



Two COVID-19-related video-accompanied cases of severe ataxia-myoclonus syndrome

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ABSTRACT

Aim of the study. The pandemic state of COVID-19 has resulted in new neurological post-infection syndromes. Recently, several papers have reported ataxia-myoclonus syndrome following SARS-CoV-2 infection. The aim of this study was to present our two cases and compare them to previously reported cases.

Materials and methods. We present two video-accompanied new cases with ataxia-myoclonus syndrome following SARS-CoV-2 infection and discuss the studies published so far.

Results. Ataxia-myoclonus syndrome, isolated myoclonus, opsoclonus-myoclonus syndrome as post-COVID-19 syndrome following infection have been described in 16 patients (including our two cases). Patients have been treated with intravenous immunoglobulins and/or steroids except for 4 patients, which resulted in a significant improvement within 1–8 weeks.

Conclusions and clinical implications. The increasing number of patients with a similar symptomatology shows a significant relationship between COVID-19 infection and ataxia-myoclonus syndrome. The subacute onset of neurological symptoms after a resolved COVID-19 infection and prominent response to immunotherapy may suggest that the neurological manifestations are immune-mediated. Although recovery is highly possible, it may take several weeks/months, and clinicians should be aware of this diagnosis and the beneficial effects of immunological treatment administered as soon as possible.

Key words: COVID-19, SARS-CoV-2, ataxia, myoclonus, voice tremor

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The pandemic state of COVID-19, now having lasted more than 12 months, has resulted in new clinical manifestations and neurological post-infection syndromes of SARS-CoV-2 infection, involving both central and peripheral nervous systems [1]. The most commonly occurring in the acute phase of infection include ischaemic and haemorrhagic strokes, cerebral venous thrombosis, posterior reversible encephalopathy (PRES), and those of autoimmunological origin presenting as Guillain-Barre, Miller Fisher syndromes and Bickerstaff's encephalitis, acute demyelinating encephalomyelitis (ADEM), acute necrotising encephalopathy (ANE), generalised myoclonus, acute transverse myelitis, limbic encephalitis, and miscellaneous encephalitis [1, 2]. Recently, several papers have reported ataxia-myoclonus syndrome following SARS-CoV-2 infection (Tab. 1) [6–12]. We present

two video-accompanied new cases of this presumably auto-immunological syndrome.

Case 1

A 49-year-old male, without co-morbidities besides lumbar surgery eight years previously, was admitted to hospital with involuntary movements of limbs and trunk accompanied by severe instability (he was almost unable to stand or walk independently). Eleven days before admission, the patient had experienced an episode of one-day fever (38° C) with excessive sweating without any other infection symptoms. These symptoms resolved spontaneously after a few days and he was not tested for COVID-19 infection. One week later, he developed hand tremors, jerky movements of all limbs,

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Table 1. Characteristics of patients with ataxia-myoclonus syndrome associated with COVID-19

Article	Age/ /gender	COVID-19 severity of infectious stage	Neurological symptoms	Time between acute infection and appearance of neurological symptoms	Treatment/outcome
Our cases	49/M	Mild/ asymptomatic	• Myoclonus • Ataxia • Voice tremor	11 days	Methylprednisolone 1 g/day, 5 g total followed by oral prednisone 60mg/day for two weeks; significant improvement after three weeks
	62/M	Mild	• Myoclonus • Opsoclonus • Ataxia	11 days	IVIg 0.4 g/kg for five days, methylprednisolone 1g/day, 5g total followed by oral prednisone (1 mg/kg/day) for two weeks with gradual dose reduction; significant improvement after two weeks
Emamikhah et al. 2021 [6]	51/M	Mild	• Myoclonus • Opsoclonus • Ataxia • voice tremor	2 weeks	Clonazepam 0.5 mg 4x1, levetiracetam 500 mg 2 x 1, IVIg 2 g/kg, total dose 150 g; complete recovery after four weeks
	54/M	Moderate	• Myoclonus • Ataxia	4 days	Levetiracetam 2,000 mg/day, sodium valproate 1,000 mg/day IVIg in total dose 100 g; Partial recovery after one week
	52/M	Moderate	• Myoclonus • Ataxia • Voice tremor	16 days	Sodium valproate 1,000 mg/day, clonazepam 1mg 4 x 1; partial recovery after two months
	42/F	Mild	• Myoclonus • Ataxia • Voice tremor	10 days	Sodium valproate, clonazepam; no data
	44/M	Mild	• Myoclonus • Opsoclonus • Ataxia • Voice tremor	3 days	Sodium valproate, clonazepam, IVIg; complete recovery after two months
	52/M	Mild	• Myoclonus • Ataxia • Voice tremor	3 weeks	Clonazepam, IVIg in total dose of 100 g; significant improvement after four weeks
	39/M	Severe	• Myoclonus • Opsoclonus • Ataxia • Voice tremor	10 days	Levetiracetam, sodium valproate, clonazepam, IVIg, dexamethasone; no data
Wright et al. 2020 [7]	79/M	Mild	• Opsoclonus • Ataxia • Cognitive impairment	13 days	No data; improvement of cognitive function and resolution of eye movement abnormality after 19 days; death after 27 days due to general physical decline
Dijkstra et al. 2020 [8]	44/M	Mild	• Myoclonus • Ataxia • Voice tremor • Transient ocular flutter (no evident opsoclonus) • Cognitive impairment	1 week	Methylprednisolone 1 g daily for five days, IVIg 0.4 g/kg for three days; partial recovery after 15 days, full recovery within two months
Schellekens et al. 2020 [9]	48/M	Mild	• Myoclonus • Ataxia • Saccadic intrusions of eye movement (no opsoclonus)	13 days	Levetiracetam; partial recovery within two months
Foucard et al. [10]	83/M	No data	• Myoclonus • Opsoclonus • Ataxic dysarthria • Confusion	10 days	IVIg 0.4 g/kg for five days, steroids 1g/day for five days, diazepam; significant improvement after one week
	63/M	No data	• Myoclonus • Ataxia • Ataxic dysarthria	6 weeks	IVIg 0.4 g/kg for five days; significant improvement after one week
Shah et al. 2020 [11]	Middle aged/M	No data	• Myoclonus • Opsoclonus • Ataxia • Ataxic dysarthria	3 weeks	Methylprednisolone 1 g/day, sodium valproate 20 mg/kg/day, clonazepam 2 mg/day, levetiracetam 2 g/day; recovery within one week
Grimaldi et al. 2020 [5]	72/M	Moderate	• Myoclonus • Ataxia • Ataxic dysarthria	17 days	IVIg 0.4 g/kg/day for five days, methylprednisolone 1 g/day for five days; recovery within two weeks

and posture and gait instability with diarrhoea lasting for three days. Because of these symptoms, he was admitted to the Emergency Unit (EU). On neurological examination, he presented dysarthria with voice tremor, generalised myoclonus exacerbated by intentional movements, bilateral limb ataxia and wide-based gait (see video, segment 1). In the EU he was treated with clonazepam 1 mg i.v., biperiden 2 mg p.o. and levetiracetam 500 mg i.v. but with no effect. Nasopharyngeal RT-PCR test for SARS-CoV-2 was negative. Brain computer tomography (CT) and magnetic resonance imaging (MRI), as well as a general examination of cerebrospinal fluid (CSF), were normal. Antibodies testing (blood and CSF) for NMDAR, VGKC, *Borrelia burgdorferi* IgG and IgM antibodies were negative. Viral neurological panel (Adenovirus, CMV, EBV, HSV-1, HSV-2, VZV, Enterovirus, Parechovirus, Parvovirus B19, HHV-6, HHV-7) and soluble antigens in CSF were also negative. Oligoclonal bands in CSF showed type 4 according to the Charcot Foundation. Blood laboratory tests for onconeural antibodies (anti-Hu, anti-Ri, Anti-Yo), anti-nuclear antibodies (ANA) were negative, and vitamin B12, B1 and folic acid were within normal ranges.

Due to the infection episode 11 days before admission, serum level of SARS-CoV-2 IgG and IgM antibodies testing was performed, with a positive result for IgG (IgG 38.6 AU/ml, IgM 2.2 AU/ml). Treatment with intravenous methylprednisolone (1g/day for five consecutive days, 5 g in total) followed by oral prednisone (60 mg/day) for two weeks and motor rehabilitation resulted in a significant improvement after three weeks (see video, segment 2).

Case 2

A 62-year-old male with a history of arterial hypertension, benign prostatic hyperplasia, and kidney stones, was 11 days after resolution of a COVID-19 infection confirmed with a nasopharyngeal RT-PCR test, admitted to the EU with imbalance, gait disturbance, generalised tremor and ataxia. On neurological examination, he had jerky oscillatory movements of eyes (diagnosed as opsoclonus), generalised myoclonus and ataxia. This made the patient unable to stand or walk independently (see video, segment 3). Head MRI with MRI-angiography as well as general CSF examination were normal. Fast CSF tests for the presence of viral (CMV, Enterovirus, HSV-1, HSV-2, HHV-6, Parechovirus, VZV) and bacterial (*E. coli*, *H. influenzae*, *L. monocytogenes*, *N. meningitidis*, *S. agalactiae*, *S. pneumoniae*) antigens were negative as well. Auto-immune encephalitis antibodies in serum (NMDAR, AMPAR 1 and 2, CASPR 2, LGI-1, GABA-B receptor), *Borrelia* IgM and IgG antibodies and onconeural antibodies (anti-Hu, anti-Ri, Anti-Yo, anti-PNMA2, anti-CV2, anti-amphiphysin) were not detected. Ganglioside antibody panel was negative. Chest and abdomen CT were normal. Tumour markers (CA-125, CA-19-9, CEA) were negative. Electroencephalography (EEG) on admission showed bilateral theta waves in the

central and frontal areas which resolved at release. Treatment with intravenous methylprednisolone (1g/day, 5g in total) was initiated followed by intravenous immunoglobulins (IVIg) for five days (0.4 g/kg) and oral prednisone (1 mg/kg/day) for two weeks with gradual dose reduction. The administered treatment and motor rehabilitation resulted in a significant improvement after two weeks (see video, segment 4).

Discussion

Understanding regarding the neurological complications of SARS-CoV-2 infection is still limited. Brain damage can be caused by hypoxia, direct brain invasion of the coronavirus, or post-infectious autoimmune mechanisms. The hypothesis of a possible neuroinvasiveness of SARS-CoV-2 causing neurological symptoms during the acute state of the infection has been proposed [2]. Widespread neuronal ACE2 expression in brainstem cardiorespiratory neurons, motor cortex, the raphe nucleus, and others may suggest the direct invasion of virus, which may result in diverse neurological symptoms.

While ACE2's role in the brain is incompletely understood, this diverse central nervous expression pattern may provide SARS-CoV-2, and other CoVs, with a 'port of entry' into the brain [3]. On the other hand, opsoclonus-myoclonus syndrome (OMS) is a rare disorder of apparently autoimmune paraneoplastic or parainfectious aetiology. This presents with opsoclonus, limbs and trunk myoclonus, and ataxia. Paraneoplastic OMS is generally observed in patients with breast adenocarcinoma or small cell lung carcinoma, while parainfectious OMS has been observed in patients with HIV, *Mycoplasma pneumoniae*, *Salmonella enterica*, rotavirus, cytomegalovirus, human herpesvirus 6, hepatitis C, and *Rickettsia conorii*. Treatment with corticosteroids or IVIg is usually successful [4]. Therefore, its aetiology is considered to be autoimmunological.

The subacute onset of neurological symptoms after resolved COVID-19 infections (however, only 11 days after) in both presented cases, and the prominent response to immunotherapy, may suggest that the neurological manifestations are immune-mediated. However, it is difficult to entirely exclude a direct viral effect of COVID-19, given that we know that acute COVID infection can benefit from steroids. The brain ¹⁸F-FDG-PET (fluorodeoxyglucose Positron Emission Tomography) study of a patient with ataxia-myoclonus syndrome associated with COVID-19 performed by Grimaldi et al. showed a diffuse pattern compatible with encephalitis and especially cerebellitis. Moreover, nerve tissue immunostaining with serum and CSF showed the presence of autoantibodies directed against the nuclei of Purkinje cells, striatal and hippocampal neurons. The titre of the IgG autoantibodies in serum and CSF was high (serum 1/25,000, CSF 1/96) and both in serum and CSF the same intensity and reactivity were observed at the same IgG concentration [5]. These observations may confirm the autoimmune origin of the post-COVID-19 ataxia-myoclonic syndrome.

Ataxia-myoclonus syndrome, isolated myoclonus, OMS as post-COVID-19 syndrome following infection have been described in several case series and reports (Tab. 1). The increasing number of patients with a similar symptomatology suggests that there may be a significant relationship between infection and the described neurological symptoms, adding SARS-CoV-2 to the list of possible pathogens. Because recovery is highly possible, although it may take several weeks/months, clinicians should be aware of this diagnosis and the beneficial effects of immunological treatment administered as soon as possible.

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