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Child Neurology: Neuromyelitis optica spectrum disorders

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A 3-year-old girl presented with 4 days of progressive bilateral vision loss. Medical history included presumed autoimmune hepatitis at 6 months of age, when she had an extensive evaluation including hepatitis A immunoglobulin G (IgG) detected in her serum, thought to represent maternal antibodies. Liver biopsy suggested autoimmune hepatitis and she was treated with oral prednisolone 2 mg daily for 2 weeks and remained on maintenance 1 mg daily. Family and social histories were unremarkable.

Neurologic examination demonstrated severely decreased central vision in both eyes; pupils were slowly reactive to light without relative afferent pupillary defect. She had a left Babinski sign. The remaining general and neurologic examinations were normal, including funduscopy.

MRI brain, orbits, and spine with contrast demonstrated bilateral optic neuritis (ON; figure) and no other lesions.

CSF contained 0 nucleated cells/μL, 1 erythrocyte/μL, glucose 47, protein 30, no oligoclonal bands, and elevated IgG index at 0.81 (0.28–0.66). The patient had normal folate, cyanocobalamin, and sedimentation rate/C-reactive protein, and was antinuclear antibody (ANA)–positive at 1:640 with a nucleolar pattern; other rheumatologic antibodies were absent. Serum aquaporin-4 IgG (AQP4-IgG) was pending at the time of treatment.

The patient was treated empirically for neuromyelitis optica (NMO) spectrum disorder (NMOSD) with plasma exchange (PLEX) and 20 mg/kg/d IV methylprednisolone (IVMP) on the day of presentation. With 5 sessions of PLEX/IVMP, her vision improved significantly. She was discharged with oral prednisone and serum AQP4-IgG returned positive at 73 units/mL. She was given rituximab 375 mg/m^2 on days 1 and 15, and then every 3 months thereafter. Her vision subjectively improved somewhat after her first cycle of rituximab.

DISCUSSION Eugène Devic first coined "neuromyelitis optica" in 1894 while describing a novel syndrome of acute myelitis and ON. Discovery of the pathogenic AQP4-IgG led to the development of international diagnostic criteria that include AQP4-IgG status.[1] Clinical features include ON (severe/bilateral), longitudinally extensive transverse myelitis (≥3 vertebral segments), and area postrema syndrome (intractable hiccups, nausea/vomiting). Brainstem and diencephalic syndromes such as narcolepsy/hypersomnolence and endocrine dysfunction have also been recognized in NMOSD. It is important to distinguish NMOSD from multiple sclerosis (MS) and other disorders as treatment differs among these and prompt treatment is important for minimizing disability.

The differential diagnosis of ON has recently been reviewed and will not be covered in detail.[2] Infectious etiologies should be considered when there are infectious signs/symptoms or highly inflamed CSF. Deficiencies in cyanocobalamin, folate, and copper should be considered when there is bilateral optic neuropathy, especially in an at-risk patient (e.g., malabsorption syndromes, gastrointestinal surgery). The clinical features and subacute–progressive time course of NMOSD and other demyelinating conditions help to distinguish them from other diagnoses, which may tend to be more hyperacute (vascular) or chronic (genetic/nutritional).

Clinical features of NMOSD in children. In one analysis of children with NMOSD, the most common presenting features included visual, motor, and constitutional syndromes.[3] In the largest report of children with NMO, 83% and 78% of children with AQP4-IgG had at least one episode of ON or transverse myelitis, respectively, while 45% had other symptoms such as encephalopathy, seizures, ophthalmoparesis, ataxia, or area postrema syndrome.[4] Children with NMOSD were older than those with acute disseminated encephalomyelitis (ADEM) (mean 10–12 vs 5 years), but approximately the same age as those with MS (13 years).[3,4] Female patients and non-Caucasians are overrepresented in NMOSD. NMOSD is associated with additional autoimmunity, with 42% and 76% of patients with other autoimmune diagnoses or

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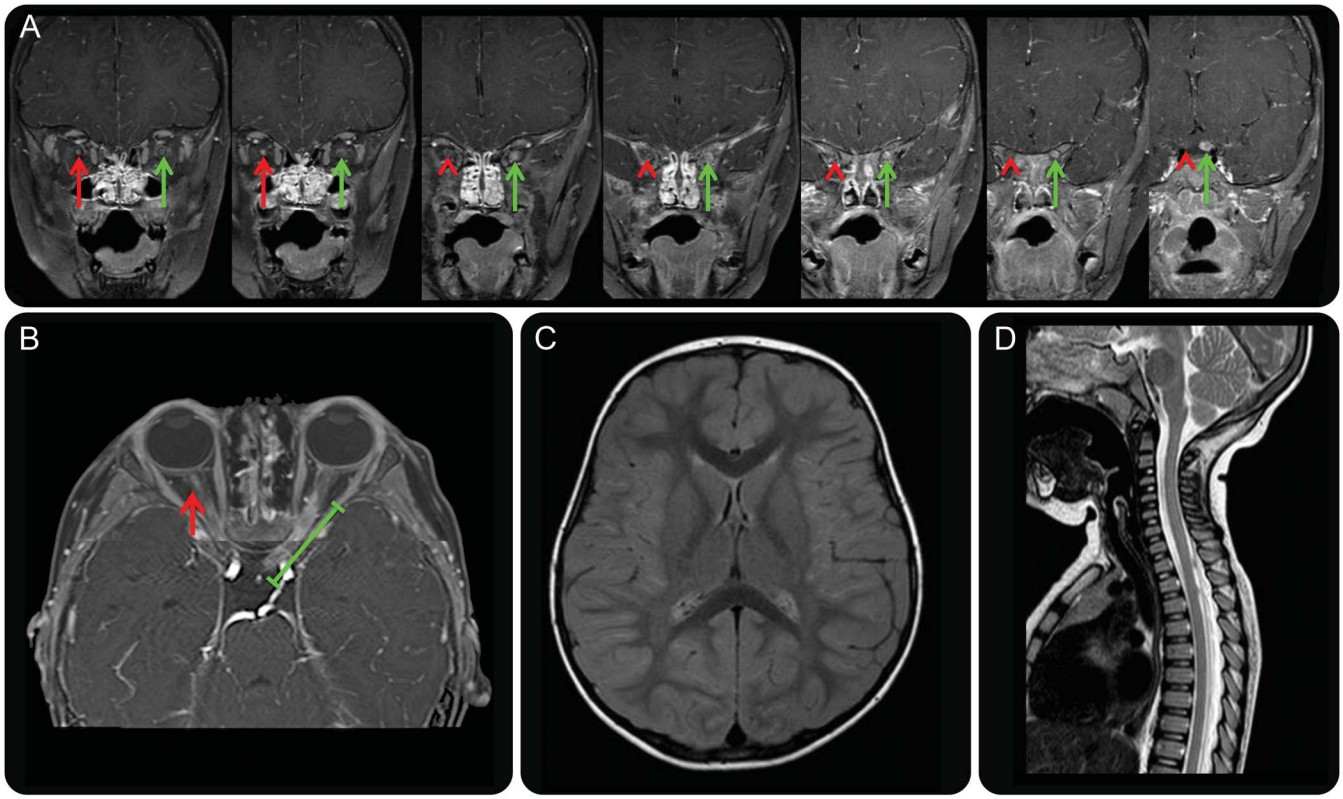
Figure MRI brain, orbits, and spine with and without gadolinium



(A) Coronal T1-weighted postcontrast MRI demonstrates enhancement of both optic nerves. The left optic nerve is indicated with green arrows/arrowheads and the right is indicated with red. The arrows indicate areas of contrast enhancement, while the arrowheads indicate optic nerve without significant contrast enhancement. (B) Axial T1-weighted postcontrast MRI of the orbits demonstrate longitudinally extensive contrast enhancement in the left optic nerve involving the rostral chiasm (green bracket) and a short segment of contrast enhancement in the distal right optic nerve (red arrow; 2 separate MRI, 5 mm apart, are combined in this image in order to demonstrate the length of the optic nerve). There were no other enhancing lesions in the brain or spinal cord. (C) Axial fluid-attenuated inversion recovery MRI of the brain is normal. (D) Sagittal short tau inversion recovery MRI of the spine is normal.

autoantibodies, respectively.[4] Sixty-four percent have a positive ANA, as in our case. There is one other case of autoimmune hepatitis associated with NMO reported in the literature.[5]

Imaging features of NMOSD in children. MRI with gadolinium is the imaging modality of choice for evaluating possible demyelinating disease, although there are no definitive radiologic criteria for NMO in children. MRI brain, orbits, and cervical ± thoracic spinal cord should be imaged as clinically indicated. Among 56 patients with MRI data included in one study, 56% had brain parenchymal abnormalities and 34% had optic nerve contrast enhancement; 5 had involvement of the chiasm and 1 had bilateral ON.[4] ON caused by NMOSD is more likely to be clinically severe, bilateral, and longitudinally extensive, and to involve the optic chiasm, compared to other causes of ON.[6] Features that help distinguish NMOSD myelitis from MS include longitudinally extensive (≥3 spinal segments) myelitis involving the central cord with >50% of the cross-sectional area, compared to the shorter, smaller, and more dorsolateral lesions seen in MS.[6]

Brain lesions are common in pediatric NMOSD and may overlap with MS or ADEM. NMOSD lesions tend to be periependymal T2 hyperintense lesions predominantly. Periventricular NMOSD lesions tend to be longer than the Dawson fingers seen in MS, which are usually shorter and confined to the pericallosum. Lesions in the corpus callosum occur in NMOSD, where they are often large and follow the ependymal lining, while those seen in MS tend to be smaller, ovoid, or flame-shaped and oriented radially to the ventricles.[6] Extensive and confluent predominantly white matter hemispheric lesions, which may be associated with encephalopathy, can make it difficult to distinguish NMOSD from ADEM.[4] In that setting, laboratory features, particularly the presence of AQP4-IgG, can be critical to the diagnosis.

Laboratory features of NMOSD in children. Roughly 65% of children with NMOSD tested positive for AQP4-IgG, rates similar to those observed in adults with NMOSD, but seropositivity may occur up to 4–5 years after onset.[3] Testing for AQP4-IgG is the most sensitive and cost-effective when performed on

serum, which is the source recommended by the Mayo Clinic laboratory.[7] In ON from NMOSD, the CSF may appear bland, while during an episode of myelitis, CSF may be highly inflamed, with pleocytosis >100 cells/μL, commonly with neutrophils or eosinophils. Oligoclonal bands are observed in roughly 25% of patients with NMOSD. This is contrasted with CSF in MS, which commonly contains oligoclonal bands (90%) and only rarely is pleocytosis >50, typically lymphocytic.[6] CSF studies in children with ADEM are variable and often nondiagnostic; however, oligoclonal bands are only rarely present.[3] Children with features of NMOSD but with negative serum AQP4-IgG should have CSF AQP4-IgG testing and may also be tested for myelin-oligodendrocyte glycoprotein antibodies (in the United States, only available through research laboratories). AQP4-IgG may appear up to 4 years after disease onset, and sequential testing should be employed for initially seronegative patients.

Diagnostic criteria in children. The Wingerchuk 2006 criteria were 49% sensitive for a diagnosis of pediatric NMO, while the 2015 updated international panel for NMO diagnosis criteria, which allowed for diagnosis after one attack and the presence of AQP4-IgG, were 97% sensitive and can be applied to children.[3] This is in part due to the lower lesion accrual in pediatric NMO.

Treatment of NMOSD in children. In contrast to MS, in which disability is driven primarily by progressive disease and there is relatively good recovery after acute exacerbations, in NMOSD, acute exacerbations can be severe with little recovery and drive virtually all of the disability. In addition, 93%–95% of children with NMOSD have relapsing disease,[3,4] and there is some evidence that acute exacerbations respond more favorably when the patient is on preventative medicaiton.[8] Therefore, prompt recognition and initiation of acute abortive therapy and preventative medication is critical. Some disease-modifying therapies used in MS (including interferons, fingolimod, and natalizumab) are ineffective and may worsen NMOSD.[6] No randomized controlled trials have been conducted in adult or pediatric NMOSD; therefore, all treatments are considered off-label and based on available literature and expert recommendations.

Acute treatment. Acute exacerbations are commonly treated with IVMP (in children 20 mg/kg/d for 5 days), an approach extrapolated from data on treating other immune-mediated neurologic conditions. We advocate for urgent PLEX as a first-line therapy for NMOSD exacerbations based on evidence demonstrating improved outcomes in patients treated with PLEX and IVMP compared to IVMP alone.[8,9] At Vanderbilt Children's Hospital, we exchange 1.5 volumes of plasma 5 times over 5–8 days. Complications are uncommon in experienced centers, but include those related to the central line, electrolyte abnormalities, and coagulopathy associated with the exchange process and transfusion-related complications. IV immunoglobulin may be beneficial and can be considered when there is a poor response to steroids and contraindication to PLEX exists. Children with NMOSD should be given a prednisone taper over several months.

Preventative therapy. The most common preventative agents include azathioprine, prednisone, mycophenolate mofetil, and rituximab. There is evidence to support the use of rituximab or mycophenolate over azathioprine.[6] The same strategies used to treat adults with NMOSD have been applied to children, and results appear comparable.[3] Studies intended to assist with the dosing and monitoring of rituximab for pediatric NMOSD have begun to emerge in the literature.[10]

As recently demonstrated,[3] the updated international panel for NMO diagnosis criteria are sensitive for the diagnosis of NMOSD in children. Prompt recognition and treatment of exacerbations followed by initiation of preventative agents are critical for minimizing disability. Strong consideration should be given to treating acute exacerbations with urgent PLEX in addition to IVMP, which appears to be more effective than IVMP alone.

AUTHOR CONTRIBUTIONS

Michael J. Bradshaw: treating clinician, literature review, clinical review, imaging review, manuscript preparation, editing. NgocHanh Vu: manuscript review, editing. Tracy E. Hunley: treating clinician, manuscript review. Tanuja Chitnis: manuscript review, editing.

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