78-year-old woman with opsoclonus myoclonus ataxia syndrome secondary to COVID-19

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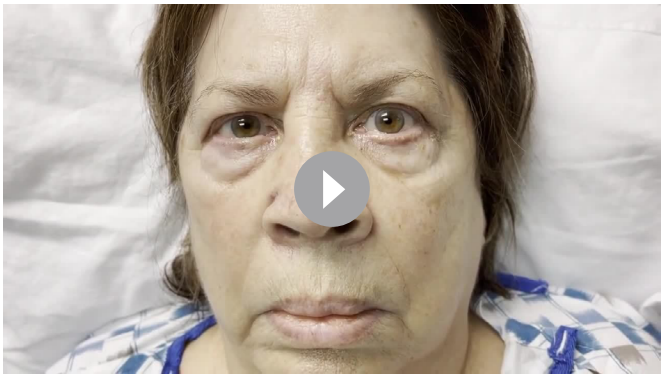
DESCRIPTION

A 78-year-old woman presented to the hospital with generalised weakness and inability to walk 2 weeks after testing positive for COVID-19. Her COVID-19 symptoms were primarily limited to the upper respiratory tract. She received prednisone 40 mg for 5 days at home and also took non-steroidal anti-inflammatory drugs frequently. Her medical history was only significant for hypothyroidism and she took armour thyroid routinely. In the emergency department, her vital signs were stable. She was awake, alert and oriented. Neuro-ophthalmic examination revealed intermittent saccadic rapid conjugate horizontal and vertical eye movements in the horizontal and vertical planes, consistent with opsoclonus (video 1). No gaze palsy or visual field defects were present. Diffuse high amplitude myoclonus was noted in all four extremities that were worsened with activity. No motor or sensory abnormalities were identified. Mild myoclonic twitching was also noted in the face, predominantly near the angle of the mouth on the right side. The patient was unable to stand on her feet due to ataxia. Cardiac and pulmonary examinations were normal. Her laboratory workup revealed normal electrolytes and no hepatic or renal dysfunction. A CT scan of the head was negative for any intracranial pathology. CT scan of the chest, abdomen and pelvis were unremarkable (figure 1). MRI of the brain demonstrated no mass lesion, any evidence of encephalitis or ischaemia. A lumbar puncture was performed, and the results are shown in table 1. A detailed evaluation for infectious disease and paraneoplastic antibodies, including antineuronal nuclear antibody type 2 (ANNA-2) were negative. The patient was diagnosed with opsoclonus myoclonus ataxia syndrome (OMAS) secondary to SARS-CoV-2 infection. She was treated with intravenous immunoglobulin (0.4 g/kg/day for 5 days) and systemic corticosteroid (methylprednisolone 1 g/day for 5 days). The opsoclonus improved after 3 days of therapy. However, due to the persistence of disabling myoclonus and ataxia, levetiracetam (1 g/day for 7 days) was initiated with a significant improvement in her symptoms. After a period of 10 days, she was discharged to a nursing home. The dose of levetiracetam was decreased to 500 mg/day on discharge.

OMAS is characterised by a variable combination of opsoclonus (irregular, involuntary and arrhythmic eye movement in horizontal, vertical and diagonal directions), myoclonus (brief, sudden, lightning-like spasms of several muscles leading to jerky movement) and ataxia (inability to stand or ambulate). In addition, a change in mental status may also be present. OMAS is a rare disease, seen more frequently in children than adults. Paraneoplastic (occurring with neuroblastoma or ganglioneuroblastoma) and parainfectious OMAS are the most common aetiology among children.[1] OMAS in adults is an ill-defined syndrome and is often caused by paraneoplastic antibodies (anti-Ri, anti-ANNA-2 antibodies in the setting of extracranial solid tumours).[2] The lung and breast carcinomas appear to be the most commonly identified malignancy in these patients.[2] Parainfectious OMAS is less common in adults. In a significant number of patients, a definite aetiology cannot be identified (idiopathic OMAS), and these patients typically have a better prognosis than patients with paraneoplastic OMAS.[3] Here, we present the case of a 78-year-old woman who developed OMAS 2 weeks after suffering from COVID-19.

Since the beginning of the pandemic, researchers have reported central nervous system (CNS) involvement with SARS-CoV-2. In general, the mechanisms of CNS injury can be divided into three categories, (a) direct viral invasion causing encephalitis, (b) secondary to systemic diseases, such as hypoxia with severe respiratory compromise or cerebrovascular accidents with vascular injury and thrombosis and (c) due to autoimmunity.[4] Several cases of OMAS following SARS-CoV-2 infection has been recently reported.[5 6] Foucard *et al* reported a total of seven patients, three of whom demonstrated signs and symptoms consistent with OMAS (opsoclonus, myoclonus and ataxia simultaneously present).[5] The other patients manifested myoclonus and ataxia without opsoclonus. These patients presented between 10 days and 6 weeks following COVID-19 diagnosis.

The exact pathogenesis of OMAS is presently unknown. OMAS is thought to be an autoimmune mediated inflammatory phenomenon in patients with COVID-19.[7] A favourable response to immunosuppressive medications is also suggestive of an immunological mechanism. Direct viral invasion has been theorised as a possible aetiology for neurological manifestations in COVID-19. There are reports of isolating viral particles from the brain tissue on autopsy studies.[8] Similarly, some authors have reported a positive PCR for SARS-CoV-2 in the CSF.[9] In contrast, the majority of literature reported negative SARS-CoV-2 PCR from CSF.[10] However, it is crucial to emphasise that a negative PCR does not necessarily rule out viral invasion.



Video 1 Neuro-ophthalmic examination showing intermittent saccadic rapid conjugate horizontal and vertical eye movements in the horizontal and vertical planes, consistent with opsoclonus. Mild myoclonic twitching was also noted in the face, predominantly near the angle of the mouth on the right side.

Many patients with OMAS did not have any evidence of encephalitis and demonstrated normal CSF and MRI findings. Therefore, a parainfectious process rather than actual tissue invasion is more likely responsible.[10] COVID-19 can be associated with cytokine storm, and a cytokine mediated neuronal dysfunction may play a role in the pathobiology of OMAS.[11] Another hypothetical explanation for the occurrence of COVID-19 associated OMAS could be molecular mimicry. The spike protein of SARS-CoV-2 not only binds to the cell surface ACE 2 receptor but also to ganglioside dimers present on the cell surface. There is cross-reactivity between the epitopes present in the glycolipids of the peripheral nerves and SARS-CoV-2 spike protein-bearing ganglioside. This similarity is the likely pathogenic factor for COVID-19 associated Guillain-Barré syndrome.[12] Whether such a mechanism is the culprit for OMAS, and the exact cellular component against which the antibody may be directed, is currently unknown.[13]

The brainstem and cerebellum appear to be involved in the pathogenesis of OMAS. In fact, autoantibodies against cerebellar neurons and Purkinje cells have been detected in patients with OMAS.[14] The dysfunctional cerebellar neurons cause myoclonus either by sending increased excitatory signals to the motor cortex or by stimulating brain stem motor nuclei by direct projections from the cerebellum.[13]

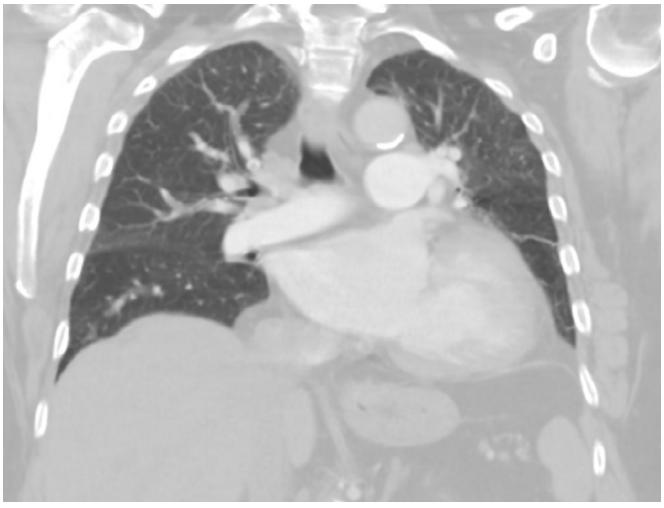


Figure 1 Coronal view of the chest CT did not show any significant pulmonary abnormalities.

Table 1 Cerebrospinal fluid (CSF) study result

Parameters (normal value)	Results
CSF opening pressure (10–18 cm of H_2O)	15 cm of H_2O
Colour	Clear
White cells (0–5 $\times 10^9$/L)	5
Mononuclear cells (50%–90%)	60%
Polynuclear cells (0%–10%)	40%
Glucose (40–70 mg/dL)	69 mg/dL
Total protein (15–45 mg/dL)	55 mg/dL
VDRL test	Non-reactive
Lyme IgM and IgG (immunoblot)	Not detected
Saint Louis encephalitis virus IgM and IgG	<1:1
Human herpes virus 1 and 2 PCR	Negative
Gram stain and culture	Negative
Cryptococcal antigen	Negative
Anti-ganglioside GQ1B antibody (<1:100)	<1:100
Paraneoplastic antibodies	Negative

VDRL, venereal disease research laboratory.

COVID-19 associated OMAS typically follows a benign course. Similar to previously reported cases, our patient also improved with Intravenous Immunoglobulin (IVIG) and systemic corticosteroid therapy. Most reported cases of OMAS due to COVID-19 typically received high dose systemic steroid (mainly intravenous methylprednisolone) and IVIG for 3–5 days.[5] Antiepileptic therapy has also been used, and our patient was significantly benefitted from the levetiracetam.[6 15]

With the ongoing pandemic, similar patients are likely to be encountered at different healthcare settings by clinicians of diverse backgrounds. Knowledge of this rare entity will ensure appropriate triage and management of these patients.

Learning points

- Opsoclonus myoclonus ataxia syndrome (OMAS) is a rare neurological complication of COVID-19.
- OMAS likely results from an autoimmune phenomenon that affects the neurons and Purkinje cells of the cerebellum.
- The prognosis is favourable as most patients recover with Intravenous Immunoglobulin (IVIG), systemic corticosteroid and antiepileptic therapy within a few weeks.

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Disclaimer Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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