POST-INFECTIONOUS SARS CoV-2 OPSOCLONUS MYOCLONUS ATAXIA SYNDROME

Jodi Nelson D.O.,a
Gregory Blume M.D.,a
Saurabh Bansal M.D.,c
Jacqueline Kaufman APN,b
Florence Woods, APN,b
Xiaojun Zhang, M.D.,a
Jorge Kattah, M.D.,a

a Department of Neurology, University of Illinois College of Medicine Peoria, Illinois
Neurologic Institute. OSF St. Francis Medical Center, Peoria, Illinois
b Department of Neurology, Illinois Neurologic Institute OSF St. Francis Medical Center, Peoria, Illinois
Department of Internal Medicine, University of Illinois College of Medicine Peoria, OSF St.
Francis Medical Center, Peoria, Illinois

Corresponding Author:
Jorge C Kattah, M.D.
Department of Neurology, University of Illinois College of Medicine Peoria, St. Francis Medical Center. 530 NE Glen Oak Ave, Peoria, IL, USA 61637
Telephone: 309-655-2702, FAX 309-655-2040
Email: kattahj@uic.edu

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Abstract

Background: The opsoclonus-myoclonus-ataxia syndrome (OMAS) represents both a pathophysiology and a diagnostic challenge. Even though the diverse etiologies likely share a common mechanism to generate the ocular, trunk and limb movements, the underlying cause may be a paraneoplastic syndrome, as the first sign of cancer, or may be a post-infectious complication and thus, outcome depends on identifying the trigger mechanism. A recent hypothesis suggests increased GABA_A receptor sensitivity in the olivary-ocular motor vermis (OMV)-fastigial nucleus (FN) - premotor saccade burst neuron circuit in the brainstem. The management therefore, will focus on immunosuppression and modulation of GABA_A hypersensitivity with benzodiazepines.

Methods: We serially video recorded the eye movements at the bedside of one patient with SARS-CoV-2 IgG serum antibodies, but twice-negative nasopharyngeal reverse transcriptase polymerase chain reaction (RT-PCR). We tested cerebrospinal fluid (CSF), serum, and nasopharyngeal samples. In addition to an MRI brain and CT chest-abdomen pelvis. We treated our patient with clonazepam and high-dose solumedrol, followed by a rituximab infusion after her formal eye movement analysis 10 days later.

Results: The recordings throughout her acute illness demonstrated different eye movement abnormalities. While on high-dose steroids and clonazepam, she had initially macrosaccadic oscillations (MSO), followed the next day by brief ocular flutter during convergence; ten days later she had bursts of opsoclonus during scotopic conditions with fixation block with otherwise normal eye movements. Concern for a suboptimal response to high-dose Solumedrol motivated an infusion of Rituximab, which induced remission. An investigation for a paraneoplastic etiology was negative. CSF testing showed elevated neuron specific enolase. Serum IgG to SARS-CoV2 was elevated with negative reverse transcriptase polymerase change reaction (RT-PCR) nasopharyngeal testing.

Conclusion: A recent simulation model of macro-saccadic oscillations, and OMAS, proposes combined brainstem/cerebellar pathology due to increased GABA_A receptor sensitivity. Here, we report one patient with elevated CSF NSE, macro-saccadic oscillations, ocular flutter and OMAS as a SARS-CoV2 post-infectious complication. Opsoclonus emerged predominantly with fixation block and suppressed with fixation, providing support to modern theories on the mechanism responsible for these ocular oscillations involving cerebellar-brainstem pathogenesis.
Introduction:

The opsoclonus-myoclonus-ataxia syndrome (OMAS) is the result of diverse etiologies with a common mechanism responsible for the ocular, trunk and limb movements. The underlying cause may be a paraneoplastic syndrome, as the first sign of cancer, or may be a post-infectious complication[^4]. A recent hypothesis suggests increased GABA_A receptor sensitivity in the olivary-ocular motor vermis (OMV)-fastigial nucleus (FN) - premotor saccade burst neuron circuit in the brainstem[^5]. The management therefore, will focus on immunosuppression, search for a possible underlying malignancy or infectious etiology and modulation of GABA_A hypersensitivity with benzodiazepines.

Case

A 57-year old female without significant past medical history presented with a day of speech changes and persistent jerking movements in late February 2021. Of note, her son and husband had SARS CoV-2 pneumonia with positive SARS CoV-2 nasopharyngeal RT-PCR test obtained at the local city public testing facility and performed at our Institution in January 2021, after a family trip to Georgia. On 2/1, she had a negative SARS CoV-2 nasopharyngeal RT-PCR test. No family history of ataxia or abnormal movements. Review of systems was negative for night sweats, unintentional weight loss, fevers, rashes, respiratory complaints, or change in olfaction or taste. Her recent mammogram was normal.

On examination, she had a non-rhythmic truncal titubation (Video 1), hyperekplexia, pronounced limb and truncal ataxia, intention tremor and dysdiadochokinesis. Cranial nerves, strength, sensation to pinprick, vibration, and proprioception were intact with symmetric deep tendon reflexes without pathologic reflexes. On hospital day 4, before steroids were started, her MOCA score was 25/30 (-3 delayed recall, -1 for copying, -1 floor of the hospital). Her eye exam showed unsteady visual fixation with macrosaccadic oscillations (Video 2 Section 1), recorded the day after her first dose of 1 G of intravenous Methylprednisolone (i.v. MP) and convergence-induced brief ocular flutter (Video 3) recorded the following day, after two days of 1 G, i.v. MP.

CSF testing: Clear, colorless fluid with 1 nucleated cell and 1 red blood cell, normal protein (35.5 mg/dL) and glucose (57 ng/dL). Her CSF NSE was elevated at 34 ng/dL (normal <15 ng/dL). Gram stain was negative for organisms. Cytology was negative for malignancy. Flow cytometry was negative for abnormal lymphoid population. AMPA-A, Amphyphysin, Anti-glial nuclear, anti-neuronal nuclear type 1-3, CASPR 2 IgG, CRMP-5, DPPX, GABA-B-R, GAD65, GFAP, glycine R, IgLON5, LGI1 IgG, mGlur1, NIF, NMDAR, and Purkinje cell cytoplasmic antibodies were negative (Mayo Clinic Laboratory). Oligoclonal bands were absent.

On admission, she had a second negative SARS CoV-2 nasopharyngeal RT-PCR test, but she had positive serum testing: IgG to SARS CoV-2 virus 6.9 S/C (normal <1/4 S/C),, the lactic acid
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3.8, CRP 0.75 (normal <0.5 mg/dL). Normal serum testing: GQ1B antibodies, Mayo Clinic PAVAL panel, CBC, CMP, ANA, ENA, and ESR. Negative nasopharyngeal testing: SARS CoV-2 RT-PCR (tested twice), influenza, parainfluenza, RSV, mycoplasma, bordetella pertussis, bordetella parapertussis, chlamydia pneumoniae, rhino/enterovirus, metapneumovirus, and adenovirus. A chest x-ray on admission showed patchy opacities, but no ground glass opacities, in the right lung representing pneumonia.

MRI of the brain w/wo contrast on hospital day 2 showed modest caudate nuclei hyperintensities in T2 Fluid attenuated inversion recovery (FLAIR) sequence and DWI but without restricted diffusion. A 30-minute EEG on hospital day 2 and an overnight EEG from days 3-4 were negative for seizures or epileptiform discharges. Neuropsychological evaluation on hospital day 3 (prior to starting Solumedrol) showed symmetrically impaired fine motor dexterity speed bimanually. Her encephalopathy manifested as slower mental processing speed, particularly in performing visual-construction tasks with a heavier executive demand, mental flexibility, visual memory, or non-contextual verbal encoding. We treated her with 1000mg IV Solumedrol for 5 days and clonazepam 0.25mg BID and 0.5mg at night. She improved after her second dose of Solumedrol. She was able to ambulate more steadily, and her ocular flutter was only present with convergence whereas before it was also present with vertical and horizontal saccadic eye movements. We discharged her on day 5 with an oral steroid taper.

Ten days after discharge, she had residual, albeit improved, limb and trunk ataxia, and the family noted that occasional eye movements present behind closed eyelids, which were present previously, has resolved. We recorded the eye movements using the Otometrics Chartr-200 goggles with the head fixed (Trustup, Denmark). She had normal eye movements and steady fixation in response to visual targets; however, she had intermittent bursts of multidirectional, fast, large amplitude saccades without an intersaccadic interval, characteristic for opsoclonus, exclusively with fixation block (Figure 1, Video 2 section 2). These oscillations persisted throughout the five-minute recording. We did not see these movements with eyelid closure at a quick glance. This was concerning for suboptimal response to steroids, therefore, we initiated further workup and administered a 750mg Rituximab infusion. CT chest abdomen pelvis was negative for cancerous lesions but showed pulmonary ground-glass opacities in the right lower lung that appeared improved from her CXR showing a larger opacity limited to the right lower lung 19 days earlier. Serum ANA, ENA, CA-125, CEA were negative. She showed significant improvement two weeks after the Rituximab infusion. The examination and video recording four weeks after symptom onset and hospitalization were normal; the patient returned to work.

Discussion:

The striking myoclonus and hyperekplexia represent a dramatic, but potentially curable, neurologic syndrome. In our patient, the initial eye abnormalities were more severe prior to the
first bedside eye movement video n (recorded after the first high-dose of steroids on hospital day 4). Macro-saccadic oscillations (MSO) were present primarily during vertical saccade refixations (Video 2, first section).

Whereas the etiology of OMAS in children and older adults is paraneoplastic, in younger adults it is often post-infectious. Regardless of age, brain imaging may be normal. Also, opsoclonus does not occur in natural or experimental lesions in primates[1]. Additionally, neuropathological examination in paraneoplastic opsoclonus typically lacks definitive macro- or microscopic abnormalities[1, 2]. In particular, the pause cells, initially proposed as the principal OMAS cell – group target, showed no microscopic abnormalities[3]. However, one patient with paraneoplastic opsoclonus had sparse gliosis and mild lymphocytic infiltrates in the fastigial nucleus (FN) and inspired the first OMAS computer model[2].

The current theoretical mechanisms to explain the ocular oscillations in these patients involve simultaneous neuron dysfunction in the brainstem and cerebellum[1, 4, 5]. The brainstem circuitry theoretically involves omnipause neuron (OPN) inability to regulate post-inhibitory rebound (PIR) from oscillating excitatory (EBN) and inhibitory burst neuron (IBN) circuits in the pons[6-8]. Disruption of this mechanism causes back-to-back saccades without intersaccadic intervals (Figure 1). Although not documented with Video-nystagmography (VNG) in this case, convergence/divergence refixations (known to suppress OPN)[7, 9] caused transient ocular oscillations in our patient. They likely represent ocular flutter, and thus support a brainstem role as well (Video 3), recorded on day 5 of admission, and the second day of high-dose steroids)[7].

In addition to altered membrane excitability in the EBN/IBN circuit and PIR, disinhibition of the FN causes increased, non-rhythmic eye oscillations. In humans, lesions of the fastigial nucleus cause saccade hypermetria[1, 7, 10]; our patient had similar saccades (Video 2, Section 1). In a study, serum from three out of seven patients with opsoclonus had anti-Purkinje cell antibodies with punctate staining in the cerebellar molecular layer, presumably directed against the parallel-fiber-Purkinje cell synapse[11]. Moreover, PET scan hyperactivation of cerebellar nuclei supports the potential role of deep cerebellar nuclei[12].

A recent simulation model[5] based on opsoclonus related to anabolic steroids, which modulate GABA_A receptors, implies mistimed neuronal activity in the brainstem and cerebellum in the pathogenesis of opsoclonus. This may explain the findings in our patient[5, 13]. In their mathematical model, the steroids increased sensitivity of the GABA_A receptor leading to increased GABA inhibition of neurons in the FN, and OPN. FN inhibition did not allow saccades to stop on target. Delayed OPN reactivation caused a return movement with no saccadic interval, driven by PIR. The varying degree of FN, OPN inhibition leads to a continuum of movements including MSO, ocular flutter, and opsoclonus; our patient had these same eye movements. This suggests a simultaneous brainstem-cerebellar mechanism[2, 5, 11, 12].
As a potential example, using abnormal eye movements in OMAS, one could draw an analogous explanation for the head and truncal tremor in our patient have a similar etiology. Irregular oscillations of motoneurons innervating the trunk and neck may originate in the cerebellum, particularly regions of the FN that control movement of axial musculature [5, 14] (Video 1). In our case, elevation of NSE (a neuronal lesion marker) and the absence of white matter MRI changes [15] suggests Purkinje cell, cerebellar deep-nuclei and pontine neurons rather than cerebellar outflow tracts as the cause of the abnormal eye movement and the symmetric limb and truncal ataxia. Of note, elevated NSE did not preclude full recovery of function after treatment. In general, alteration of function in OMAS responds well to management and this may be predicted by the fact that PET CT has shown cerebellar deep nuclei hyperactivity, and not hypoactivity as one would expect with irreversible injury.

The waveform of the oscillations in these patients includes large amplitude back-to-back saccades and, as seen in this case, MSO and flutter [16]. The oscillations remained with eyelid closure, as noted by the patient’s family. In a previous instance, they occurred during REM sleep [17]. In some cases, they developed in lateral gaze [18] and in some instances triggered by position changes [19]. Interestingly, we recorded overt opsoclonus with fixation-block ten days after symptom onset (Figure 1); this suggests that PIR may be fixation-suppressed and equivalent to previous studies that showed persistent opsoclonus with eye closure [1, 3]. Therefore, vision may be important in restoring or hastening the proper timing of neuronal activation in the EBN/IBN/omnipause neuron circuit.

Treatment typically includes combinations of steroids, IVIG, and plasma exchange. However, others used azathioprine, rituximab and mycophenolate mofetil with success [20, 21]. We chose Rituximab in our case since it has a longer half-life than IVIG. Rituximab improved opsoclonus-myoclonus syndrome in children with or without neuroblastoma [22]. The mechanism may be through CD20- B cell population normalization; however, an exact explanation is unclear. While there is minimal data on adults, we could apply the pediatric experience to adults. Our patient’s VOG two weeks later showed steady fixation in all testing conditions, possibly reflecting the beneficial effect of Rituximab on the presumed post-viral OMAS antibody. The paraneoplastic syndrome often precedes diagnosis of cancer and improves at slower pace after tumor resection or cancer specific treatment [3]. Idiopathic/non-paraneoplastic etiologies appear to be monophasic with hastened recovery following immunotherapy, as in our case [23].

Our case highlights a SARS CoV-2 para/post-infectious OMAS in the setting of subclinical pneumonia. Recent reports suggest that OMAS may be an infrequent post –SARS-CoV-2 neurologic syndrome [24-27]. The bilateral caudate hyperintensities on MRI, high NSE and encephalopathy suggest additional CNS targets [28, 29]. CSF may be normal in patients with OMAS, [22, 25, 29] however; to our knowledge, NSE was not tested. We add to previous post-
SARS-CoV2 OMAS reports with serial clinical, ocular motor and immunologic findings before and after Rituximab-associated remission. Serum immunologic testing is valuable when confronting unexplained neurologic abnormalities in patients exposed to SARS CoV-2 and negative nasopharyngeal RT-PCR testing.
REFERENCES

Figure and Video Legends:

Figure 1. Video-Oculography Recording of primary eye position with fixation block. Note a burst of conjugate, non-rhythmic, 40- deg amplitude saccades without intersaccadic interval (A), with a frequency of 7 Hz, and a vertical component. There are also oscillations with intersaccadic interval and one square wave jerk.
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Video 1. Note truncal oscillations and Finger to nose dysmetria with open and closed eyes

Video 2. Section 1 the patient has vertical saccadic oscillations during saccade refixations; the Video recorded one dose of high-dose steroids. Section 2 recording with fixation block, ten days later shows irregular saccade bursts, they are primarily horizontal conjugate, fast saccades, with a small vertical component. (We obtained Figure 1 during this video recording).

Video 3. Obtained 24 hours after Video 1; it shows brief ocular flutter during convergence
Statement of Authorship

1. Category 1:
   a) Conception and design
      Jodi Nelson, D.O.
      Jorge C Kattah, M.D.
   b) Acquisition of data
      Jodi Nelson, D.O.
      Gregory Blume, M.D.
      Saurabh Bansal, M.D.
      Jacqueline Kaufman, APN
      Florence Woods, APN
      Xiaojun Zhang, M.D.
      Jorge Kattah, M.D.
   c) Analysis and interpretation of data
      Jodi L Nelson, D.O.
      Jorge C Kattah, M.D.

2. Category 2:
   a) Drafting the manuscript
      Jodi L Nelson, D.O.
      Jorge C Kattah, M.D.
   b) Revising it for intellectual content
      Jodi Nelson, D.O.
      Gregory Blume, M.D.
      Saurabh Bansal, M.D.
      Jacqueline Kaufman, APN
      Florence Woods, APN
      Xiaojun Zhang, M.D.
      Jorge Kattah, M.D.

3. Category 3:
   a) Final approval of the completed manuscript
      Jodi Nelson, D.O.
      Gregory Blume, M.D.
      Saurabh Bansal, M.D.
      Jacqueline Kaufman, APN
      Florence Woods, APN
      Xiaojun Zhang, M.D.
      Jorge Kattah, M.D.