Clinical Reasoning: A 57-year-old woman with ataxia and oscillopsia
Varicella-zoster encephalitis

SECTION 1

A 57-year-old immunosuppressed renal transplant recipient experienced 2 months of oscillopsia, vertigo, ataxia, and headaches. The headaches were described as constant, bifrontal, dull, and associated with photophobia and nausea but no aura or positional component. She described rotational vertigo, both at rest and provoked by leftward head turn and gait instability that developed gradually over the last 4 weeks. Six months prior to presentation, she had a similar episode of headaches, dizziness, and ataxia that resolved spontaneously over 3 months. This was preceded by a dermatomal vesicular rash on the arm. She had undergone renal transplantation 12 years earlier. Three years ago, she had left C2-3 distribution zoster. She denied infectious or rheumatologic symptoms. Her only current medication was mycophenolate mofetil 360 mg PO BID.

Neurologic examination. Visual acuity was 20/20 OS and 20/20 OD. Extraocular movements were full without nystagmus. All attempts at fixation led to intermittent bursts of ocular flutter. There were also hypometric saccades to the left and hypermetric saccades to the right (video on the Neurology® Web site at Neurology.org). Dix-Hallpike and other otolith repositioning maneuvers did not elicit vertigo or nystagmus. There was intention tremor in both arms without dystadiadochokinesia or dysesthesia. Gait was wide-based and ataxic and the patient was unable to walk tandem without falling to the left. Romberg sign was absent and the remaining neurologic and general examinations were normal.

Questions for consideration:
1. What is the localization?
2. What are some clinical features of saccadic intrusions, such as ocular flutter, and what is the relevant functional neuroanatomy?
SECTION 2

The patient’s neurologic signs and symptoms localized to multiple lesions, including the medulla (vertigo) and pons/cerebellum (oscillopsia and ataxia).

Ocular fixation is normally not completely stable but relies upon small involuntary fixational movements. Saccadic intrusions are single, biphasic disruptions of fixation that are seen in normal individuals and in individuals with neurologic disease, where they tend to be higher frequency or amplitude. Saccadic intrusions can be divided into those with normal intersaccadic intervals (square wave jerks, square wave pulses, macrosaccadic oscillations, and saccadic pulses) and those without, which are also known as saccadic oscillations (ocular flutter and opsoclonus).

Square wave jerks are couplets of conjugate horizontal movements ranging from 0.5° to 5° centered on the focal point with an intersaccadic interval of ~200 ms. They are the most common saccadic intrusion, can be seen in normal individuals, and generally do not cause oscillopsia. Pathologic square wave jerks can be seen in cerebellar disease, Huntington disease, progressive supranuclear palsy, Friedreich ataxia, motor neuron disease, and hemispheric disorders.1,2

Ocular flutter is characterized by rapid horizontal conjugate oscillations limited to one plane (generally horizontal). Ocular flutter predominates in primary gaze, particularly following refixation, and causes oscillopsia. Opsoclonus is similar to ocular flutter but is not limited to one plane, varies in amplitude, and may accompany ataxia, myoclonus, and encephalopathy (e.g., opsoclonus-myoclonus syndrome).

It has been proposed that pause cells in the paramedian pontine reticular formation (PPRF) tonically inhibit burst cells during fixation and that lesions in the medial region of the PPRF just ventral to the sixth nerve nucleus cause ocular flutter and opsoclonus by disrupting this pathway.3 Both ocular flutter and opsoclonus can result from dysfunction of pause cells in the pons related to cerebellar or brainstem disease.

Functional MRI of 2 patients with opsoclonus revealed activity in the deep cerebellar nuclei that abated when the eyes were closed.4 This finding supports the hypothesis that disinhibition of the fastigial nuclei inhibits the pause neurons and can cause opsoclonus and perhaps other saccadic intrusions. Alternatively, lesions in the cerebellum may disrupt the chain of inhibitors. Normally, Purkinje cells inhibit the fastigial nuclei that inhibit the pause cells, which in turn inhibit the burst cells and thereby assist in fixation. Lesions of the Purkinje cells functionally disinhibit the fastigial nuclei, leading to inhibition of pause cells2 and ultimately to ocular flutter and opsoclonus. There is also clinical evidence to suggest that lesions in the PPRF can produce opsoclonus, as in our patient.3

Questions for consideration:
1. What should be included on the differential diagnosis in this case?
2. What further investigations should be conducted?
SECTION 3
The differential diagnosis of subacute ataxia with abnormal extraocular movements includes multiple sclerosis, neuromyelitis optica, Behçet disease, neurosarcoidosis, anti-GQ1b or anti-GAD antibodies, and paraneoplastic cerebellar degeneration; infectious disorders including progressive multifocal leukoencephalopathy, herpesvirus infection, and tuberculosis; nutritional disorders including celiac disease, alcoholism, cyanocobalamin, and thiamine deficiencies; and primary or metastatic malignancy.

Further investigations included laboratory values, a brain MRI (figure) with and without contrast, and CSF analysis. Normal laboratory studies included complete blood count, basic metabolic panel, transaminases and bilirubin, sedimentation rate, vitamin B₁₂, methylmalonic acid, thiamine, thyroid-stimulating hormone, free T₄, triiodothyronine, antinuclear antigen, antineutrophil cytoplasmic antibodies panels, SSA, SSB, rapid plasma reagin, aquaporin-4 antibodies, and paraneoplastic panel.

MRI revealed multiple areas of increased signal in the pons and brain, particularly involving the subcortical and periventricular white matter and deep gray matter (figure). The insular cortex was affected bilaterally, and there was nodular enhancement in the left frontal and occipital lobes (not shown). The lesions were not distributed in a vascular pattern. CSF contained 30 nucleated cells per microliter (100% lymphocytes), 62 erythrocytes, elevated protein at 70 mg/dL, oligoclonal bands, elevated immunoglobulin G (IgG) index at 1.25, and anti–varicella-zoster virus (VZV) IgG antibody level of 2.427 (normal <1.1). PCR did not amplify VZV, JC virus, or cytomegalovirus DNA. CSF angiotensin-converting enzyme level was normal at 13 μg/L. Cytology and flow cytometry were both negative for malignancy.

Question for consideration:
1. What is the diagnosis and how should this patient be treated?
SECTION 4
The patient later developed zoster on the pinna of the left ear that resolved after 2 weeks. The multiple lesions in the brain and brainstem in a nonvascular pattern are consistent with encephalitis, most likely produced by VZV based on the temporal relationship of zoster to the development of neurologic symptoms and signs and as virologically verified by elevated anti-VZV IgG antibody in CSF. She did not meet clinical criteria for any rheumatologic diagnosis and laboratory studies that might support this were negative. The appropriate treatment is IV acyclovir 10–15 mg/kg 3 times daily for 2 weeks. Whether a short course of steroids confers additional benefit remains to be determined. After treatment, the patient’s symptoms gradually resolved and MRI revealed resolution of the lesions.

DISCUSSION VZV is a double-stranded DNA herpesvirus, which after primary infection (chickenpox), establishes a latent state in the cranial nerve, dorsal root, and autonomic ganglia. With advancing age or immunosuppression, cell-mediated immunity to VZV wanes and the virus can reactivate to produce zoster (shingles). Zoster can be further complicated by cranial nerve palsies (e.g., Ramsay Hunt syndrome), zoster paresis, vasculopathy, myelopathy, cerebellitis, brainstem encephalitis, and meningoencephalitis, all of which may develop in the absence of rash. VZV is also found in most temporal arteries of patients with giant cell arteritis (GCA), suggesting the role of the virus in triggering the immunopathology of GCA.

We report a case of VZV encephalitis manifesting as chronic recurrent episodes of oscillopsia, vertigo, and headaches with ocular flutter and axial ataxia. MRI demonstrated multiple lesions in the brain and brainstem, including one in the left paramedian pontine reticular formation that accounted for oscillopsia and ocular flutter.

The presence of multiple lesions in the brain and brainstem in a random nonvascular pattern is characteristic of encephalitis. Furthermore, chronic protracted neurologic disease is typical of VZV infection of the CNS. In our patient, not only did the close temporal relationship of zoster to encephalitis suggest that VZV was the cause of disease, but also the detection of anti-VZV antibody in CSF clinched the clinical diagnosis of VZV encephalitis. The detection of VZV DNA by PCR or detection of anti-VZV IgG antibody in CSF or both would confirm that VZV produced the neurologic disease. Importantly, the detection of anti-VZV IgG antibody, but not VZV DNA, in the CSF of our patient with VZV encephalitis parallels earlier findings in patients with VZV vasculopathy and VZV myelopathy with brainstem involvement, which showed that the detection of anti-VZV IgG antibody in CSF was superior to that of VZV DNA. More cases of VZV encephalitis need to be studied virologically. Treatment of VZV encephalitis is IV acyclovir, 10–15 mg/kg 3 times daily for 2 weeks.

AUTHOR CONTRIBUTIONS
Dr. Bradshaw: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Dr. Gilden: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. P. Lavin: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, contribution of vital reagents/tools/patients, obtained video of abnormal eye movements. S. Sriram: study concept or design, accepts responsibility for conduct of research and final approval, acquisition of data, initial physician making the diagnosis.

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REFERENCES
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