Movement Disorders
CLINICAL PRACTICE

EDITORIAL COMMENTARY

Myoclonus and COVID-19: A Challenge for the Present, a Lesson for the Future

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On December 8, 2019, severe acute respiratory syndrome-coronavirus type 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), was first diagnosed in the city of Wuhan, in central China, and has since spread across the entire world. Although several countries have implemented measures to control the epidemic, because of the outbreak, on March 11, 2020, the World Health Organization declared the situation a pandemic. To date, confirmed cases are 28,584,158, and confirmed deaths are 916,955 (World Health Organization data, September 13, 2020).

Compared with the genetically related to SARS-CoV (the first pandemic threat of a coronavirus that emerged in late 2002) and Middle East respiratory syndrome coronavirus (another coronavirus that is not currently presenting a pandemic threat), SARS-CoV-2 is less deadly but far more transmissible and with a broad clinical spectrum.[1] This has become soon evident by the severity range of the respiratory illness, from asymptomatic to critical, but more important, it has been demonstrated by the striking incidence of extrapulmonary manifestations.[2] In fact, although the most common symptoms of COVID-19 include fever, cough, shortness of breath, and a substantial pulmonary disease (from pneumonia to acute respiratory distress syndrome), SARS-CoV-2 appears to affect other organs, including the nervous system. Apart from the well-known reported anosmia and dysgeusia, other reported neurological manifestations include encephalopathies, para/postinfective central nervous system (CNS) syndromes, cerebrovascular diseases (ischemic and hemorrhagic), and the prototypic infection-triggered neurological autoimmune disease Guillain-Barré syndrome.[3]

Nevertheless, a less expected and relatively unusual neurological complication has emerged as a consequence of COVID-19. In this issue of *Movement Disorder Clinical Practice*, 4 cases are reported in which myoclonus is the predominant, or almost isolated, clinical manifestation, following resolution of acute respiratory COVID-19 syndrome.[4–7]

All cases presented with multifocal/generalized myoclonus, predominantly action induced, mostly involving the limbs and affecting walking. Myoclonus was positive and negative in 3 cases[4–6] and sensitive to touch in 2 cases[5,7] and to auditory stimuli in 1 case.[7] Although in 2 cases myoclonus was isolated,[4,5] in the other 2 cases it was accompanied by cerebellar signs (such as saccadic intrusions, hypermetric saccades and ocular flutter on eye movement assessment, and ataxia)[6,7]; 1 patient also had cognitive dysfunction.[7] Electrophysiological testing was performed in 1 case[5] and revealed a combination of long-duration electromyographic bursts with no sign of cortical discharges time locked to individual myoclonic jerks, consistent with a subcortical origin of the myoclonus. In 3 patients, myoclonus improved following treatment with clonazepam or levetiracetam, drugs that are typically effective in cortical myoclonus rather than subcortical or spinal myoclonus.[4–6] In 1 case, the authors suspected a postinfectious etiology and started treatment with steroids followed by immunoglobulin infusion with a good response[7]; however, whether the improvement was related to a natural and self-limited evolution of the disease is not known.

The most fascinating aspect, common to all of the cases, is the delayed onset of the myoclonus with respect to the underlying infection and likely related to the presumed causative mechanisms.

SARS-CoV-2 can cause CNS damage by th following 3 main processes: (1) as a consequence of the associated pulmonary and systemic disease (eg, stroke and posthypoxic encephalopathies), (2) direct viral CNS invasion (via trans-synaptic or spread across the blood–brain barrier), and (3) postinfectious (immune mediate).[8] A posthypoxic cause is supported in 1 patient by the presence of cortical and brainstem ischemic brain lesions on magnetic resonance imaging, even though there was no respiratory or cardiac arrest.[4] A postinfectious possibility is supported in the remaining 3 cases by the lack of other potential causes identified and the improvement after immunotherapy.[5–7] Interestingly, analysis of cerebrospinal fluid (CSF) revealed no pleocytosis and no SARS-CoV-2 RNA in these cases, suggesting an immune-mediated pathogenesis. In 1 case there were signs of blood–brain barrier disruption together with elevated CSF interleukin-6 levels and increased interleukin-8 CSF/blood ratio involved in COVID-19 secondary hyperinflammation syndrome.[9]

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Several hypotheses exist on the pathophysiological mechanisms underlying postinfectious immune-mediated neurological disorders, including autoimmunity driven by molecular mimicry. For instance, Guillain-Barré syndrome is thought to be caused by an antibody-mediated attack on the nerve axolemma driven by molecular mimicry between microbial and axolemmal surface molecules. The molecular mimics are capable of inducing antibody responses against structurally identical glycans present on nerve gangliosides. In the case of COVID-19, the spike protein, which allows the viruses to penetrate host cells, interacts with the ganglioside dimers for anchoring to cell surface. As a result of this interaction, cross-reactivity between epitopes within the COVID-19 spike-bearing gangliosides and residues of surface peripheral nerve glycolipids is a very likely a possibility.[10] We might assume that similar mechanisms occur in postinfective myoclonus. However, the antigenic target to which antibodies are directed is not easily identifiable. In opsoclonus-myoclonus-ataxia (OMA) syndrome, a rare paraneoplastic/postinfective (immune-mediated) disorder, different autoantibodies binding to neurons or cerebellar Purkinje cells have been detected.[11,12] The brainstem and the cerebellum seem to be mainly implicated in the pathophysiology of OMA, and both are known to play a role in myoclonus.[13,14] In 2 of the COVID-19-related myoclonus cases described in this issue, as frequently occurs, myoclonus was associated with cerebellar signs, including eye movement abnormalities, and although no opsoclonus was observed, a parallelism with OMA syndrome was made. It is therefore tempting to speculate that, in postinfective myoclonus, an autoimmune process against cerebellar or brainstem neurons might change neuronal excitability and trigger mechanisms that generate myoclonic jerks. This might happen either (1) increasing the cerebellar excitatory output to the primary motor cortex through a disynaptic excitatory connection via the thalamus, leading to a hyperactivation of corticospinal tract neurons or (2) by abnormal activation of brainstem nuclei per se, or via cerebellar–brainstem projections, causing activity in descending pathways from the brainstem such as the reticulospinal or rubrospinal tract.

This hypothesis is also supported by the case with parainfectious saccadic oscillations and ataxia complicating SARS-CoV-2 infection, described by Wright and colleagues in this issue.[15] Ocular flutter and opsoclonus associated to ataxia, as observed in this case, is part of the OMA spectrum disorder even in the absence of myoclonus, and likely mediated by the same brain areas and mechanisms previously discussed.

The time required to develop an autoimmune response may explain the delayed onset of the postinfective myoclonus. On the other hand, it could be that chronic posthypoxic myoclonus is the consequence of abnormal plastic network rearrangement occurring after the brain insult and for which days or weeks are necessary.[16] The structures involved are very likely the same as in postinfective myoclonus, as supported by the sensorimotor cortex and brainstem ischemic lesions observed in the case presented in this issue.

The duration of the symptoms and response to treatment was variable among the cases, but all recovered well after a certain period of time. Nevertheless, whether we should expect chronic complications remains an open the question. In fact, it has been observed that in postinfectious disease of the nervous system, a self-sustained autoimmune response or an unrecognized persistent infection, even after the infection has been apparently cleared, might drive chronic inflammation with consequent nervous system damage and long-standing sequelae.[17]

In addition, other possible implications of SARS-CoV-2 infection need to be considered. A non-post-encephalitic parkinsonism case probably attributed to COVID-19 has been recently described,[18] and this has raised the question of whether SARS-CoV-2 CNS invasion might cause movement disorders. Also, SARS-CoV-2 RNA has been detected in CSF, although in a few cases so far.[19,20] Isolated anosmia/ageusia reported in COVID-19 suggests that, among others, the olfactory nerve is a potential way of entry in the CNS.[21] For instance, some studies performed in transgenic mice showed that both SARS-CoV and Middle East respiratory syndrome coronavirus administered intranasally may gain access to the brain and rapidly spread toward specific areas.[22] Following direct or indirect olfactory pathways connections, we might expect involvement of the amygdala, hypothalamus (especially the supraoptic nucleus), hippocampus, thalamus, and brainstem.[22] Moreover, because SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor to penetrate human cells, the presence of the ACE2 receptor in tissues determines viral cellular tropism in humans. It has been proposed that ACE2 is expressed in neurons, astrocytes, and oligodendrocytes and is highly concentrated in the substantia nigra, middle temporal gyrus, posterior cingulate cortex, and olfactory bulb.[22]

Considering this, a historical parallel with encephalitis lethargica seems to be inevitable. This spread across Europe and then the world around 1920, characterized in its acute form by excessive sleepiness, ocular motility disorders, fever, and movement disorders and followed by a chronic phase known as postencephalitic parkinsonism.[23] The latter would normally develop 1 to 5 years (or even more than a decade) after onset of encephalitis lethargica. Its etiology is still unknown, but an infectious and autoimmune process has been considered.[23] Von Economo conjectured that encephalitis lethargica was an influenza encephalitis,[23] and recently Mori[24] suggested that it entered the CNS via an olfactory vector.

Although this scenario might look less than reassuring, we should be confident that our clinical skills and the diagnostic and treatment tools at our disposal will help us to handle the current and possible future challenges.

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