Asymptomatic myelitis in neuromyelitis optica and autoimmune aquaporin-4 channelopathy

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Neuromyelitis optica (NMO) is an autoimmune inflammatory CNS disease associated with pathogenic aquaporin-4 autoantibodies (AQP4-IgG); optic neuritis (ON) and myelitis are required to fulfill diagnostic criteria.¹ NMO spectrum disorders (NMOSDs) are defined as one or more typical NMO syndromes accompanied by AQP4-IgG seropositivity but not yet fulfilling NMO diagnostic criteria (e.g., AQP4-IgG-seropositive recurrent ON). Non-Caucasian ethnicity and coexisting autoimmunity are common in NMO/NMOSD.² Transverse myelitis episodes in patients with NMO/NMOSD are characteristically longitudinally extensive (extending ≥ 3 vertebral segments on MRI), and the resulting clinical phenotype is typically severe, with paraplegia and wheelchair dependence at nadir a frequent finding.² In contrast, multiple sclerosis (MS) myelitis episodes are typically mild and often asymptomatic.³ Herein we report 3 AQP4-IgG-seropositive⁴ women with asymptomatic myelitis in the setting of NMO/NMOSD.

Case reports

Case 1 A 24-year-old white woman with myasthenia gravis (MG) was evaluated for recurrent ON occurring during maintenance mycophenolate mofetil (1,000 mg twice daily) and oral prednisone (8 mg daily) for MG. Examination revealed only hand movements perceptible in the left eye with optic disc pallor and relative afferent pupillary defect. Head MRI revealed left optic nerve enhancement without other lesions. A cervical spine MRI was performed (although no myelitis symptoms/signs were present) and revealed an enhancing short cord lesion (< 3 vertebral segments; figure, A); enhancement resolved 2 months later. Antinuclear antibody (ANA) was elevated and CSF including oligoclonal band assessment was unremarkable. AQP4-IgG was positive by transfected cell-based assay, leading to NMO diagnosis. Rituximab was then used in place of mycophenolate for maintenance treatment of NMO and MG.

Case 2 An 18-year-old Hispanic woman with intractable nausea and vomiting 3 months prior developed double vision. She had no symptoms of myelitis or ON. MRI revealed brainstem lesions and a separate enhancing short cervical cord lesion (figure, B). The enhancement

Practical Implications

Asymptomatic myelitis does not exclude aquaporin-4-IgG testing or neuromyelitis optica spectrum disorder diagnosis, particularly in those with other risk factors.

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Figure MRI features of patients with asymptomatic myelitis in aquaporin-4-IgG-associated neuromyelitis optica and its spectrum disorders

A short (approximately 1 vertebral segment in length) T2 hyperintense lesion on sagittal (A.a, arrow) and axial (A.b, arrow) images is shown with associated enhancement on T1 postgadolinium images (A.c, arrow). A short T2 hyperintense cervical cord lesion adjacent to the first cervical vertebra is shown (B.a, arrow) with a separate lesion in the medulla (B.a, arrowhead). On axial T2-weighted images, the cervical cord lesion is located in the left lateral cord (B.b, arrow) and shows a wisp of enhancement on T1 postgadolinium images (B.c, arrow). MRI thoracic spine reveals a short T2 hyperintense lesion extending approximately 2 vertebral segments (C.a, arrows) with central T2 hyperintensity on axial images (C.b, arrow) and associated enhancement on T1-weighted postgadolinium images (C.c, arrow).

resolved 10 days later. ANA, anticentromere, and anti-double-stranded DNA antibodies were elevated. CSF was not analyzed. AQP4-IgG was detected by transfected cell-based assay and NMOSD was diagnosed. Rituximab treatment was commenced.

Case 3 A 52-year-old African American woman with ON in her 20s developed severe bilateral ON. She was otherwise asymptomatic. Brain MRI revealed left optic nerve enhancement but no other lesions. CSF revealed elevated oligoclonal bands. IV methylprednisolone was prescribed followed by an oral prednisone taper. During the taper, a thoracic spine MRI revealed an enhancing short cord lesion (figure, C). ANA and anti-double-stranded DNA antibodies were elevated. AQP4-IgG was detected by transfected cell-based assay, leading to NMO diagnosis and initiation of azathioprine treatment. Two months later she developed symptomatic longitudinally extensive cervical myelitis.

DISCUSSION

This study demonstrates that myelitis episodes in AQP4-IgG-seropositive NMO/NMOSDs may be asymptomatic. Absence of symptoms and lesion length less than 3 vertebral segments should not dissuade clinicians from considering this diagnosis in those with other risk factors.

To our knowledge, only 2 AQP4-IgG-seropositive patients with asymptomatic myelitis have been described previously, and both had preceding ON but no prior myelitis.⁵ The lesion was short in both cases (central cord, 1; peripheral cord, 1) and occurred 7 and 12 years after NMOSD onset, respectively.⁵ All patients in our study also had short lesions, suggesting

asymptomatic myelitis in NMO is likely to be accompanied by a short (rather than long) lesion. In contrast to adult MS, in which short lesions are typical,³ short lesions represent just 14% of initial myelitis episodes in NMO/NMOSD; their presence delays NMOSD diagnosis and treatment.⁶ Nonenhancing lesions may represent the residua of previous long lesions, but all cord lesions in this series were enhancing, indicating lesional activity. Distinguishing between MS and NMO early in the course is important, as starting NMO treatment may prevent future attack-related disability,² whereas misdiagnosis and treatment as MS may worsen NMO.⁷ Preceding immunotherapy in 2 patients may have contributed to the lack of symptoms and shorter lesions.

The frequency of asymptomatic cord lesions in NMO/NMOSD is unknown, but we suspect they occur in less than 5%. Future clinical trials in NMO/NMOSD may use MRI spine outcome measures, so asymptomatic lesions will need to be distinguished from symptomatic lesions. The broadening of the myelitis spectrum beyond severe necrotic myelopathy in NMO/NMOSD highlights the need to pay attention to risk factors that can help select those with demyelinating variants in whom AQP4-IgG testing is appropriate. Clues to an NMO diagnosis in this series included higher-risk non-Caucasian ethnicity in 2 of 3 (the majority of patients seen at Mayo Clinic are Caucasian), preceding symptoms (severe ON with poor recovery, bilateral ON and prolonged nausea/vomiting episode), personal/serologic evidence of autoimmunity, and a brain MRI without typical MS lesions.

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