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Editorial

Acute-Onset Polyneuropathy Associated with SARS-CoV-2

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The severe acute respiratory syndrome coronavirus (SARS-CoV)-2 that turned up in late 2019 is highly transmissible and marks the third zoonotic introduction of a highly pathogenic coronavirus into the human population [1]. The emergence of SARS-CoV-2 has caused the ongoing coronavirus disease 2019 (COVID-19) pandemic and has a disruptive impact on health and socioeconomics. The SARS-CoV-2, concordant with SARS-CoV-1 and Middle East respiratory syndrome coronavirus, belongs to the beta-coronaviruses family, which mainly infects the human respiratory system [2]. As the spike protein of SARS-CoV-2 has a receptor-binding domain with a stronger binding affinity for the angiotensin-converting enzyme 2 (ACE2) in the host cell surface, SARS-CoV-2 has higher transmissibility than SARS-CoV-1 [3]. The fusion of cell and membrane of SARS-CoV-2 is further facilitated by cleavage processing of the spike protein via the transmembrane protease serine 2 protease and cathepsin L host protease [2].

COVID-19 has been described to be involved in multiple systems in humans with varying degrees of onset and severity. Despite the mounting reports of the neurological manifestation of COVID-19 [4], the underlying molecular mechanisms of the nervous system involvement remain elusive. The neuronal retrograde route has been considered as an essential pathway for SARS-CoV-2 entry to the central nervous system (CNS) [5,6]. In this scenario, SARS-CoV-2 infects neurons in the periphery and enters the CNS via the axonal transport machinery [6]. The hematogenous route is another proposed mechanism of neuroinvasion, which holds that SARS-CoV-2 can infect endothelial cells of the blood-brain barrier (BBB) and breach the BBB to allow the dissemination of inflammatory cytokines and immune cells into the CNS [5,6]. This hypothesis is supported by that the expression of ACE2 found in endothelial cells, pericytes, astrocytes and the epithelium of the choroid plexus [7]. Aberrant immune responses including extreme release of proinflammatory cytokines and chemokines called cytokine storm have be associated with neuropathy [5,6]. Additionally, endocrine mechanism can be considered as a potential route. SARS-CoV-2 induces ACE2 depletion through receptor endocytosis upon viral entry leaving the accumulation of angiotensin II whereby enhancing the proinflammatory effects and organ damage [8].

Cumulative evidence implicates that SARS-CoV-2 infection is associated with the development of Guillain-Barré syndrome (GBS) [9]. GBS which is clinically characterized by acute flaccid paralysis and/or sensory/autonomous dysfunction [10], is thought to be the prototype of postinfectious polyneuropathy usually developing 1 - 3 weeks after an acute infection [11]. In the absence of sufficiently sensitive diagnostic biomarkers, the diagnosis of GBS relies mainly on characteristic clinical presentations, and ancillary investigations such as laboratory examination and electrodiagnostic studies [10]. Albuminocytologic dissociation, i.e. an increased level of albumin with a normal cell count in the cerebrospinal fluid is a hallmark of GBS [10].

Given that *Campylobacter jejuni, Mycoplasma pneumoniae*, *Haemophilus influenza*, cytomegalovirus, Epstein-Barr virus, influenza A, varicella-zoster, hepatitis (A, B and E), Zika and Chikungunya viruses are typically associated with GBS [10], it is not surprising SARS-CoV-2 is suspected to play a role in the pathogenesis of GBS. While the exact mechanism by which SARS-CoV-2 causes acute polyneuropathy is still poorly understood, the occurrence of GBS in SARS-CoV-2 is mediated by an autoimmune response triggered by molecular

mimicry, leading to the production of antiganglioside antibodies [12]. Additionally, cytokine storm may contribute to the occurrence of acute polyneuropathy [13].

The cause-and-effect association between COVID-19 infection and GBS still cannot be assumed. The association between SARS-CoV-2 and GBS was initially postulated based on case reports, and subsequently was analyzed in a small cohort from Italy [14] and the French-Swiss border [15] where an unusual cluster of GBS cases occurred in the COVID-19 pandemic. An observational multicentre study from two Italian hotspot regions revealed that the incidence of GBS was increased during the COVID-19 outbreak [16]. These reports suggest a pathogenic link between SARS-CoV-2 infection and GBS. Contradictorily, an epidemiological and cohort study finds no epidemiological or phenotypic clues of SARS-CoV-2 being causative of GBS [17]. However, caution might be needed when interpreting results from this epidemiological study. A reduction of GBS incidence during the coronavirus epidemic may result from the lockdown measures, stricter hand hygiene, mask wearing, and social distancing. Missing of cases may also lead to the under-estimation of the association or causality. About one-third of patients have a mild form of GBS which are able to walk without assistance and can recover even left retreated [10]. Moreover, to prevent SARS-CoV-2 infection, the mildest cases with GBS might remain at home instead of going to hospital. To clarify whether SARS-CoV-2 is associated with GBS, large trials and standardized case-control studies are to be conducted.

GBS as a complication of SARS-CoV-2 infection should be diagnosed with caution as well. On one hand, GBS is a disease entity comprising several subtypes. The diagnosis of GBS can be difficult in patients with distinct variants. Hospitals and even neurologists may differ substantially in case ascertainment. Predefined case definition for GBS diagnosis and follows-up, and uniformity in the electrodiagnostic criteria applied is greatly necessary. On the other hand, the post-infectious nature of GBS is named onset of symptoms after the resolution of prodromal infections. The rapid onset of polyneuropathy after SARS-CoV-2 infection in some cases reflects para-infectious rather than post-infectious mechanisms [18]. SARS-CoV-2 associated acute polyneuropathy may not necessarily represent late-onset immune-mediated nerve injury; instead, peripheral nerves may be infected by COVID-19 directly.

Some patients with COVID-19 are critically ill and require care in the intensive care unit (ICU). The prolonged mechanical ventilation of patients with severe COVID-19 may increase the susceptibility to intensive care unit-acquired weakness (ICUAW). ICUAW may originate from either critical illness polyneuropathy (CIP), or critical illness myopathy (CIM), or a combination of both, which usually presents as flaccid quadriparesis, neuromuscular respiratory failure, diaphragmatic dysfunction, reduced muscle tone, normal or reduced deep tendon reflexes [19]. CIP and CIM is detected in 30% to 50% of ICU-admitted patients and the incidence may reach up to 70% in patients with systemic inflammatory response syndrome [19]. The molecular mechanisms of CIP and CIM mainly include the hyperreactive inflammation and dysfunction of peripheral nerves [19]. As mentioned above, virally-driven cytokine storm has been identified as a pathophysiological feature of COVID-19. In this regard, CIP and CIM tend to be more prevalent among patients with COVID-19 in ICU [20]. Early recognition of ICUAW is of crucial importance, considering that this entity is known to be associated with increased mortality and, usually, with a long incomplete recovery. However, there is no gold standard for the early diagnosis of ICUAW. Indeed, patients with COVID-19 are less likely to receive a complete clinical and/or neurophysiological evaluation, due to their isolation and consequently to the technical difficulties in performing instrumental examinations in the ICU. Several therapeutic modalities may mitigate the clinical and neurophysiological impairments whereby reducing the mortality and the recovery time, which include aggressive sepsis treatment, aggressive glucose lowering therapy, avoidance of high-protein nutrition, enteral feeding, and early mobilization [21].

The differentiation between GBS and ICUAW associated with SARS-CoV-2 infection is crucial for the treatment option, although it might be difficult especially when subject to pandemic-imposed restrictions in the routine clinical setting. First, electrophysiological studies are a valuable tool to aid differential diagnosis. Even if electrophysiological studies are performed for severe cases, examiners could not differentiate CIP from axonal GBS without evidence of albumino-cytological dissociation within the cerebrospinal fluid. Notwithstanding, lumbar puncture and electrophysiological studies are less likely to be applied on patients because of the high infection risk of COVID-19. Moreover, the performance of nerve conduction studies on patients in the ICU may be hindered by electrical interference. Second, hand-grip strength testing and the Medical Research Council sum score which are usually used by bedside for ICUAW diagnosis in awake and

cooperative patients seems not inapplicable to differentiate ICUAW from GBS and because they all present as muscles weakness. Thirdly, ICUAW superimposed on GBS is easy to be overlooked and be more difficult to diagnose. Last but not the least, because SARS-COV-2 is neurotropic, it may invade the meninges, etc., an increased level of proteins in cerebrospinal fluid may confound the discrimination between GBS and ICUAW.

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