Opsoclonus-Myoclonus Syndrome Secondary to West Nile Encephalitis

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INITIAL PRESENTATION

Chief Complaint

Abnormal eye movements

History of Present Illness

A 52-year-old man with a history of degenerative joint disease, migraines, and viral encephalitis 15 years prior presented to the Emergency Department with two weeks of progressive back pain, maculopapular rash, fever, night sweats, headache, and photophobia following a trip to Indiana. A CT brain without contrast was unremarkable. A subsequent MRI brain with and without contrast and MRI spine were performed, and no causative pathology was identified. An atraumatic lumbar puncture showed normal glucose concentration, increased protein concentration (49 mg/dl; reference range 15 to 45 mg/dL), and 109 nucleated cells, 63 neutrophils, and 31 lymphocytes. He was started on intravenous vancomycin, ceftriaxone, and acyclovir and admitted due to concern for meningitis. On hospital day one he developed involuntary abnormal eye movements, which were intermittent until hospital day two, when they became constant and debilitating.

Past Ocular History

- Hyperopia with astigmatism both eyes
- No history of trauma or ocular surgery
- No ophthalmic medications

- Opsoclonus-Myoclonus Syndrome secondary to West Nile Virus Encephalitis

CLINICAL COURSE

Based on the patient's clinical findings of chaotic, macrosaccadic eye movements with myoclonus, he was diagnosed with opsoclonus-myoclonus syndrome. An extensive systemic work-up was performed, as detailed above. The immunology team was consulted for therapeutic options for his opsoclonus-myoclonus syndrome in the setting of active West Nile virus encephalitis. Initially, they recommended 1 gram of methylprednisolone daily for three days, but the patient was unable to tolerate this due to severe psychosis. He went on to receive three days of intravenous immunoglobulin (IVIg) with minimal improvement. Five days after the last IVIg dose, he was given 1 gram of IV rituximab with a second dose given 10 days later. His opsoclonus and myoclonus started to improve after the first rituximab dose and were markedly improved after the second dose. Following discharge, he was maintained on rituximab and mycophenolate mofetil (Cellcept). At his one-month follow-up visit, his ophthalmic exam had returned to normal, and by his three-month follow-up visit, he was able to ambulate without aid.

DISCUSSION

Introduction

Opsoclonus-myoclonus syndrome (OMS), alternately known as opsoclonus-myoclonus ataxia or dancing eye syndrome, is a disorder characterized by involuntary, multidirectional eye movements with myoclonic jerks of the limbs and trunk with or without ataxia (1). Eye movements in opsoclonus have a high frequency and large amplitude. The saccades may be vertical and horizontal and lack an intersaccadic interval.

Etiology/Epidemiology

OMS is exceedingly rare, with an estimated incidence of 1 per 5 million people per year (2). The etiologies of OMS may be divided into three main categories: paraneoplastic, para-infectious, and idiopathic. The type of primary malignancy identified in paraneoplastic cases varies based on age. In children, roughly 50% of OMS may be attributed to neuroblastoma or tumors of neural crest origin (3). A recent review of 116 adult onset OMS cases in the literature reported 51% of cases were paraneoplastic in etiology (4). Female adults under 40 years of age are most likely to develop paraneoplastic OMS secondary to ovarian teratoma, whereas adults over 40 years most often develop OMS in the setting of small cell lung cancer, breast cancer, or ovarian malignancies (5). In the second category, para-infectious OMS has been described in association with streptococcal infection, Lyme disease, varicella zoster, HIV/AIDS, and others (6). Most other cases of OMS are idiopathic, although rare cases also have been reported in association with toxic and metabolic abnormalities (4).

West Nile virus is a flavivirus first described in Uganda in 1937. It is spread by mosquitoes, with most cases in the United States presenting in the summer and fall. According to the Centers for Disease Control and Prevention, one in five people infected with West Nile virus develop symptoms. Of these people, one in 150 develop a CNS illness (*e.g.,* encephalitis and meningitis), with a 10% mortality rate (7). At timing of this publication, only eight cases of OMS have been reported due to West Nile virus (8).

Pathophysiology

The pathophysiology of OMS remains largely unknown but is thought to be related to dysfunction in the generation of saccades. There are two leading hypotheses. The first points to cerebellar dysfunction. In general, the cerebellum is responsible for fine tuning of saccadic eye movements, including saccadic speed, accuracy,

and neural integration (1). Purkinje cell dysfunction in the cerebellar vermis could cause disinhibition of neurons within the caudal vestigial nucleus leading to saccadic dysregulation. The second hypothesis implicates damage to omnipause cells, which normally inhibit saccade-generating burst neurons in the parapontine reticular formation and prevent unwanted saccades. Both posited mechanisms result in uncontrolled, involuntary horizontal, vertical, and torsional saccadic intrusions that persist even during sleep and with eyelid closure (1 ,6).

It is worth clarifying that OMS is not directly due to infection, neoplasm, or metabolic insult. Rather it is thought to be due to immune response to neoplasm, infection, or other cause (5). Our patient had a past history of viral encephalitis. It is likely that his immune system was primed by cryptic neuronal antigens exposed during the inflammatory response of that prior episode.

Signs/Symptoms

Patients may complain of blurred vision or oscillopsia due to the large amplitude and high frequency saccades (10-15 Hz with opsoclonus (https://collections.lib.utah.edu/details?id=180305)). Additional symptoms of poor balance or falls are due to associated cerebellar ataxia, postural tremor, or myoclonus (6). A Mayo Clinic review of 21 patients with adult-onset OMS reported that myoclonus of the extremities with opsoclonus to be the most common sign at presentation, followed by craniocervical myoclonus and brisk deep tendon reflexes. A flu-like prodrome was reported in 29% of patients (4).

Ocular flutter (https://collections.lib.utah.edu/details?id=180316) is another form of saccadic intrusion that may also be seen prior to development of opsoclonus or in association with OMS. It is characterized by involuntary, small amplitude, high frequency (10-15 Hz) horizontal eye movements (1 ,4). Both ocular flutter and opsoclonus may occur with myoclonus and ataxia. The pathophysiology of ocular flutter is also poorly understood (1).

It may be difficult to distinguish these saccadic intrusions from nystagmus. An important point to remember is that nystagmus *always* has a slow phase during the eye movements, whereas saccadic intrusions do not.

Testing/Laboratory work-up

Adult patients younger than 40-years-old are more likely to have idiopathic or infectious OMS. Aggressive investigations for occult neoplasm or paraneoplastic antibodies may not be necessary, with the exception of ovarian teratoma (5). HIV infection should always be excluded as HIV-related OMS has no characteristic clinical features. Further work-up for para-infectious etiologies may include CSF and/or serum serologies for streptococcus, treponema pallidum, VZV, EBV, CMV, HSV 1 and 2, JC virus, and Lyme antibodies. In older patients, lung cancer, especially small cell carcinoma, is the most common paraneoplastic cause, followed by breast and gynecologic cancers (5).

Auto-antibody studies are frequently sent as part of work-up for OMS. However, roughly two thirds of patients do not have identifiable neuronal antibodies (5). Those antibodies that are identifiable include antibodies against neuronal surface antigens (*e.g.,* GABA receptor, Glycine receptor, NMDA receptor) and antibodies against intracellular antigens (*e.g.,* Anti-Hu, anti-Yo, anti-Ri). The latter are generally T-cell mediated and considered to be markers of paraneoplastic syndromes, often with poor prognosis (9). Overall, neuronal antibodies have not been found to be syndrome-specific and likely reflect a wider autoimmune process (9).

OMS secondary to West Nile virus is diagnosed with IgM and IgG antibodies against West Nile virus in cerebrospinal fluid or serum (8). West Nile virus specific IgM antibodies are usually detectable three to eight days after onset of illness and persist for 30 to 90 days (7).

Imaging

MRI Brain with and without IV contrast may be performed but this has not been reported as a requirement for diagnosis. Body imaging may be completed as part of paraneoplastic work-up.

Treatment/Management/Guidelines

There are no prospective controlled trials on management of patients with OMS that address specific treatment methods and long-term outcomes. Patients with paraneoplastic OMS should be treated for their underlying malignancy (6). Use of immunotherapies such as steroids, IVIg, and plasma exchange is associated with good outcome in patients with idiopathic or parainfectious OMS (5). These initial immunotherapies were not tolerated by our patient, but he responded well to rituximab infusion followed by maintenance therapy with mycophenolate mofetil. Symptomatic control of opsoclonus may include medications such as benzodiazepines and gabapentin. OMS may return after initial treatment. One study reported the rate of relapse as 15% (5). This may be more frequent in patients with paraneoplastic OMS (5). Interestingly, all previously reported cases of OMS secondary to West Nile virus described complete recovery despite dramatic presentation and variable treatment methods (8).

EPIDEMIOLOGY OR ETIOLOGY • Very rare (1 per 5,000,000 per year) • Immune mediated with unclear mechanism • Usually paraneoplastic or idiopathic, but may also be parainfectious, toxic, metabolic, or autoimmune	**SIGNS** • Opsoclonus with myoclonus • May also see ataxia, ocular flutter, brisk deep tendon reflexes, symptoms of associated illness. • May be preceded by flu-like prodrome • Lymphocytosis in CSF or serum, uncommonly neuronal antibody positivity
SYMPTOMS • Oscillopsia • Blurred vision • Tremor • Imbalance	**TREATMENT/MANAGEMENT** • Immunotherapy, including steroids, IVIg, plasmapheresis, rituximab, and azathioprine • Investigate for neoplasm in children or adults >40 years old, rule out ovarian teratoma in young women. • Supportive cares include benzodiazepines and gabapentin

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Past Medical History

- Degenerative joint disease
- Migraine headaches
- Viral encephalitis 15 years prior without residual symptoms

Medications

- Sumatriptan as needed

Allergies

- metoclopramide (dystonia)
- ondansetron (rash)

Family History

- Non-contributory

Social History

- Recently traveled to Indiana to attend a football game, otherwise non-contributory.

Review of Systems

- Positive for recent upper respiratory illness symptoms, fatigue, night sweats, nausea, and vomiting. Negative for acute decrease in vision.

OCULAR EXAMINATION

Visual Acuity with Correction (Snellen)

- Right eye (OD): 20/200
- Left eye (OS): 20/200

Ocular Motility/Alignment

- Full versions in both eyes (OU). Remarkable for horizontal and vertical erratic, large, rapid, macrosaccadic movements (see Video 1).

cannot be played here.

Watch on Vimeo

Intraocular Pressure (by Tonopen)

- OD: 21 mmHg
- OS: 21 mmHg

Pupils

- OD: 5 mm in dark, 3 mm in light, no relative afferent pupillary defect (RAPD)
- OS: 5 mm in dark, 3 mm in light, no RAPD

Confrontation visual fields

- OU: Full by count fingers

External

- OU: Normal

Slit lamp exam

- Lids/lashes:Normal OU
- Conjunctiva/sclera: Clear and quiet OU
- Cornea: Clear OU
- Anterior chamber: Deep and quiet OU
- Iris: Normal architecture OU
- Lens: Clear OU

Dilated fundus examination (DFE)

- Vitreous:Normal OU
- Disc: Small OU, no hemorrhage or edema OU
- Cup-to-disc ratio: 0.4 OU
- Macula: Normal, flat OU
- Vessels: Normal OU
- Periphery: Normal OU

Neurologic Exam

- No nuchal rigidity or focal neurologic deficits. Remarkable for jerking contractions (myoclonus) of the bilateral upper and lower extremities (see Video 2).

Differential Diagnosis:

- Opsoclonus (https://collections.lib.utah.edu/details?id=180305)
  - Paraneoplastic
  - Para-infectious
  - Idiopathic
  - Autoimmune
  - Toxic/metabolic
- Ocular flutter (https://collections.lib.utah.edu/details?id=180316)

Additional testing

- **Repeat MRI Brain with and without contrast:** Unremarkable
  Repeat Lumbar puncture
  - Traumatic (11,000 RBCs)
  - 66 nucleated cells (19 neutrophils, 27 lymphocytes, 19 histiocytes, and 1 eosinophil)
  - Elevated protein (89 mg/dl)
  - Normal glucose (51 mg/dl)

  Laboratory Testing
  - CSF flow cytometry: CD4 T-cell predominant with reactive morphology
  - West Nile virus serum IgM 5.97 (reference range <=0.89)
  - West Nile virus antibody IgM, CSF 7.59 (reference range <=0.89)
  - Negative studies (Serum and CSF):
    - Paraneoplastic panel, including antibodies for ANNA-1, ANNA-2, and PCA-1
    - Infectious panel, including Lyme antibody, HSV 1&2 with PCR, treponema pallidum particle agglutination (TPPA) assay, JC virus, VZV, EBV, CMV

DIAGNOSIS