Para-Infectious Opsoclonus Myoclonus Syndrome with COVID-19

Sir,

'Opsoclonus–myoclonus syndrome' (OMS) in adults or 'Opsoclonus–myoclonus-ataxia syndrome' (OMAS) is a classic neurological disorder with chaotic multidirectional spontaneous eye movements and multifocal myoclonus. It is most commonly idiopathic, although paraneoplastic and parainfectious causes have been established. OMS has recently been associated with COVID-19 as a parainfectious complication. We report the first case of OMS with COVID-19 from India.

A 53-year-old woman developed fever and breathing difficulty. She was diagnosed with COVID-19 after a positive nasopharyngeal swab for SARS-CoV-2 RT_PCR. She developed severe COVID-19 pneumonia, which was treated with non-invasive ventilation. Twelve days later she became confused and drowsy. On day 14, when she became stuporous, she was referred to us. She had a past history of hypothyroidism on thyroid supplementation. On admission, she was drowsy, normoxemia and had opsoclonus with multifocal myoclonus [Video 1]. She was electively intubated for altered mental status.

The initial differential diagnoses were Opsoclonus-myoclonus syndrome (OMS) due to COVID encephalitis, autoimmune or paraneoplastic encephalitis, Hypoxic/toxic-metabolic encephalopathy or an acute disseminated encephalomyelitis (ADEM). Blood results showed an elevated CRP (266.5 mg/L), D Dimer (2270 ng/ml), and elevated TSH (25.44 uIU/ml) with normal thyroid antibodies. MRI brain showed scattered cerebellar infarcts with a normal MR angiogram and venogram [Figure 1]. The dose of levothyroxine was increased. CSF study was normal and NMDAR, VGKC and paraneoplastic antibody evaluation were negative.

She was started on antibiotics, 500 mg of IV Methyl Prednisolone (IVMP) for 5 days along with three cycles of plasmapheresis. Her sensorium improved over the next 3 days and she became conscious without any focal deficits. A follow-up MRI on day 10 showed no interval changes. She was transitioned to oral steroids, but her sensorium deteriorated after 4 days. She was given 1 gm IVMP for the next 5 days and she completed 5 cycles of plasmapheresis. She improved once more for 5 days and had a repeat sensorial deterioration on oral steroids. Another 3 gm of IVMP was given over 3 days. Rituximab 500 mg was also administered. She improved 48 hours after Rituximab, but had persistent behavioural changes, which improved over the next 10 days. She received another cycle of Rituximab 500 mg.

On day 32, she had no focal neurological deficits (mRS 0) and was discharged on two anticonvulsants (oral Levetiracetam and Clobazam) and Prednisolone 1 mg/kg/day. Due to the temporal relationship to COVID-19 illness, with OMS, a para-infectious OMS was diagnosed.

'Opsoclonus–myoclonus syndrome' refers to chaotic multidirectional back-to-back multidirectional conjugate saccades without an inter-saccadic interval, accompanied by ataxia, encephalopathy, and myoclonus. To fulfil the diagnostic criteria for OMS, at least three of four supportive findings are required, namely a) Opsoclonus b) Myoclonus and/or ataxia, c) Behavioral change and/or sleep disturbance d) Tumorous conditions and/or presence of antineuronal antibodies.[1] True seizures are extremely rare in OMS, occurring in <1% of cases, although the multifocal myoclonus and encephalopathy can be clinically mistaken for epilepsy.[2] Either brainstem 'saccadic burst cell' disinhibition or cerebellar nucleus disinhibition may result in opsoclonus. Oculomotor 'saccadic burst cells' may become hyperexcitable due to intrinsic increased neuronal excitability or due to reduced inhibition from omnipause cells. Alternatively, dysfunctional cerebellar Purkinje cells lower their inhibition of the fastigial nucleus, which in turn over-inhibit the omnipause neurons. Thus, the saccadic burst neurons are freed from their omnipause inhibition and are free to oscillate in every direction.

A third of adult OMS is paraneoplastic (39%), but the majority are idiopathic or para/post infectious or rarely

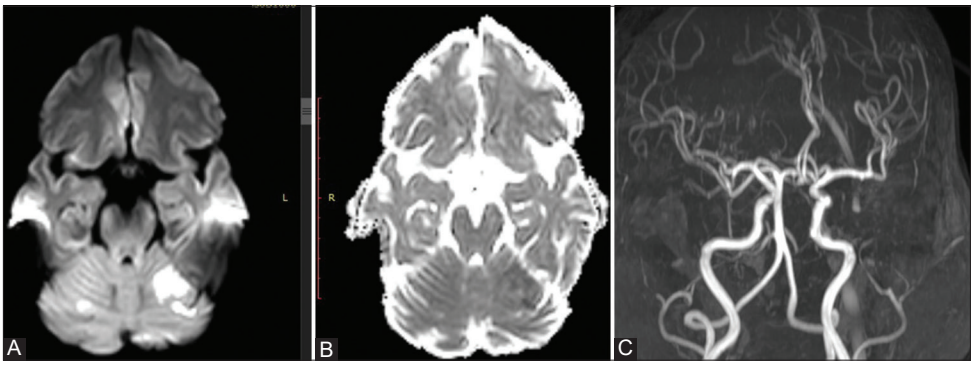

Figure 1: Panel A and B; Diffusion and ADC images showing a small left cerebellar infarct. Panel C. Intracranial MRI showing normal intracranial vesses

Table 1: Cause of OMS

Idiopathic
Paraneoplastic
Lung
Breast
Autoimmune
NMDA
GAD 65
Para/post infectious
COVID-19
HIV infection (including HIV seroconversion illness or with immune reconstitution after initiating antiretroviral therapy)
Mycoplasma pneumonia
Cytomegalovirus
Human herpesvirus 6
Hepatitis C
Psittacosis
Salmonella
St Louis encephalitis
Rickettsia conorii.
Metabolic
Hyperosmolar nonketotic diabetic coma intoxication
Toxic
Cocaine
Toluene
Phenytoin
Venlafaxine

toxic-metabolic [Table 1]. Click or tap here to enter text.[3,4] Infections associated with OMS include HIV, Mycoplasma pneumonia, cytomegalovirus, human herpesvirus 6, hepatitis C, and so on. Autoimmune causes include NMDA encephalitis. OMS following COVID-19 illness or COVID-19 vaccination is rare and overshadowed by other neurological manifestations.[5-7] Rarely, pre-existing OMS can also be exacerbated by COVID-19.[8]

Although both humoral and cell-mediated immune mechanisms are implicated in the pathogenesis, only 11% of patients have onconeural (surface or intracellular antibodies), even in paraneoplastic adult OMS. The most common antibody detected is ANNA-1. The vast majority of OMS patients have no detectable neuronal antibodies and are seronegative.

In the absence of a definite anti-neuronal antibody or CSF pleocytosis, we used published criteria to diagnose a possible autoimmune encephalitis.[9]

COVID-19 is associated with viremia in the initial phase and a strong host immune response after the first week of illness. In fact, a dysregulated host immune response against the viral infection is primarily responsible for most of the complications and multi-organ dysfunction.[10] Patients may have high levels of inflammatory markers such as C reactive protein, lactate dehydrogenase, ferritin, D-dimer, and Interleukin-6 concentrations. There may also be a higher level of autoantibodies such as antinuclear antibodies, antineutrophil cytoplasmic antibodies, and ASCA immunoglobulin A antibodies. Those who develop a *de novo* autoimmune response may have a worse prognosis and outcome.[11]

COVID-19 can present with a *de novo* OMS as a para-infectious neurological manifestation. Combination immunomodulatory treatment with IV methylprednisolone, IVIg or plasma exchange are often used. OMS may require prolonged immunosuppressive treatment due to its propensity to relapse on medication withdrawal. Additionally, anticonvulsants such as Levetiracetam, Sodium valproate, or Clonazepam may be required to control myoclonus. Long-term treatment with oral steroids, Mycophenolate mofetil or azathioprine may be required. OMS occurring with COVID-19 is treated with the same treatment regimens as classical OMS. Second-line therapies such as rituximab or cyclophosphamide are used for recurrent disease, and relapses should be treated as early as possible. Early treatment with Rituximab in recalcitrant disease can improve outcomes and reduce disability. To the best of our knowledge, this is the first case report of COVID-19 associated with OMS from India.

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Conflicts of interest

There are no conflicts of interest.

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