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A Case of Opsoclonus-Myoclonus-Ataxia With Neuronal Intermediate Filament IgG Detected in Cerebrospinal Fluid

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Abstract

A 62-year-old man presented with headache, fever, and malaise. He was diagnosed with *Anaplasma phagocytophilum*, confirmed by serum polymerase chain reaction, and started on oral doxycycline. After 5 days of treatment, the patient began to experience gait imbalance with frequent falls, as well as myoclonus, and confusion. Examination was notable for opsoclonus-

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myoclonus-ataxia (OMA) and hypometric saccades. Cerebrospinal fluid (CSF) autoimmune encephalitis panel demonstrated a markedly elevated neuronal intermediate filament (NIF) immunoglobulin G antibody titer of 1:16, with positive neurofilament light- and heavy-chain antibodies. These antibodies were suspected to have been triggered by the *Anaplasma* infection. Repeat CSF examination 8 days later still showed a positive immunofluorescence assay for NIF antibodies, but the CSF titer was now less than 1:2. Body computed tomography imaging was unrevealing for an underlying cancer. Our patient illustrates a postinfectious mechanism for OMA and saccadic hypometria after *Anaplasma* infection.

Dr Galetta and Dr Merati:

A 62-year-old man with a history of hyperlipidemia presented with headache, fever, and malaise after discovering multiple ticks on his lower extremities while chopping wood. He presented to his primary care physician, who diagnosed Anaplasma phagocytophilum, confirmed by serum polymerase chain reaction (PCR). The patient completed 5 days of oral doxycycline but then developed imbalance with frequent falls, myoclonus, and confusion.

When the patient presented to the hospital, examination was notable for disorientation, OMA, and both vertical and horizontal hypometric saccades. Serum inflammatory markers were elevated, with an erythrocyte sedimentation rate of 39 mm/h and C-reactive protein of 11.6 mg/dL. A serum Lyme IgM antibody was positive. Electroencephalogram was normal. Cerebrospinal fluid (CSF) analysis demonstrated an elevated protein of 243 mg/dL and a lymphocytic pleocytosis of 160 white blood cell (WBC)/cubic mL. Cerebrospinal fluid Lyme PCR was negative. The patient had a markedly positive CSF Lyme IgM titer of 16.2. However, because of a high albumin level in the CSF, the Lyme titer was considered equivocal. There were no Babesia seen on the peripheral blood smear, and no Anaplasma were seen on buffy coat. The blood smear was negative for Plasmodium, Trypanosoma, and microfilaria. Serum paraneoplastic panel, meningitis/encephalitis panel, and venereal disease research laboratory (VDRL) were negative. The patient was treated with intravenous doxycycline for 4 additional days in the hospital and then discharged home on oral doxycycline.

Dr Hu:

MRI of the brain 1 week after the symptom onset was normal (Fig. 1). MRI of the spine showed compression deformities of T8 and T13 vertebrae but no cord abnormalities.

Dr. Galetta and Dr. Merati:

The patient's condition then worsened while at home. Less than 3 weeks after the symptom onset, he returned to the hospital with worsening tremor, unsteady gait, and word finding difficulty; examination demonstrated worsening signs of OMA (See Supplemental Digital Content, Video, https://links.lww.com/WNO/A582). Intravenous ceftriaxone was initiated.

Dr. Hu:

Repeated neuroimaging was again unremarkable (Fig. 2).

Dr. Galetta and Dr. Merati:

Cerebrospinal fluid studies demonstrated a lymphocytic pleocytosis that had improved compared with the previous findings, with 139 WBC/cubic mL and 98-mg/dL protein. Cerebrospinal fluid autoimmune encephalopathy evaluation demonstrated a markedly elevated neuronal intermediate filament (NIF) titer of 1:16 (normal, <1:2). The saccadic hypometria, OMA resolved on ceftriaxone.

Final Diagnosis

OMA with neuronal intermediate filament immunoglobulin G (IgG) detected in CSF.

Dr. Galetta and Dr. Merati:

Similar to our patient, NIF-IgG parainfectious disease has been reported with ehrlichiosis, a tick-borne disease closely related to anaplasmosis (1). Neuroimaging in our patient was normal, but CSF analysis was concerning for a neuroinfectious process. When the patient worsened clinically on oral doxycycline, there was concern for an alternative infectious or inflammatory etiology related to Lyme disease or anaplasmosis. Initially, it was clinically unclear whether the prominent OMA were due to an infectious or postinfectious etiology. Similar symptoms have been reported as a manifestation of neuroborreliosis, but this case was not examined for the presence of anti-NIF antibodies (2). Once our patient's CSF resulted with NIF-IgG antibodies, evaluation was performed for an underlying cancer because NIF-IgG, when detected by immunofluorescence assay, is often accompanied by neoplasia (particularly small cell or other neuroendocrine carcinomas expressing neurofilament light-chain IgG) (3). Computed tomography (CT) scans of the chest, abdomen, and pelvis were negative for evidence of occult malignancy. Our case, therefore, illustrates a postinfectious mechanism for OMA and saccade hypometria after *Anaplasma* infection.

Treatment consideration in autoimmune encephalitis can include use of immunotherapy, although spontaneous recovery does occur. Our patient completed 4 weeks of ceftriaxone. His OMA and saccade hypometria resolved, and his cognition returned to baseline.

Dr. Galetta, Dr. Rucker, and Dr. Merati:

An unusual aspect of this case deserving of further discussion is the coexistence of opsoclonus with horizontal and vertical hypometric saccades, a combination very rarely reported (4,5).

Saccades are generated by excitatory burst neurons (EBN) that activate agonist muscles, located in the paramedian pontine reticular formation in the pons for horizontal saccades. Inhibitory burst neurons (IBN), in the medullary reticular formation for horizontal saccades,

inhibit antagonist muscles during saccades. Burst neurons are inhibited by omnipause neurons (OPN) at all times, other than during saccades. The cerebellar dorsal vermis and caudal fastigial nucleus (FN) also play a role in saccades. The FN contralateral to saccade direction firing early in a saccade to activate IBN ipsilateral to saccade direction to drive the saccade. Meanwhile, the FN ipsilateral to saccade direction fires late in the saccade to activate IBN contralateral to saccade direction to choke the saccade (Fig. 3) (6). Fastigial nucleus discharge is modulated by Purkinje cells in the overlying dorsal vermis.

Saccades in the presence of opsoclonus are typically either normometric (landing on target) or hypermetric (7-9). A unifying mechanism for opsoclonus involves delayed activation of OPN (10). This delay in OPN activation keeps EBN active longer than they should be, thus facilitating oscillation in the EBN/IBN circuits, which are intrinsically prone to oscillation (11-13). We propose that the hypometric saccades, coupled with periodic opsoclonus, in our patient likely resulted from cerebellar vermis dysfunction. Neuronal intermediate filament antibodies show a characteristic pattern of staining in the cerebellum, most prominently at the level of the Purkinje cells—a pattern that was confirmed from our patient's CSF (Fig. 4).

Dr. Galetta, Dr. Rucker, and Dr. Merati:

In conclusion, autoimmune encephalitis testing should be considered in patients with neurological symptoms from tick-borne diseases. The 2 classic etiologies of OMA include parainfectious and paraneoplastic causes. This case suggests that they may not be mutually exclusive. Neuronal intermediate filament autoantibodies not only define a paraneoplastic central nervous system disorder but also define a parainfectious process that may guide treatment (Fig. 5).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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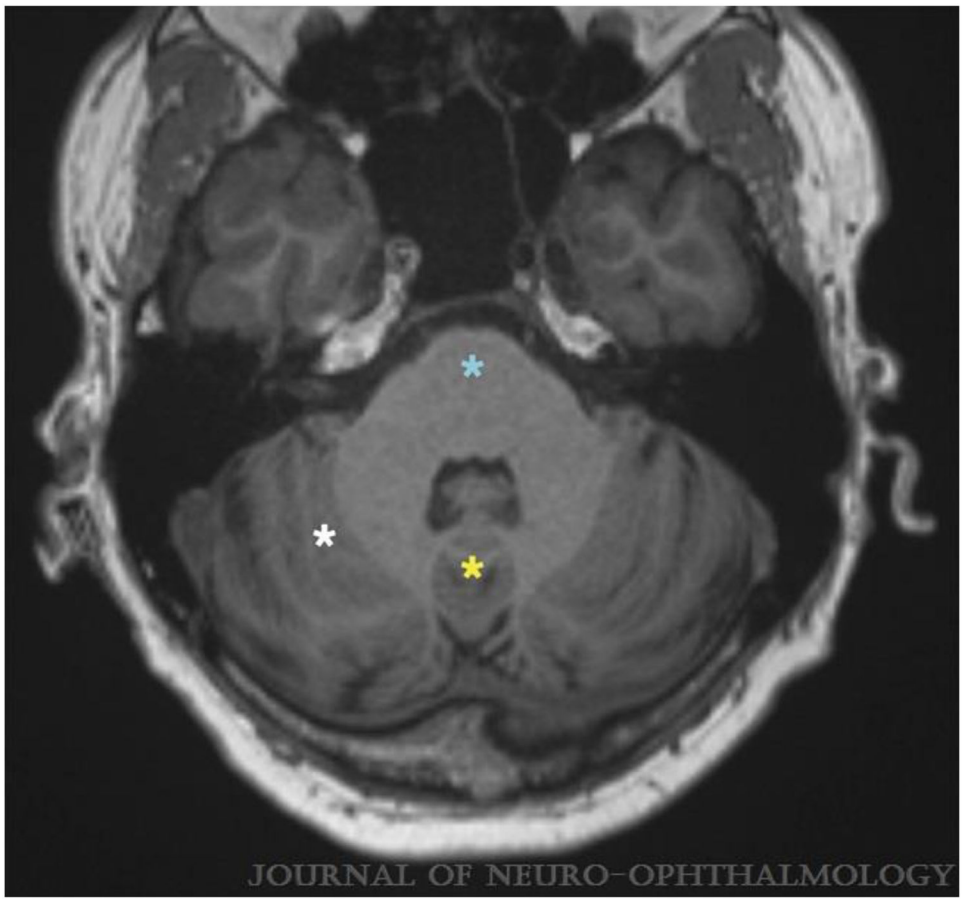

Fig 1.

MRI brain axial multiplanar reformation (MPR) noncontrast through the level of the cerebellum and brachium pontis, demonstrating the normal-appearing right cerebellar hemisphere (blue star), the pons (white star), and the cerebellar vermis (yellow star)

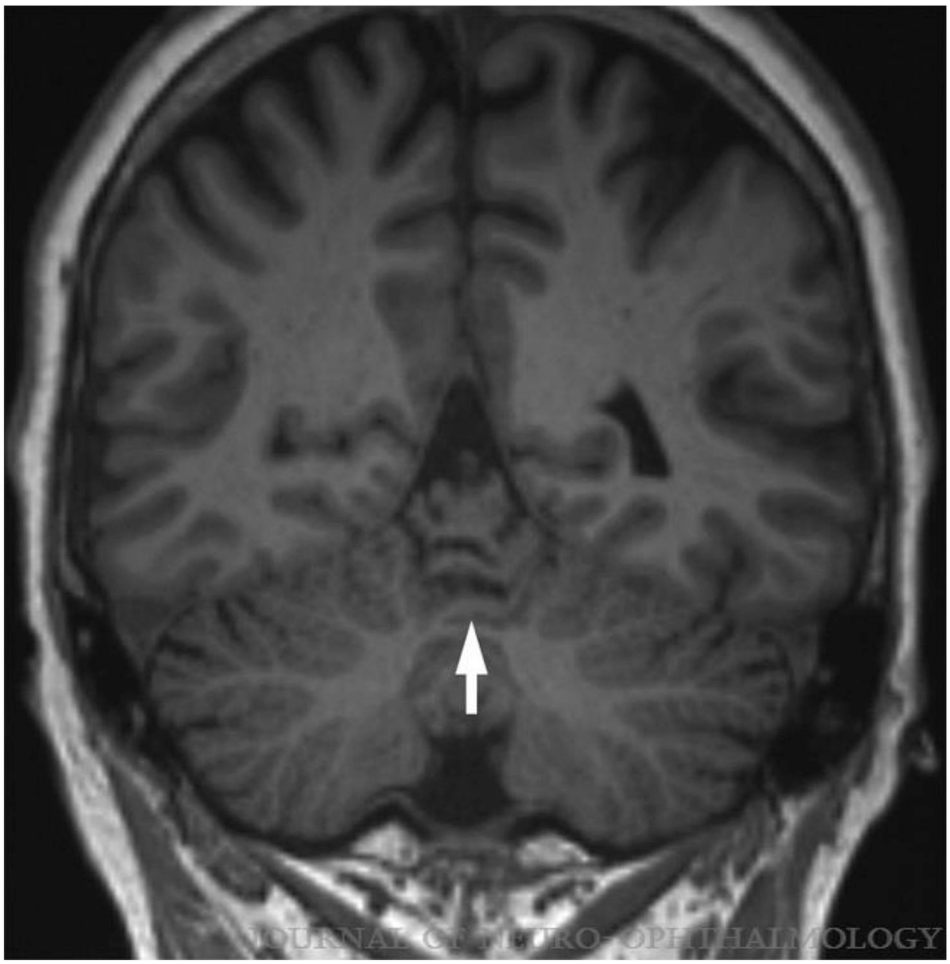

Fig 2.

Coronal 3D multiplanar reformation (MPR) noncontrast study of the cerebellum, demonstrating the normal cerebellar vermis (arrow).

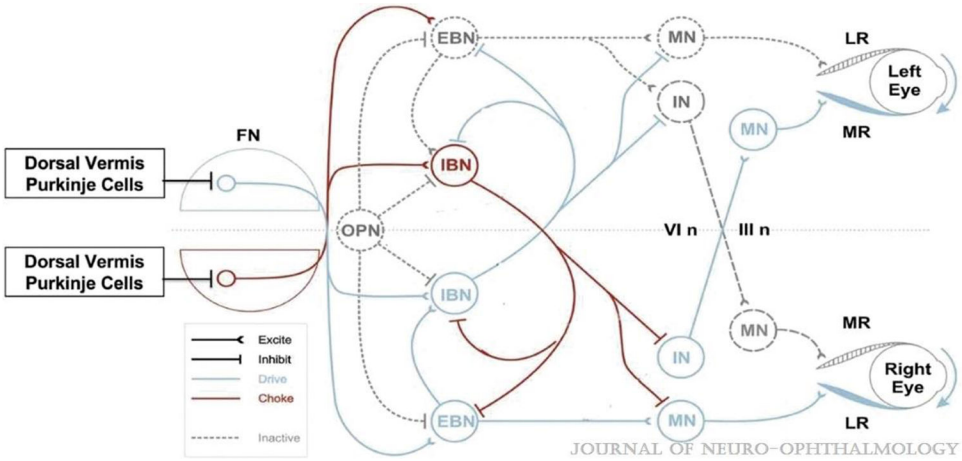

Fig 3.

Brainstem circuit detailing excitatory burst neuron (EBN) and inhibitory burst neuron (IBN) involvement in generating saccades. The horizontal recti muscles (medial and lateral recti, MR and LR) are innervated by the abducens (VIn) and oculomotor (IIIn) nuclei. Excitatory burst neurons provide drive for ipsilateral movement, whereas the IBN prevent activity on the contralateral side. To generate a rightward saccade, the omnipause neurons shut off allowing a saccade to the target. The right EBN and IBN will turn on (light blue “drive” circuit). The EBN drive the ipsilateral abducens motor neurons (MN) and interneurons (IN) to activate the right lateral rectus and left medial rectus, respectively. The right-sided IBN inhibit the left abducens nucleus, EBN, and IBN (light blue “drive” circuit). The cerebellar dorsal vermis and fastigial nucleus (FN) on the side contralateral to saccade direction fire early in the saccade (light blue “drive” circuit). At the end of the saccade, the cerebellar dorsal vermis and FN on the side ipsilateral to saccade direction fire late in the saccade to activate IBN contralateral to saccade direction to “choke” the saccade (red “choke” circuit). Adapted from Fig. 1 in Modeling gaze position-dependent opsoclonus, Lance M. Optican, Janet C. Rucker, John-Ross Rizzo, Todd E. Hudson. Prog Brain Res. 2019;249:37. doi: 10.1016/bs.pbr.2019.01.002. Epub 2019 Mar 2. PMID: 31325994, and Fig. 2 in Mechanism of interrupted saccades in patients with late-onset Tay-Sachs disease, Optican LM, Rucker JC, Keller EL, Leigh RJ. Prog Brain Res. 2008;171:569. doi:10.1016/S0079-6123(0800681-X).

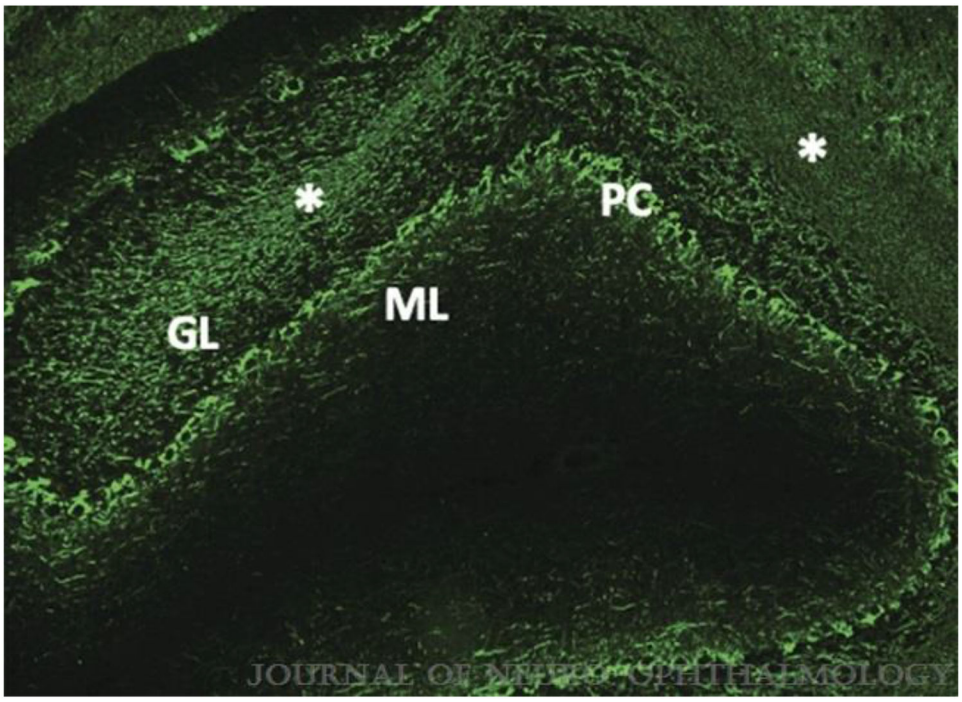

Fig 4.

Mouse tissue-based indirect immunofluorescence assay using our patient's cerebrospinal fluid. Here, the typical filamentous staining pattern of cerebellum characteristic of neuronal intermediate filament immunoglobulin G (IgG) is demonstrated. Staining is brightest in the Purkinje cell layer (PC) and white matter (*) with less prominent staining of the molecular layer (ML) and granular layer (GL). Neuronal intermediate filament–specific cell-based assays confirmed this finding and revealed an IgG profile that included both neurofilament heavy- and light-chain IgGs.

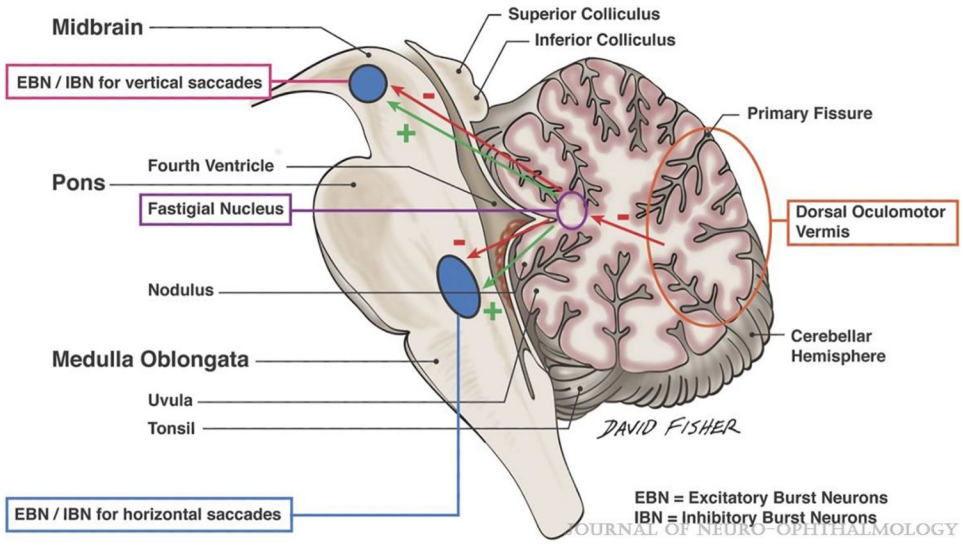

Fig 5.

Sagittal illustration of the brainstem highlighting structures involved in generating saccades.