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Letter to the Editor: New Observation

Myelin Oligodendrocyte Glycoprotein-Related Isolated Internuclear Ophthalmoplegia Mimicking Multiple Sclerosis

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We describe a previously healthy young woman who noticed sudden onset of diplopia and on exam demonstrated left internuclear ophthalmoplegia (INO). Diagnosis of multiple sclerosis (MS) was suspected, however, atypical MRI findings led to further work up and she was eventually diagnosed with myelin oligodendrocyte glycoprotein-associated disorder (MOG-AD). This case highlights the importance of performing MOG antibody testing in every case of isolated INO with absence of other imaging findings characteristic of MS.

A 32-year-old healthy woman noticed acute onset of diplopia. She also noticed that her left eye (LE) was crossing outwards. The following day she went to an emergency department where she was suspected of having a third nerve palsy and underwent CT/CT angiography, which was unremarkable. She was seen in neuro-ophthalmic consultation 5 days later when diplopia was already improving. She endorsed having had a COVID infection two months prior. On exam, visual acuity was 20/20 in each eye, there was no relative afferent pupillary defect, and anterior and posterior segment examination of each eye was normal. Ocular motility showed limitation of adduction in the LE (95% of normal) with corresponding incomitant exotropia of 2 PD in primary gaze, which was worse in right gaze. There was nystagmus of the right eye on abduction. There was no anisocoria or ptosis and convergence was intact. The rest of her neurological exam was normal. The presentation was consistent with left INO, and given her age, demyelinating disease was suspected. MRI brain with contrast performed 3 days later unexpectedly revealed a peculiar T2-hyperintense lesion (Fig. 1a,b) in the midbrain with mild enhancement on post-contrast sequence (Fig. 1c). No other brain lesions were present. As the midbrain lesion was thought to be unusual appearing for a demyelinating process, extensive work up was undertaken. MRI of the spine showed a small focal T2 signal alteration at the right cervical spinal cord without clinical correlation (Fig. 1d). Venerial disease laboratory testing, angiotensin-converting enzyme, anti-nuclear antibody, perinuclear anti-neutrophil antibody, and neuromyelitis optica antibody titers were all negative, however, MOG antibody titers returned as moderately positive (fixed cell-based assay). When seen in follow-up 6 weeks later, diplopia had resolved and ocular motility and alignment testing were normal thus no treatment was pursued. Follow-up MRI brain 5 months after initial presentation showed significant decrease in the size of the lesion and absence of post-contrast enhancement.

MOG-AD has become increasingly known to cause a variety of neurological manifestations.[1] Yet, while the association of MOG-AD with optic neuritis and transverse myelitis is now well established, little is known about its possible manifestations as an isolated brainstem syndrome. Jarius et al. identified 15 out of 50 patients with brainstem involvement in MOG-AD-related ON and/or transverse myelitis.[2] However, all these cases presented chiefly with either optic neuritis and/or transverse myelitis. Brainstem involvement was often severe with poor outcomes (including death in one case). A recent systematic review on ophthalmic manifestations of MOG-AD other than optic neuritis listed only one report of INO from Vecchio et al.[1] However, in that case, INO was associated with longitudinally extensive transverse myelitis with rapid worsening to tetraparesis and need for mechanical ventilation.[3]

While brainstem involvement in MOG-AD seems to be a risk factor for negative clinical outcomes, our case raises awareness that isolated INO with fast spontaneous recovery can occur. Thus, treatment approach to patients with isolated clinical syndromes secondary to MOG-AD is challenging. Ambrosius et al. reported that disability progression in MOG-AD is relapse-dependent, which furthers the clinical dilemma about initiation of treatment.[4] Thus the decision about starting long-term immunosuppression must be considered on an individual basis and reserved for patients with poor recovery after the first episode of MOG-AD or for those who experienced a second attack.

While the mechanism of demyelination in MOG-AD involves antibody reactivity against MOG and likely involves molecular mimicry induced by parainfectious/inflammatory processes,[5] it is not well understood why there seems to be a higher likelihood of the optic nerve being affected as opposed to brainstem. A plausible explanation is the concept of intrinsic and adaptive myelination.[5] Intrinsic myelination is defined as genetically predefined myelination that occurs around birth and in early childhood. Adaptive myelination, on the other hand, is modified by environmental factors and occurs according to the needs of a neuronal network. For instance, there might be little adaptive myelination in "one way" information pathways, whose task is simply to conduct impulses as fast as possible, such as in the spinal cord or optic

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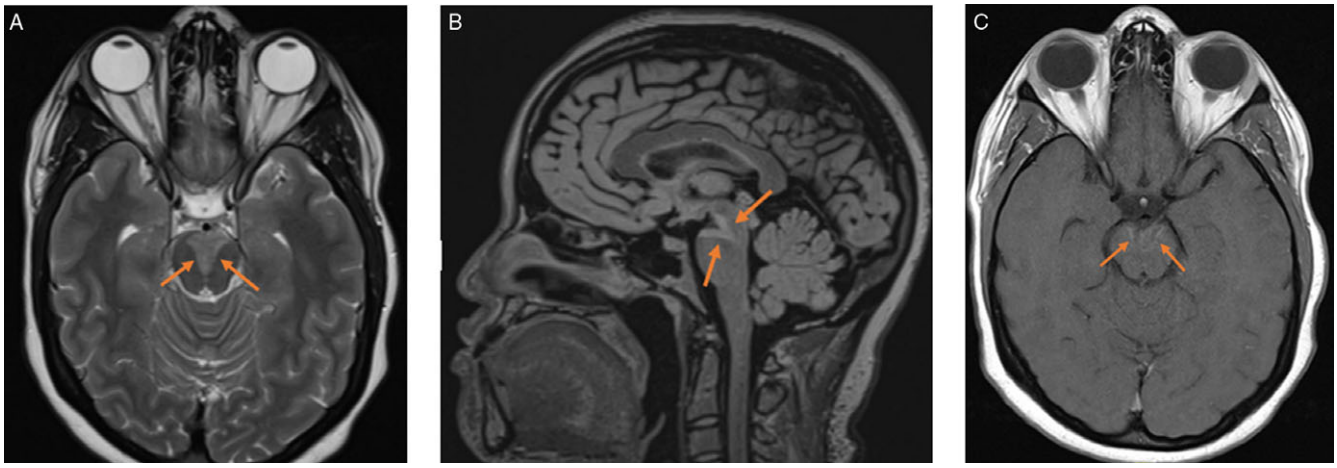

Figure 1: ***a***. T2 axial sequence demonstrating symmetric prominent T2-hyperintensity of ventral midbrain (arrow). ***b***: Fluid attenuated inversion recovery sagittal sequence demonstrating prominent ventral midbrain lesion (arrow). ***c***: T1 post-contrast axial sequence demonstrating mild enhancement of ventral midbrain lesion (arrow). ***d***: T2 axial sequence demonstrating small focal T2 signal alteration at the cervical spinal cord at the right anterior lateral cord.

nerve. Thus, the less altered intrinsic myelin might be more prone to be affected by anti-MOG antibodies and might explain why the brainstem is less often involved in MOG-AD as it does not represent a "one way" pathway. Similarly, axons in the cortex are often myelinated in two phases. The first phase occurs early in development that lays the groundwork which is then followed by a second phase that is believed to depend on sensory input. This myelin plasticity again might explain why ADEM predominantly occurs in childhood and is less likely in the further evolved adult brain.

Our patient presented two months after an infection, which is typical in MOG-AD and it has been hypothesized that post-infectious breakdown of blood-brain barrier poses an increased risk of preexisting anti-MOG antibodies reaching the central nervous system provoking an attack.[2] This raises the question if patients are at higher risk of a relapse after future episodes of infections if they have persistently positive anti-MOG antibody titers. To our knowledge, there is currently no study that has addressed this question. Hence, we believe that patients should be counseled about the possibility of a postinfectious MOG-AD relapse in the future.

In summary, we described the first case of isolated INO secondary to MOG-AD. Clinicians should always consider MOG-AD in the differential diagnosis of unusual-appearing lesions in the brainstem and in all patients with INO who do not demonstrate other typical demyelinating lesions in the brain, as this has important therapeutical implications.

Competing interests. None.

Statement of authorship. All authors contributed equally to data gathering, manuscript preparation, writing, and final approval.

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