Neuromyelitis optica in children: a review of the literature

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Neuromyelitis optica (NMO) is a rare and severe inflammatory disease of the central nervous system (CNS), which constitutes up to 5% of pediatric aquired demyelinating diseases. The optic nerves and the spinal cord are the most affected sites. The discovery of an autoantibody called NMO-IgG, which targets aquaporin-4, the main water channel in the CNS, gave a new direction to understanding the underlying immunologic mechanisms. This specific biomarker also helps to distinguish the disease from other demyelinating disorders. Here, we review the clinical and paraclinical features, immunological properties and treatment options of the disease as reported in the literature.

Key words: neuromyelitis optica, aquaporin-4, children, optic neuritis, transverse myelitis.

Neuromyelitis optica (NMO) is a rare and severe inflammatory disease of the central nervous system (CNS) in which the spinal cord and optic nerves are affected[1]. Most reported cases are adults; therefore, knowledge about the immunopathogenesis and clinical course of the disease is based mainly on this age group. When NMO presents in childhood, distinguishing it from other acute childhood demyelinating disorders on the basis of clinical and radiological features may be challenging[2,3].

A serum autoantibody highly specific for NMO was discovered in 2004, and within a year the target antigen was defined as aquaporin-4 (AQP-4), the main water channel in the CNS[4,5]. The discovery of this specific biomarker, NMO immunoglobulin G (NMO-IgG), or aquaporin-4 antibody (AQP-4 Ab), provided new insight into the pathogenesis and differential diagnosis of the disease. We here review the characteristics of NMO and NMO spectrum disorder (NMO-SD), AQP-4 based immunopathogenesis and treatment options as reported in the literature.

History

The first coexistence of optic neuritis (ON) with myelitis to be brought to light in the Western literature was reported in 1804 by the French anatomist and pathologist Antoine Portal[6]. Later in the 19th century, several physicians described patients with similar clinical features[7-9]. In 1894, Devic and his student Gault reviewed the clinical features of 17 patients with ON and myelitis, and used the term "acute optic neuromyelitis" for the first time in the literature[9].

Historically, NMO was considered a monophasic disorder, with ON and myelitis occurring simultaneously. The relapsing form of NMO had been regarded as a severe form of multiple sclerosis (MS). The clinical features of Asian-type "opticospinal MS," in particular, are identical to the current concept of NMO[10]. In the late 1990s it was shown that 80 to 90% of NMO patients had a relapsing course[11]. Also, case series have been published where not only the spinal cord and optic nerves but also the brain was involved[12]. The discovery of AQP-4 Ab, the highly specific serologic marker of NMO, provided further explanation of clinical manifestations[4].

Epidemiology

Epidemiologic studies are lacking for NMO, but several case series report a prevelance in the range of 0.5–4.4/10^5 in the general population[13]. NMO constitutes up to 5% of pediatric acquired demyelinating diseases[14]. It is more common in non-Caucasians; although rates vary among studies, up to 40% of all

demyelinating diseases have been reported as NMO in non-white populations[13,15]. Female preponderance is observed in both the adult and pediatric age groups[1,14,16,17].

Neuromyelitis optica predominantly affects adults, with a median age in the late 30s at presentation[11], but also children and the elderly[1,18]. The median age of children diagnosed with NMO ranges from 10 to 14 years in recent reports, the youngest reported being a 23-month-old boy[1,19].

Most NMO cases are sporadic. Familial cases have been reported and comprise about 3% of all cases, with no features that distinguish them from sporadic ones[20].

Diagnostic Criteria

In 1999 Wingerchuck et al.[11] examined NMO from demographic, clinical, cerebrospinal fluid (CSF) and MRI perspectives, highlighted the differences from MS, and proposed new diagnostic criteria[11]. The autoantibody NMO-IgG described in 2004 helped to further distinguish NMO from other demyelinating disorders[4]. In the following year, the target antigen of this specific antibody was reported to be the predominant water channel of the CNS, AQP-4[5]. Pittock et al. showed that brain involvement, previously accepted as an exclusion criterion for NMO, was not uncommon[12]. These developments prompted reconsideration of the diagnostic criteria: the 2006 revision included NMO-IgG positivity and removed the exclusion of brain involvement at onset (Table I)[15].

The International Pediatric Multiple Sclerosis Study Group proposed consensus definitions for pediatric demyelinating disorders[21], and the following criteria were required in the diagnosis of pediatric NMO: *both ON* and *acute myelitis* as major criteria, and *either* a spinal MRI lesion extending over three or more segments, *or* NMO antibody positivity[21]. The main difference from 2006 was that brain MRI was not included. In 2013 the same group made a revision and proposed the use of adult NMO criteria published in 2006[3]. In the revised version, it is accepted that initial or subsequent attacks in children can manifest with NMO-SD (discussed below) or an acute disseminated encephalomyelitis (ADEM)-like clinical picture, and brain lesions can be localized to the supratentorial area and/or the brainstem, especially around the fourth ventricle and hypothalamus[3].

Availability of NMO-IgG testing also allowed the definition of a group of patients not fulfilling the diagnostic criteria of NMO, but showing seropositivity. These limited forms include recurrent or bilateral ON, isolated or recurrent longitudinal extensive transverse myelitis (LETM), ON or LETM associated with systemic autoimmune disease, and ON or myelitis associated with brain lesions typical of NMO. They are designated as NMO-SD or high-risk syndrome (HRS), as these patients are considered to be at high risk of developing definite NMO[22,23].

Aquaporin-4, Immunopathogenesis and Pathologic Features of NMO

Serum antibodies against a perivascular brain antigen, NMO-IgG, can be detected in individuals with NMO but not in patients with MS[4]. These antibodies characteristically bind to cerebral microvessels, *pia mater* and Virchow–Robin spaces[4]. The target of these antibodies

Table I. Diagnostic Criteria for NMO[15]

Revised diagnostic criteria for NMO
Two absolute criteria
Optic neuritis
Acute myelitis
At least two of three supportive criteria Contiguous spinal cord MRI lesion extending over 3 vertebral segments
Brain MRI not meeting diagnostic criteria for multiple sclerosis
NMO-IgG seropositivity

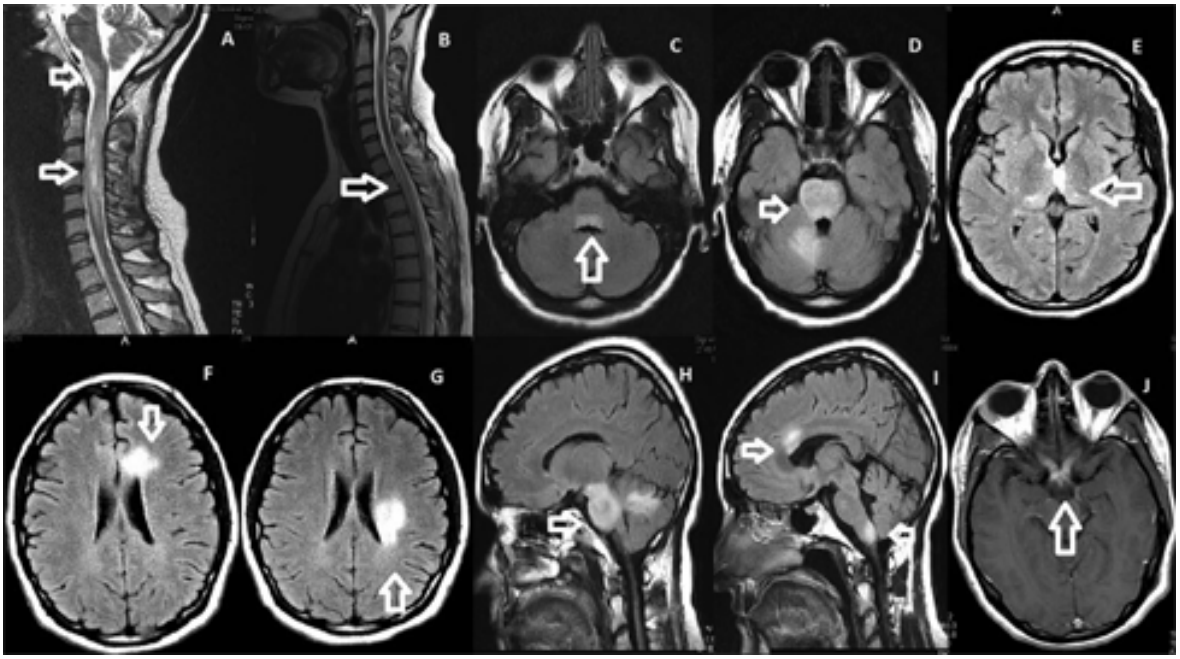

Fig. 1. Brain and spinal MRI of definite NMO patient showing the involvement of AQP-4-rich sites such as the optic chiasm, medulla spinalis, brainstem and regions adjacent to the ventricular system. Upper cervical lesion extending to the medulla **(A)**. Spinal cord involvement (C2-C3, C7-T4) **(B)**. Periependymal lesions surrounding the fourth ventricle **(C-D)** and the brainstem **(D, H)** and cerebellar involvement **(H)**. Periependymal lesions surrounding the third **(E)** and lateral ventricle **(F-G, I)**. Optic chiasm involvement **(J)**.

is the AQP-4 on astrocyte foot processes[5]. Discovery of this specific antibody helped to distinguish NMO and NMO-SD from other demyelinating disorders, MS in particular[4].

The aquaporins are a family of small integral membrane transport proteins whose primary function is to facilitate water movement across cell membranes in response to osmotic gradients[24]. In the CNS, AQP-4 is the predominant water channel and has an important role in brain water homeostasis[25]. AQP-4 is most strongly expressed in the spinal cord, optic nerve and brain astrocytes, especially those located on pial and ependymal surfaces in contact with the CSF[26]. It is also present in different tissues such as the kidneys, gastric parietal cells, skeletal muscle, the airway epithelium and various glandular epithelia.[27]

Aquaporin-4 is present in two major isoforms, called M1 and M23[26]. It can form crystal-like supramolecular assemblies in the plasma membrane, which are called "orthogonal arrays of particles" (OAPs)[28]. Most AQP-4 IgG binds preferentially to OAPs, which is crucial for complement-dependent cytotoxicity[29]. Pathogenic AQP-4 IgG is synthesized in peripheral lymphoid tissue, as a response to a currently unknown stimulus[30]. It is predominantly of the IgG1 subtype, which triggers the complement cascade through the classical pathway. Complement activation disrupts the blood-brain barrier, increases permeability and causes massive leukocyte infiltration into the CNS[23]. Neuronal death, necrosis and demyelination in NMO are due to both complement-mediated and cell-mediated injury.

Immunohistochemical studies demonstrate complement and immunoglobulin deposition sites, with different characteristics in NMO as compared to MS. In NMO, complement components are deposited in a characteristic rim around the vessels, forming a rosette pattern, whereas in MS they are found along the edge of the active plaque[31,32]. AQP-4 immunoreactivity is absent in NMO lesions of all stages, while it is increased in MS lesions[33,34].

Clinical, Radiological and Laboratory Features

Neuromyelitis optica is a severe and disabling disease. Over 90% of patients show a relapsing

course. Attacks are usually more severe than in MS, sequelae are less reversible and disability develops faster[10].

The relapsing form is more common and more severe than the monophasic form. In a cohort of children with NMO, a relapsing course was reported in from 50% to 93% of patients, and in a small series, in up to 100% of patients[2,16,17,35]. Simultaneous ON and myelitis occurred more often in monophasic courses, whereas in relapsing courses these two types of attacks are usually separated in time[1,10]. Relapses occur at unpredictable intervals, but within 5 years after the first event in 90% of patients[11]. Monophasic patients experience more severe attacks, but long-term outcome is better than that for relapsing patients: in the long term, about 60% of relapsing and 30% of monophasic adult patients were functionally blind in at least one eye or had permanent monoplegia or paraplegia[11]. However, the course in children has not been described, and the median time to reach EDSS of 4 and 6 can be significantly longer in children than in adults[35].

A prodromal flu-like illness can precede the neurological symptoms and was reported in from 0% to 100% of patients in different pediatric case series[14,16,36].

Optic neuritis was the initial feature in about half of the adult NMO patients[37]. Unilateral ON is a more common presentation; bilateral ON occurred only in 20% of patients as an initial feature[38]. Visual loss is generally more severe than in MS. In NMO-related ON, 80% of patients experienced severe (>20/200) loss of visual acuity in an acute attack, and 60% experienced unilateral or bilateral blindness at a median of 7.7 years, compared with 36% and 4%, respectively, in MS patients[38]. The detection of unilateral ON can be more challenging in children, mainly because it may be unnoticed by the patient and family. Bilateral ON is suggestive of NMO in adults, but in children bilateral ON is most often related to postinfectious etiologies[39]. In a previous study that evaluated ON features in pediatric cases, only 1 of 14 bilateral ON cases was diagnosed as NMO[40]. On MRI, NMO-related ON can be extensive, involving the chiasm and adjacent hypothalamus, but may also resemble acute ON with optic nerve enlargement, T2 hyperintensity and gadolinium enhancement[38]. In adult cases, extensive ON usually suggests NMO; in children, there is no such relationship[41].

The etiological diagnosis of longitudinally extensive spinal cord lesions is also more challenging in children than in adults. In the latter, the appearance of such cord lesions may help to distinguish MS from NMO and NMO-SD, because the presence of well-circumscribed asymmetric lesions, usually involving less than 3 vertebral segments, is characteristic[15,23]. In children, however, MS and also ADEM may present with LETM: in a cohort of pediatric relapsing-remitting MS cases, 14% had longitudinally extensive spinal cord lesions[2]. Therefore, LETM does not exclude the diagnosis of MS in a child, and has a lower predictive value for NMO-SD than in adults[2]. In the first LETM attack, NMO-IgG seropositivity has a predictive value for a relapsing course in adult patients[42]. Weinshenker and colleagues[42] have documented that 40% of patients who present with a single episode of LETM are seropositive for NMO-IgG and that seropositivity predicts a high risk of a relapse of TM or the subsequent development of ON [42]. This relation has not been shown in children[2]. A recent report showed that short transverse myelitis (STM) might be an initial attack of NMO-SD[43]. Older age, nonwhite ethnicity, history of autoimmunity, tonic spasms, centrally located spinal lesions, T1 hypointensity and brain lesions that are not typical for MS are the other suggested predictors of AQP-4 IgG positivity in patients with STM[43].

There is also a group of patients who show NMO-IgG seropositivity accompanied by limited forms of the disease, which consist of recurrent LETM, recurrent ON, brain or brainstem involvement. These are classified as NMO-SD[13]. Involvement of the brain may manifest with various symptoms such as vertigo, diplopia, encephalopathy, seizure, aphasia or hypothalamic-pituitary axis dysfunction[16,17,25]. In particular, intractable vomiting and hiccups as a result of damage to the *area postrema*, the AQP-4-rich chemosensitive vomiting center, can be a unique symptom of NMO-SD[44,45]. In patients who present with encephalopathy, MRI may show lesions indistinguishable from

those associated with ADEM or posterior reversible encephalopathy syndrome[46]. Initial presentation with a cerebral syndrome has been reported in 16% of pediatric patients[17], while brain lesions in adult patients are usually asymptomatic[12]. NMO-IgG serostatus is the key to differential diagnosis in these patients. The localization of the lesions, in places such as the hypothalamus, periependymal areas and brainstem, is particularly suggestive of NMO and may be particularly helpful in the diagnosis of antibody-negative patients as well as in differentiating NMO from MS.

Brain MRI abnormalities in children with NMO are similar to those in adult patients. Brainstem lesions are most common, usually characterized by signal abnormalities extending from the medulla to the cervical spinal cord[2]. About 10% of adult and up to 25% of pediatric patients have MS-like lesions that fulfill the diagnostic criteria of MS[12,35]. In both adults and children, lesions tend to localize in periependymal areas that are rich in AQP-4, such as the hypothalamus and the periaqueductal brainstem (Fig. 1)[23].

Cerebropinal fluid findings include a mildly elevated white blood cell (WBC) count (>50 WBC/mm^3), often with neutrophilic pleocytosis and elevated protein[1,15]. CSF oligoclonal bands (OCB) are detected in 6% of pediatric patients; the highest incidence of OCB was reported as 27% in a series of 11 pediatric patients[17,35]. OCB positivity can be transient, unlike in MS[47]. Levels of neurofilament light chain protein and glial fibrillary acidic protein, markers of axonal and astrocytic damage respectively, were higher in the CSF of patients with NMO[48].

Neuromyelitis optica IgG testing is generally performed from serum samples. Retesting for NMO-IgG during acute attacks has been recommended in seronegative patients[10]. Selected patients with highly suggestive clinical and radiological features of NMO, but no serum NMO-IgG, should be tested for CSF[49,50].

Neuromyelitis optica IgG is a highly distinctive biomarker for the disease: NMO-IgG seropositivity was detected in 73% of clinically definite NMO patients, and 91% of the patients who were seropositive for NMO-IgG had clinical NMO[4]. NMO-IgG seropositivity also has a predictive value for relapsing and more severe disease courses[51,52]. NMO-IgG status can change during the course of the disease, seroconversion from negative to positive being possible in acute attacks, and vice versa following treatment[16]. In a pediatric cohort, NMO-IgG seropositivity was reported in 78% of children with relapsing NMO and 12.5% of those with monophasic NMO[2].

The mortality rate appears to be higher in NMO than in MS: the 5-year survival rate was reported as 68% in a North American study[11]. Deaths generally occurred from respiratory failure due to severe ascending cervical myelitis or brainstem involvement[11,52]. In more recent studies, the mortality rate is much lower, less than 10%[10,52]. This difference may result from increased awareness of the disease and early initiation of effective treatment[10].

There is a strong relationship between systemic and organ-specific autoimmunity and NMO. The coexistence of autoimmune diseases such as systemic lupus erythematosus (SLE), Sjögren syndrome (SS) or myasthenia gravis (MG), or of their laboratory findings, has been reported to be as high as 50%[10,23,53]. MG associated with NMO/NMO-SD is usually early-onset generalized myasthenia showing a mild course. In most cases, myasthenic symptoms preceded NMO/NMO-SD[54]. NMO-IgG testing is recommended in MG patients with atypical motor and optic symptoms that are not explained by MG[54]. NMO-IgG seropositivity was reported in SLE/SS patients with clinical signs of NMO, LETM and recurrent ON, but not in patients with other neurological syndromes[55,56]. These findings suggest the coexistence of two different diseases in the same patient; however, there is no immunopathologic study demonstrating the relationship of these disorders. One of the explanations for this co-occurrence is genetic susceptibility to autoimmunity[57].

Treatment

Disability in NMO is attack-related, so that early treatment is important both for acute attacks and for the prevention of relapses. Treatment in children is generally based on experience in adult patients and retrospective case series, since no controlled studies have been done and would seemingly be difficult to carry out in children.

In acute attacks, high-dose intravenous methylprednisolone (30 mg/kg/d for 5 days

to maximum 1000 mg daily) is recommended as first-line therapy, followed by oral prednisone taper for 2-6 months[1,48,58]. Plasmapheresis is also considered a first-line therapy in severe attacks or in case of incomplete response to high-dose corticosteroids[1,48]. Plasma exchange (1.0 to 1.5 plasma volume per exchange) every other day for 5 days provides improvement in remarkable proportions of patients in different series[48]. Effectiveness of intravenous immunoglobulin (IVIg) has not been demonstrated in acute attacks of NMO[59].

In seropositive patients and seronegative patients with relapsing courses, early initiation of immunosuppressive treatment is recommended for prevention of further attacks, while an observational approach can be considered in seronegative patients with good recovery because the disease course can be monophasic[1]. There is no consensus nor have there been randomized trials regarding the duration of immunosuppressive treatment, although the first five years after the initial attack present the highest risk for relapse[58]. For long-term immunosuppression, azathioprine (usual target dose: 2.5-3.0 mg/kg/d) combined with oral prednisolone (initial dose: 1 mg/kg/daily), or rituximab (375 mg/m^2 weekly for 4 weeks, with additional dosing depending on CD 19/20 B-cell counts) can be used as a first-line therapy[1,48,59]. In a small case series, favorable results with mycophenolate mofetil (600 mg/m^2/dose twice daily; maximum dose: 1000 mg twice daily) were also reported. Methotrexate, cyclophosphamide and mitoxantrone are other options in refractory cases[1,48,59].

Immunomodulating drugs that are used for MS, such as beta interferons, fingolimod and natalizumab, can be harmful in NMO and should be avoided[48,58-60].

Further therapy options for NMO are based on antigen-specific treatment. Recombinant monoclonal anti-AQP-4 antibodies such as aquaporumab selectively block NMO-IgG binding to AQP-4 and have shown promising results in animal models[58,61].

Conclusion

Neuromyelitis optica is a severe disorder that usually affects the optic nerves and the spinal cord. Brain involvement occurs in about one-fifth of patients as the initial presentation. NMO-IgG is a specific serologic marker of the disease and helps in early diagnosis. NMO can relapse, and disability is attack-related, heightening the importance of early recognition and treatment.

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