Movement Disorders
CLINICAL PRACTICE

LETTERS: NEW OBSERVATIONS

Acute Cerebellar Ataxia and Myoclonus in SARS-CoV-2–Related Encephalopathy Responsive to Immunotherapy: A Case Series

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Within movement disorders occurring during or after coronavirus 2019 (COVID-19), myoclonus was observed both isolated and in the context of encephalopathy, as well as with ataxia, but without opsoclonus.[1] However, pathomechanisms remain poorly understood.

We report three adult male patients with mild symptoms of COVID-19 and subacute onset of ataxia and myoclonus arising after SARS-CoV-2 infection (Table 1), a condition recently identified as "SARS-CoV-2–related acute cerebellar ataxia and myoclonus" (ACAM) syndrome.[2] Here, ACAM syndrome occurred in the context of encephalopathy and, although literature reports that spontaneous recovery occurs after 2 months in almost all patients,[3] it was rapidly sensitive to intravenous immunoglobulin (IVIg) (case 1 and 2) or plasmapheresis (PEX) (case 3). Moreover, unlike previous reports, our patients did not have structural abnormality on brain magnetic resonance imaging (MRI) or cerebrospinal fluid (CSF) evidence of SARS-CoV-2, possibly as a result of transient or undetectable virus.[3]

Overall, neurological complications of COVID-19 mostly manifest within 3 weeks from respiratory or systemic symptoms, are multifactorial, and attributable to: (1) viral neurotropism, through vascular, transcribrial, and/or neuronal retrograde dissemination; (2) multiorgan dysfunction, through cardiorespiratory and metabolic impairment; and (3) autoimmune response, through molecular mimicry and cytokine involvement.[4] The latter seems to be the most likely hypothesis, based on the time interval and prompt response to IVIg/PEX. The spike protein might interact with the ganglioside dimers for anchoring the cell surface and, because of cross-reactivity, an antibody-mediated response against structurally identical glycans on nerve gangliosides may be triggered, thereby causing post-infectious symptoms.[4]

Myoclonus is a frequent hyperkinetic movement disorder. In COVID-19, it may reflect a combination of factors, including dysmetabolism, hypoxia, medication, neurotropism, and para- or post-infectious complication.[1,2,4] Notably, all previous cases were males, with a mean age of 53.2 ± 10.6 years and a mean time of onset of myoclonus and/or ataxia after COVID-19 of 18.0 ± 10.4 days.[2] Moreover, all earlier patients did not exhibit significant pathological findings at brain MRI; we also performed electroencephalogram and CSF, without abnormal results.

Four of six patients already published received IVIg and/or steroids, with clinical improvement. However, unlike these cases, our patients were older, moderately affected by respiratory symptoms, and with a slowly progressive neurological syndrome associated with encephalopathy (eg, behavioral changes, insomnia, confabulation, etc.), which was promptly sensitive to IVIg or PEX. As in the majority of previously described reports,[2] the timing of neurological presentation, the rate of clinical progression, the positive response to immunotherapy, and the absence of clinical recurrence after interruption of treatment seem to indicate an immune-mediated mechanism.

As known, fluorodeoxyglucose (FDG)-positron emission tomography (PET) is more sensitive in detecting functional brain changes compared to computed tomography or MRI; in case 3, FDG-PET showed a mild bilateral frontal-mesial hypometabolism, as previously reported.[5] However, given that the exam was not repeated after clinical resolution, a causal

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TABLE 1 *Main clinical, laboratory, and instrumental findings of the three patients with SARS-CoV-2–related ACAM syndrome*

Variable/exam	Case 1	Case 2	Case 3
Age, sex	70 years, male	63 years, male	56 years, male
COVID-19 symptoms	Fever, dry cough	Fever	Fever, cough
Interval between COVID-19 and neurological symptoms	15 days	2 days	15 days
Neurological examination	Mild vocal tremor, dysarthria, generalized involuntary jerks involving face, trunk, and arms, worsened with movements; absent deep tendon reflexes at the lower limbs; postural instability, wide-based stance, gait ataxia; saccadic intrusions and hypermetric saccades; intentional tremor, dysmetria, and movement decomposition, with superimposed myoclonic jerks; behavioral changes; no startle response	Jerky tremor affecting the four limbs, severe ataxia, and postural instability; diffuse myoclonus	Dysmetria at the four limbs, with superimposed involuntary jerky movements, and gait ataxia; deep tendon reflexes weak at the upper limbs and absent at the lower limbs; psychomotor retardation
Drug taken (daily dosage) and response	Clonazepam (2.5 mg/mL, 3 gtt tid) + valproic acid (300 mg tid); little improvement	Intravenous diazepam, followed by intravenously levetiracetam, without any improvement	None
Extensive blood test, including onconeural antibodies (Hu, Yo, Ri, Ma2, amphiphysin, and GAD)	Normal/unremarkable	Normal/unremarkable, including anti-GM1, anti-GM2, anti-GD1a, anti-GD1B, anti-GQ1b antibodies (both IgG and IgM)	Normal/unremarkable
Electroneurography	Diffuse axonal damage	Mild axonal neuropathy with sensory impairment; normal F waves	Length-dependent sensory axonal polyneuropathy
Brain MRI	Mild signs of chronic subcortical vascular disease	Chronic signs of vascular encephalopathy	Unremarkable
CSF analysis, including oligoclonal bands and RT-PCR for neurotropic viruses, and antibodies	Normal	Normal (performed twice)	Normal
^{18}F-FDG-PET	Normal	Not performed	Modest bilateral hypometabolism in the frontal-mesial region
Specific treatment and response	Intravenously immunoglobulins 2 g/kg; progressive clinical improvement till a near-complete recovery	Intravenously immunoglobulins 2 g/kg; after 5 days: disorientation, hallucinations, confabulations, increasing psychomotor agitation; the jerky movements rapidly worsened, till unremitting generalized myoclonus	Plasmapheresis, resulting in a rapid clinical improvement
Follow-up	1 month after, he was able to walk without aid; a subtle tremor impairing fine finger movements, which disappeared after 2 months	Myoclonus disappeared 25 days after the end of intravenously immunoglobulins; 3 months later, he was able to walk without any aid and fully autonomous	Not performed

ACAM, acute cerebellar ataxia and myoclonus; COVID-19, coronavirus disease 2019; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; RT-PCR, reverse transcription-polymerase chain reaction;^{18}F-FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography.

relationship cannot be established. The same holds true for the possibility of a post-infectious axonal damage at electroneurography.

Finally, unlike other cases who spontaneously recovered,[3] our patients showed a prompt response to immunotherapy. Overall, these findings further support the hypothesis of autoimmune mechanisms possibly underlying post-SARS-CoV-2 infection ACAM syndrome.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution. (2) Manuscript: A. Writing of the First Draft, B. Review and Critique.

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L.B.: 2A, 2B.
G.L.: 1A, 2B.

Disclosures

Ethical Compliance Statement: The study was performed in accordance with the Declaration of Helsinki of 1964 and its later amendments. Written informed consent was obtained from the patients. Ethical approval was waived because of the nature of the report itself, which was based on clinical examinations and within the diagnostic workup expected for these patients. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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