

CASE REPORT

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Neuromyelitis optica spectrum disorder: a pediatric case report

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Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune demyelinating disorder of the central nervous system that predominantly affects the optic nerves and the spinal cord. Magnetic resonance imaging (MRI) has an increasingly important role in differentiating NMOSD from other inflammatory disorders of the central nervous system, particularly multiple sclerosis (MS). Specific antibodies against aquaporin-4 (AQP4) were identified and found to be directly responsible for the pathogenesis of the disease. We report on an AQP4 antibody-positive 12-year-old female with radiological findings in her brain MRI.

Keywords: Aquaporin-4, neuromyelitis optica spectrum disorder, pediatric

Introduction

Neuromyelitis optica (NMO), is an autoimmune demyelinating disorder of the central nervous system (CNS) and predominantly affects the optic nerves and the spinal cord. Currently, neuromyelitis optica spectrum disorder (NMOSD) is the new moniker for NMO [1]. NMOSD was first considered to be a variant of multiple sclerosis (MS), because optic neuritis (ON), myelitis, and inflammatory demyelination occur in both diseases. However, clinical, neuroradiologic, and immunologic data confirmed that NMOSD is a distinct disease [2].

Studies show that the prevalence of NMOSD ranges from 0.5-4 per 100,000 population [3]. The F:M ratio is 3:1 in the pediatric population [2].

In 2004, specific antibodies against aquaporin-4 (AQP4), a water channel that is found in astrocytic foot processes at the blood-brain barrier (BBB), were identified and these antibodies, also called neuromyelitis optica immunoglobulin-G (NMO-IgG), were found to be directly responsible for the pathogenesis of the disease [4]. AQP4 is responsible for glutamate and potassium regulation in the BBB, synapses, and paranodes adjacent to the nodes of Ranvier [5]. We present a rare case of pediatric NMOSD with radiological findings in brain MRI.

Case Report

A 12-year-old girl was admitted to the hospital with complaints of an inability to walk, weakness in the legs which had been increasing for a week. Her past medical

history revealed complaints of decreased vision in her left eye at the age of 10 years for which she had received steroid therapy at a different center and had a diagnosis of MS. Six months later she was admitted to the same hospital with complaints of difficulty in walking and received long-term steroid treatment and a complete resolution of symptoms was achieved. We are unaware of the patient's physical examination and brain-spinal cord MRI findings at that time.

On her physical examination at our institution, the left eye revealed optic atrophy and was sliding laterally, bilateral lower extremity muscle strength in the distal and proximal was 2/5, deep tendon reflexes were hypoaactive in the lower extremities, and bilateral extensor plantar responses were detected. She experienced decreased sensation up to her lower chest. She had bladder control problems for a few days. Other physical examinations were normal. MRI showed lesions in the dorsal brainstem, periaqueductal area, corpus callosum, white matter including both periventricular areas, centrum semiovale and peripheral white matter (Fig 1A). On spinal MRI, widespread patchy lesions, which involved both gray and white matter (Fig 1B) were seen. Visual evoked potential (VEP) examination recorded prolongation of P100 latency on the left side. Vasculitis markers, viral serology and metabolic tests were normal. The cerebrospinal fluid (CSF) biochemistry and cell count were normal. The oligoclonal band was negative and AQP4-IgG (cell-based in serum) was positive, suggesting the diagnosis of NMOS. She was treated with high dose intravenous methyl prednisolone (30 mg/kg/day), and her symptoms showed improvement after a few days of therapy. The patient revealed grade 4/5 weakness of both lower limbs, bilateral Babinski sign and visual acuity was 20/30 (left eye) before discharge. Therapy was continued with oral prednisolone (1 mg/kg/day). She continued physiotherapy at home.

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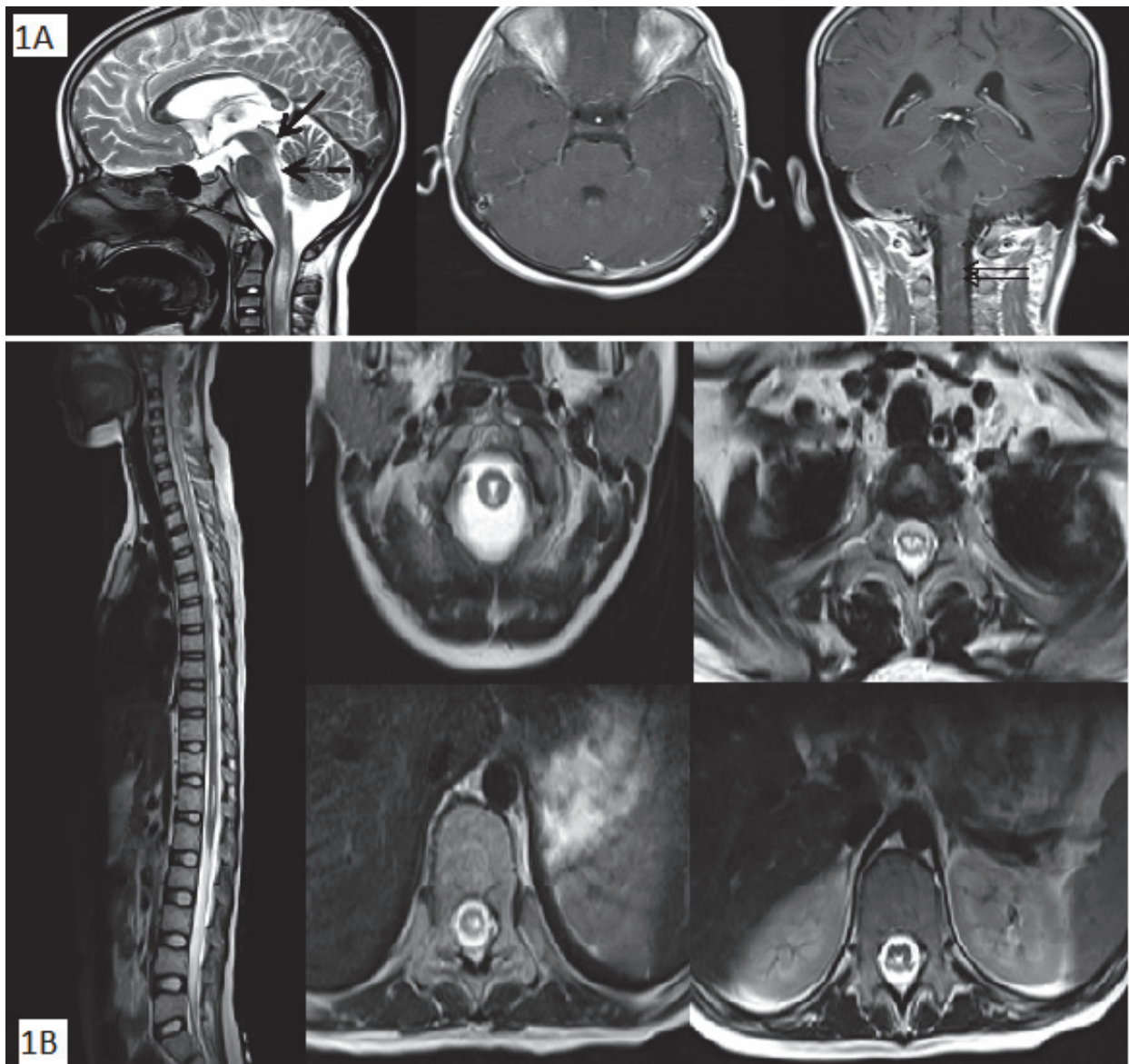


Figure 1. Cranial (A) and spinal (B) MRI at first admission to our hospital.

A. Axial FLAIR images (upper row) show hyperintense lesions of the dorsal brainstem (black arrow), diffuse chronic white matter lesions in the periventricular region and centrum semiovale.

Please note that some lesions show rarefaction (white arrows). Involvement of the corpus callosum with focal atrophy due to chronic lesions, dorsal brainstem (dashed black arrow) and periaqueductal (black arrow) lesions and swollen cervical spinal cord lesion are seen on sagittal T2W image (bottom row, left image). Supratentorial and brainstem lesions do not enhance while spinal cord lesion does (double thin black arrows).

B. Sagittal and axial T2W images display patchy, longitudinal involvement of the spinal cord. Please note that cord parenchyma around the central canal is preferentially involved in some slices. Both gray and white matter were affected.

Spinal MRI at 4 months follow-up showed that some thoracic cord lesions had resolved with loss of contrast enhancement, however widespread chronic residual lesions were still present.

The patient who was receiving oral steroid therapy for 5 months, was admitted to our hospital with a complaint of decreased vision in right eye (visual acuity 20/100, abnormal color vision). Attack therapy did not change the symptoms, and azathioprine (2 mg/kg/day) treatment was started. Cranial MRI showed rarefaction and shrinkage of brainstem lesions with no apparent change in other lesions located in the corpus callosum, and deep and peripheral white matter, which were already chronic at the initial MRI (Fig 2A). Cranial MRI revealed no remarkable interval change with respect to lesion load and appearance of the parenchymal lesions. However,

thickening and enhancement of the posterior intraorbital half of the right optic nerve were observed suggestive of acute ON (Fig 2B).

At the 11 month follow-up, almost complete resolution of the brain stem lesions was observed. Supratentorial white matter lesions were stable (Fig 3A). Partial resolution of the lesions with some chronic residual spinal cord disease was observed (Fig 3B). Long-term oral steroid therapy alone was not efficacious enough to prevent new attacks in our patient, so low-dose prednisolone (10mg/day) in conjunction with azathioprine was started. No new attacks were observed during the one year follow-up. At the last follow-up, the patient appeared healthy with no notable physical findings, and decreased vision (visual acuity 20/30 left eye and 20/50 right eye; normal color vision).

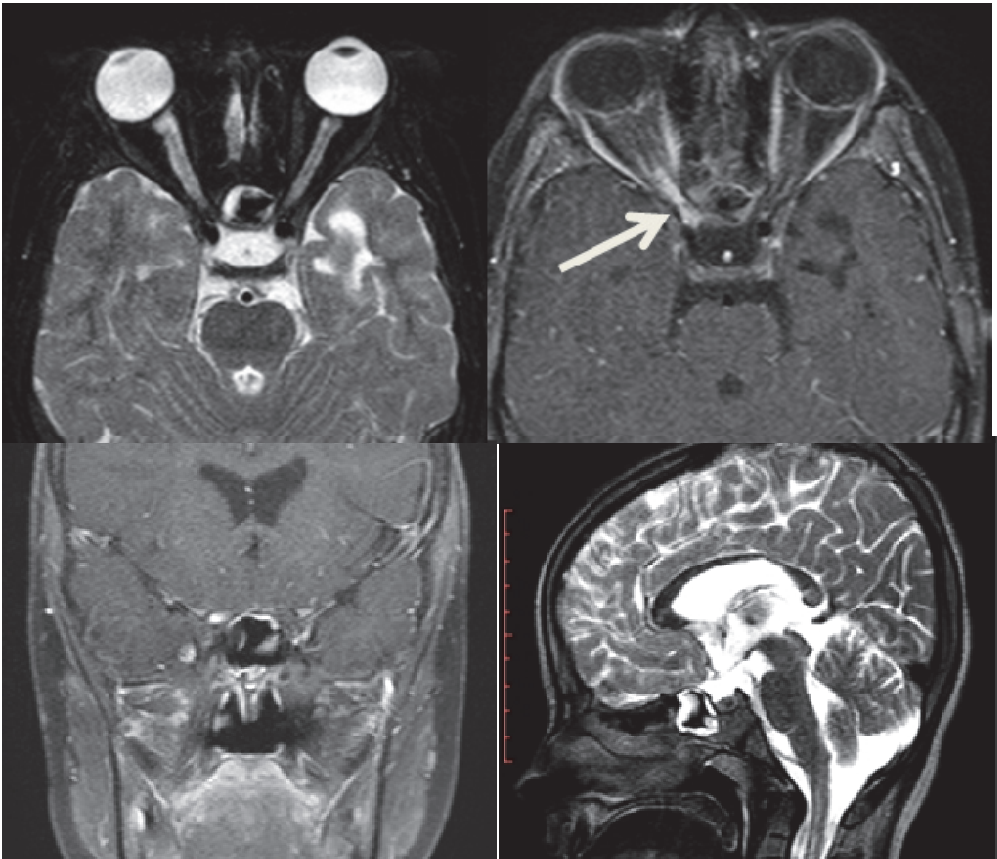


Figure 2. Cranial (A) and orbital (B) MRI at 5 months after the initial study and second admission to hospital, shows shrinkage and rarefaction of brainstem lesions (white arrow, A) with stable supratentorial white matter lesions (A). Right optic nerve is thick and enhances (white arrow, B) on posterior half of its intraorbital segment, suggestive of acute ON (B). Please note that cervical spinal cord lesions show no edema and swelling, and brainstem lesions are not seen on sagittal T2W image (bottom row, right) at this time.

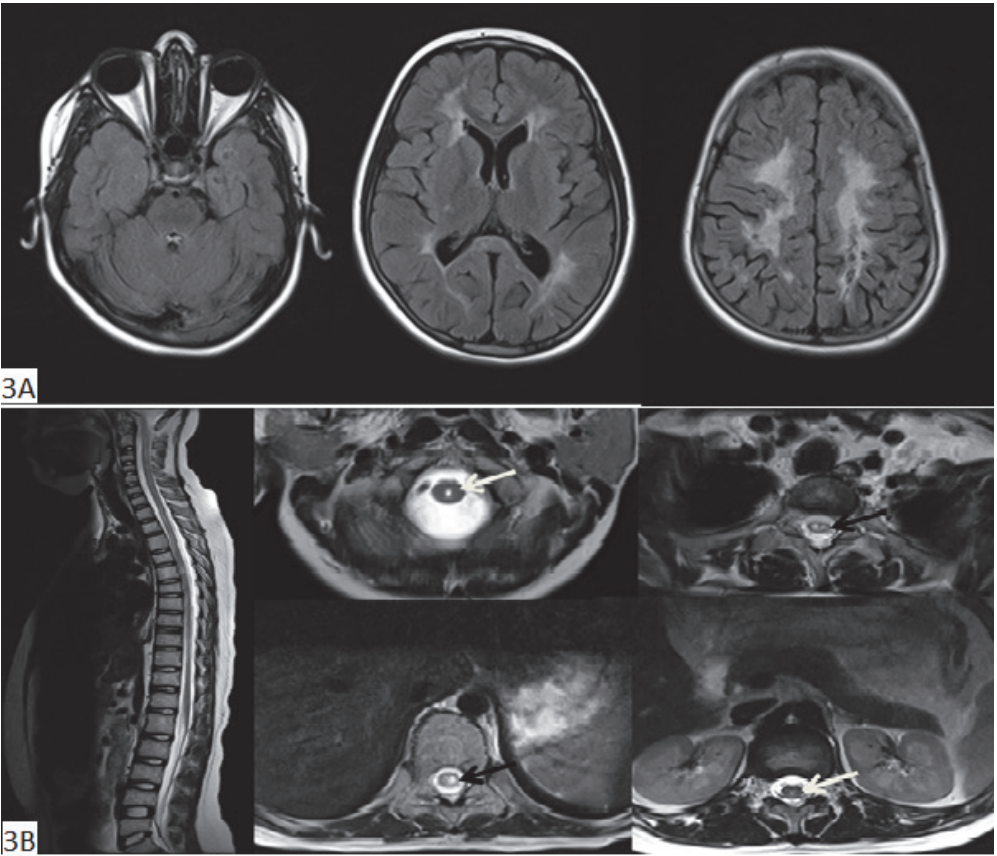


Figure 3. Cranial (A) and spinal (B) MRI at the 11 month follow up. Disappearance of the brainstem lesions is observed with stable supratentorial lesions (A). Intramedullary lesions show marked (white arrows) or mild resolution (black arrows)(B).

This report was approved by the Institutional Review Board of our institution. Patient-informed consent was obtained from the relatives.

Discussion

NMOSD lesions are characterized by humoral inflammatory response and astrocytic cell death with AQP4 loss, followed by inflammatory demyelination and axonal damage [6].

In addition to transverse myelitis and severe bilateral blindness, which are highly suspicious for NMOSD in pediatric patients, cerebral lesions in the hypothalamus, brainstem, or diffuse white matter are found in children with features of NMOSD.

In this regard, brain MRI has an increasingly important role in differentiating NMOSD from other inflammatory disorders of the CNS, particularly from MS [7].

Before the discovery of anti-AQP4 antibody, brain MRI abnormalities were reported in only 13% to 46% of patients with NMO [8]. However, when excluding the brain MRI criteria, the incidence of brain MRI abnormalities increased to 50% to 85% using the revised 2006 NMO criteria [9,10] and to 51% to 89% in seropositive patients with NMOSD [11,12].

In July 2015, a revised diagnostic criterion for NMOSD was proposed by the International Panel for NMO Diagnosis that stratified this disorder further by serologic testing (NMOSD with or without AQP4-IgG positivity). The 'core clinical characteristics' are described as clinical syndromes or MRI findings related to the optic nerve, spinal cord, area postrema, other brainstem, diencephalic presentation, and only one out of these six 'core clinical characteristics' is required for the diagnosis of NMOSD in patients with AQP4- IgG positivity. Patients who are AQP4-IgG negative must experience two or more different core clinical characteristics either in a single clinical attack or multiple attacks out of which one of the clinical events must be one of the three most common clinical characteristics of NMOSD, namely, ON, longitudinally extensive transverse myelitis (LETM) MRI lesion, or an area postrema clinical syndrome [1]. According to these criteria our patient had a relapsing type of presentation, and was AQP4-IgG positive.

Spinal cord lesions in NMOSD frequently present in the cervical and upper thoracic spinal cord segments rather than in the lower thoracic and lumbar cord segments [13]. The lesions mainly involve the central gray matter and AQP4 is abundant in the gray matter and glial cell processes adjacent to the ependymal cells of the central canal of the spinal cord [14]. Pathologically, there are different NMOSD lesions. The classic acute lesion is characterized by perivascular demyelination, severe axonal loss, and necrosis of both the gray and white matter. The second acute lesion is characterized by non-myelinated lesions with vacuolated myelin, given the potential for some lesions to be reversible. Chronic ones are characterized by gliosis, cystic degeneration,

cavitation and atrophy [15]. The cord lesions in our case displayed patchy, longitudinal involvement and were mainly centrally localized. Serially performed MRI revealed that most of the lesions persisted.

There was apparent optic nerve thickening and enhancement on orbital MRI. MRI studies have reported optic nerve sheath thickening, optic nerve hyperintensity on T2-weighted (T2W) images and gadolinium enhancement on T1-weighted (T1W) images in ON of NMOSD [16].

Detection of brain lesions in NMOSD is based on hyperintensity on T2W or fluid attenuation inversion recovery (FLAIR) images. The lesions are typically localized in the periependymal regions surrounding the lateral ventricles, the third ventricle, cerebral aqueduct, and the fourth ventricle, where AQP4 is highly expressed [17]. Other NMOSD-characteristic brain lesions involving corticospinal tracts and hemispheric white matters, where AQP4 expression is not particularly high, have been described [18]. Hemispheric white matter lesions include extensive and confluent hemispheric white matter lesions such as tumefactive lesions, long spindle-like or radial-shape lesions following white matter tracts. Occasionally, cerebral cortical involvement is also seen [12].

Cranial MRI in our case showed hyperintense lesions of the brainstem, diffuse white matter lesions in the periventricular region and centrum semiovale. There was no enhancement in these lesions. Most brain lesions in NMOSD are not enhanced, although enhanced brain lesions can be seen during the course of the disease.

Hemispheric white matter lesions serially often shrink or disappear, although they sometimes remain as cystic lesions which may cause various symptoms, depending on the area they involve [19].

NMOSD must be distinguished from MS, which is the most common disorder likely to cause CNS demyelination. Acute disseminated encephalomyelitis and other autoimmune diseases such as systemic lupus erythematosus (SLE) and Behçet disease may rarely have similar presentations. Longitudinally extensive spinal cord lesions are not specific for NMOSD. They have been described in patients with other autoimmune or inflammatory diseases, including SLE, Sjögren's syndrome, neuro-Behçet disease, MS, parainfectious disorders, and anti-NMDA receptor encephalitis. Differentiating NMOSD from other demyelinating disorders is based upon important differences with respect to clinical course, prognosis, underlying pathophysiology as well as responsiveness to MS-modifying therapies [20].

The course of NMOSD is characterized by a high relapse rate with accumulation of neurologic disability, potentially causing blindness and paralysis. Therefore, relapse prevention is crucial. Even though the optimal therapeutic regimen has not been established, acute NMOSD attacks are mainly treated with corticosteroids,

plasma exchange and IV immunoglobulin; azathioprine, methotrexate, mycophenolate mofetil, rituximab, mitoxantrone, cyclophosphamide, and tocilizumab have been used to prevent relapses [21].

Approximately 5-10% of the cases are described as monophasic, although the optimal definition for monophasic NMOSD remains elusive (the interval between index clinical events that is compatible with monophasic NMOSD is not defined).

Research has observed that patients with monophasic NMOSD are more commonly AQP4-IgG-seronegative as compared to those with established relapsing disease. In addition, patients with seronegative NMOSD tend to have different clinical features and different lesion distributions from patients with seropositive NMOSD. Several studies show a pattern of apparently monophasic NMOSD being associated with more equitable sex distribution, a relatively younger age at disease onset, a tendency to present with simultaneous myelitis and bilateral ON, a lower frequency of other autoimmune diseases, and lower prevalence of AQP4-IgG compared to relapsing NMOSD [22]. A fraction of these patients may have other serum antibodies such as MOG-IgG [23].

Conclusion

Pediatric onset NMOSD is a rare, very disabling and debilitating disease. It is essential to raise awareness of the disease and its presenting features and find out more about the disorder so that we can expand on the limited treatment options available.

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