a connection between Covid-19 and different afflictions of the peripheral nervous system (PNS) since the beginning of the pandemic, due to the increasing number of PNS manifestations in COVID patients without clearly established etiology. Recent studies have come to reinforce the initial hypothesis that the infection with SARS-CoV-2 has neurovirulence potential.

Therefore, we managed to target a variety of peripheral manifestations, including Guillain Barre syndrome and its chronic form of chronic inflammatory demyelinating polyneuropathy (CIDP), cranial neuropathies, adding the current findings.

## 2. The link between Covid-19- PNS manifestations.

If we take for example a retrospective study that took place in China, it has been shown that over 36,4% of hospitalised patients manifested neurological impairments [2].

In order to be internalized at cellular level, SARS-CoV-2 virus needs the following receptors:

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- *Receptor for Angiotensin converting enzyme-2*, facilitated by transmembrane protease for serine 2 – TMPRSS2
- *Receptor Basigin (BSG, CD147)* and *neuropilin-1 (NRP1)*, facilitated by TMPRSS11A/B, cathepsin B and L, and furin (FURIN) [3]

Neurodeterioration mediated through SARS-CoV-2 can be a consequence of downregulating ACE2-signaling with increase in ACE1 mediated neuroinflammation. ACE2 leads to an increase of nitric oxide (NO) and vasodilatation. Thus, reduced ACE2 activity leads to a reduction in NO. AT<sub>1</sub>R signaling also increases oxidative stress and neuroinflammation with the increase of IL-1, IL-6, IL-8, and IL-29, which are found in Covid patients. Sustained neuroinflammation is thought to be involved in neurodegeneration [4].

### 3. Peripheral nervous system involvement by Covid-19

Table 1 includes results showed in a large study conducted by Guerrero et al (2021) on 1414 patients about the manifestations of PNS in patients with Covid-19

Table 1. Prevalence of peripheral nervous system manifestations. [5]

<i>PNS impairment</i>	<i>Number of patients</i>
<i>Smell/Taste impairment</i>	<b>746</b>
<i>Facial palsy</i>	<b>13</b>
<i>Other cranial nerve afflictions</i>	<b>32</b>
<i>Peripheral nerve involving trunk and limbs</i>	<b>353</b>
<i>Visual impairment</i>	<b>9</b>
<i>Oculomotor impairment</i>	<b>14</b>
<i>Nerve roots and plexus disorders</i>	<b>145</b>
<i>Myopathic involvement</i>	<b>102</b>
<b><i>Total number of patients</i></b>	<b>1414</b>

#### 3.1 . Anosmia

Olfactory dysfunction such as anosmia, or more commonly known as loss of smell, is an early and frequent sign of infection with SARS-CoV-2. It can appear in the absence of other symptoms of rhinopharyngitis such as nasal congestion or rhinorrhea [6]

It is reported by approximately 80% of patients during the first week. Studies showed that the damage can be temporary, with complete recovery of smell after 30 days from the initial infection, the reason behind it being a competitive mechanism on the olfactory receptors and not a permanent injury to the cells. For reasons unestablished at the moment, olfactory symptoms are often correlated with dysfunction of taste such as ageusia (loss of taste) or dysgeusia (wrong perception of taste) [6]

#### 3.2. Dysgeusia

It has been of great scientific concern that ACE2 receptors reside in the epithelial tissue of taste buds and salivary glands in humans as well as in rhesus monkey. The presence of the virus in saliva of macaques before entering the pulmonary tract has been proven [7].

We can only assume that this leads to a dysfunction of salivary gland both in terms of quality and quantity, resulting in dysgeusia being an early symptom in patients affected.

On the other hand, it is widely known that the gustatory and olfactory functions are connected, therefore an impairment of the olfactory system can have a major effect also on taste by damaging the ACE2-expressing cells and chemoreceptors or by direct lesion of a cranial nerve involved in gustation: VII-nerve chorda tympani, IX, X [7].

An inflammatory response has also been suggested, with the interaction of Toll-like receptors in contact with the virus damaging the tissue. Inflammatory cytokines - IFN for example, can initiate apoptosis and development of abnormalities during turnover in taste cells [7].

Tissue hypoxia has also been presumed to be engaged in altering taste. Anemia and lack of proper oxygen transportation has been linked to dysgeusia. This can explain the presence of a mild symptom in severe cases with life-threatening hypoxia [7].

Another possible theory involves the levels of zinc, more explicitly hypozincemia and alteration of zinc homeostasis of oral cells, due to lowering its level through immune mechanisms during the infection. Apart from its demonstrated role in RNA polymerase activity in vitro, zinc is also regarded as an antiviral molecule [7].

### **3.3. Facial nerve palsy**

Peripheral facial paralysis is usually a result of a viral infection via an immune mediated- axonal demyelinating inflammatory reaction. In COVID-19, it can appear isolated or as a component of a syndrome such as Guillain-Barre syndrome. Patients can present with bilateral facial diplegia with absence of eye blink reflex or unilateral paralysis. It is typically diagnosed during the 10th day of the infection with SARS-CoV-2 [5,8].

Anxiety is often associated, therefore this clinical finding was proposed as a predisposing factor in developing peripheral facial paralysis [5,8]. When relating to mental health, the main psychiatric concern found is anxiety, to a great extent as a result of the pandemic that started in 2020. The pandemic included periods of lockdown, which is another exacerbating factor [9].

### **3.4. Guillain Barre syndrome**

Guillain Barre syndrome (GBS) is an immune-mediated polyradiculoneuropathy and its signs promptly appear 2-4 weeks after a viral infection. Patients typically present with muscle weakness, sensory or dysautonomous symptoms due to the demyelination and axonal change of the peripheral nerves or roots.

It has also been pointed out that it can present as cranial nerve disorder in the absence of muscle strength affection [10].

We should also note that SARS-CoV-2 PCR can remain positive for a significant period of time after COVID-19 resolution, so we must take into consideration a possible postinfectious case rather than parainfectious. Parainfectious GBS may be related to hyperimmune responses or direct toxic effect rather than molecular mimicry between the virus's epitope and the sensory or motor neurons, or an antibody attack on the myelin sheath or axon as seen in postinfectious cases [11]. Regardless of the etiopathogenesis, cures of intravenous Ig showed promising results in COVID-19 patients with parainfectious GBS [12].

### **3.5 Chronic inflammatory demyelinating polyneuropathy**

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired autoimmune

demyelinating polyneuropathy mainly presenting with loss of muscle strength in limbs. It affects large fibers, with both proximal and distal onset, symmetric or asymmetric onset and different variants regarding sensory or motor predominant forms. It has a slow course, with relapsing and aggravation of symptoms for over 8 weeks period [13,14].

It has been noted that SARS-CoV-2 infection can be a precipitating factor for clinical aggravation not only for development of its acute form- AIDP (Acute inflammatory demyelinating polyneuropathy) [15].

## **4. Vaccination and neurological manifestations**

Although released in December 2020 and many countries granting it emergency, vaccination anti SARS-CoV-2 shortly raised questions regarding the many neurological complications emerging post administration. Most common symptoms included myalgia, arthralgia, chills, fatigue which would only persist a short period of time. The most severe reported adverse effect is cerebral venous thrombosis, found more frequently in women [16].

Several cases of Bell's palsy have been described after Covid-19 vaccination, occurring especially in connection to mRNA vaccines. The study conducted by Shemer et al supports this theory, with Bells' palsy developing in the first 2 weeks after vaccination. The case responded well to oral corticosteroids [16]. Guillain Barre syndrome appearing two weeks post vaccine administration is another effect noted. Clinical and paraclinical features remain the same with proper response to immunotherapy. There were cases with facial diplegia as the only complaint [17].

## **CONCLUSIONS**

SARS-CoV-2 determines a wide spectrum of symptoms as far as peripheral nervous system concerns, varying from specific to nonspecific, impacting poorly or severely the quality of a patient's life. The most predominant features are impairment of smell, taste, eyesight, and weakness of the limbs. The neurological manifestations tend to appear in the developing state, after an average time of 1-2 days and more frequently in patients having severe comorbidities.

Moreover, it is thought to be provoked by secondary mechanisms rather than direct action of SARS-CoV-2. In a patient with previous history of CIDP, studies show that Covid-19 exacerbates the evolution. Vaccination for Covid-19 has also been linked to aggravate pre-existent PNS afflictions.

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