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A comparison of pediatric and adult neuromyelitis optica spectrum disorders: a review of clinical manifestation, diagnosis, and treatment

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Abstract: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disorder of the central nervous system (CNS). Serum immunoglobulin G autoantibodies (NMO-IgG) are identified in the majority of NMOSD patients. The Pediatric form presents before 18 years. Based on the similarity of clinical, neuroimaging, and laboratory characteristics of pediatric NMOSD to those of the adult form, the international panel suggested that adult criteria of NMOSD also are appropriate in pediatric patients. However, the proposed criteria need validation in pediatric patients. This strategy poses challenges to the study design in clinical trials in pediatric NMOSD patients.

Keywords: Neuromyelitis optica spectrum disorders - Pediatric
Introduction:

Neuromyelitis optica spectrum disorders (NMOSD) is a rare autoimmune inflammatory disorder of the central nervous system (CNS), which is stratified by anti-aquaporin-4 (AQP4) autoantibody status into AQP4-IgG-positive NMOSD and seronegative NMOSD [1]. This diagnostic biomarker expanded the insight into the pathogenesis of NMOSD and may provide the background for exploring novel therapeutic targets. The Pediatric form presents before 18 years of age [2], and 4% of NMOSD seropositive cases had pediatric onset [3, 4]. Most clinical, neuroimaging, and laboratory characteristics of pediatric NMOSD are similar to those of adult disease. However, there are some differences such as lower female: male ratio (3:1) compared with adults (9:1), a greater proportion of the monophasic course and less specificity of a longitudinally extensive transverse myelitis (LETM) MRI lesion for NMOSD diagnosis.

Since NMOSD is a severe CNS inflammatory demyelinating disorders with a less favourable prognosis than multiple sclerosis (MS) and with different treatment approaches, early stage diagnosis and treatment of NMOSD may prevent disabilities [5, 6, and 7]. New international consensus criteria for NMOSD, published in 2015, suggested that adult criteria of NMOSD may be used in pediatric patients [ref]. However, validation studies in pediatric patients groups are required.

Currently, therapy for the pediatric NMOSD patients is based on adult experiences, which necessitates evaluation of the available agents for recovery from acute relapses and prevention of attacks in the pediatric patient group. The goals of this review are to define the epidemiology, clinical features including MRI characteristic of pediatric NMOSD and to explain how to differentiate it from pediatric MS.

Evidence acquisition:

For this review study, MEDLINE and Web of Science databases were searched for English-language articles published from 1987 to 2016 using the following keywords: Neuromyelitis Optica, Devic Syndrome, Spinal Cord Multiple Sclerosis, Pediatric Devic’s Neuromyelitis Optica, optic neuritis in children, Immunoglobulin G in a child, Devic’s neuromyelitis optica in children, CNS AQP4 autoimmunity in children, Neuromyelitis optica-IgG in childhood, Spectrum of Pediatric Neuromyelitis Optica, Autoimmunity targeting Aquaporin-4, Pediatric central nervous system inflammatory demyelination, NMO-IgG, Relapsing demyelinating CNS disease, Idiopathic Inflammatory Demyelinating Disorders of the CNS in Children, NMO in pediatric patients, Neuromyelitis optica in children, clinical Manifestations epidemiology biomarkers immunology immunobiology MRI characteristics and treatment of pediatric neuromyelitis optica, Diagnostic Criteria for Pediatric Multiple Sclerosis, Juvenile Neuromyelitis Optica which have defined neuromyelitis optica characteristics.

Classification:

The international panel suggested NMOSD be classified to NMOSD with positive anti-AQP4 Ab and NMOSD without anti-AQP4 Ab.

Diagnosis:
The last international consensus on diagnostic criteria for neuromyelitis optica spectrum disorders have defined 6 core criteria for diagnosis of NMOSD, including optic neuritis, transverse myelitis, area postrema syndrome, acute brainstem syndrome, acute diencephalic clinical syndrome, and symptomatic cerebral syndrome. To diagnose NMOSD with positive AQP4-IgG, only one core criterion is enough; for NMOSD without AQP4-IgG, however, 2 core criteria are necessary for diagnosis, and at least one of these 2 core criteria should be optic neuritis, transverse myelitis, or area postrema syndrome. Moreover, to diagnose NMOSD without AQP4-IgG, additional imaging requirements for any of 2 core criteria are mandatory [1]. The international panel suggested that adult criteria are utilizable in pediatric patients, although, according to the current criteria, some cautions are supposed to be considered in pediatric patients. For example, in ADEM-like presentation in children, in addition to the encephalopathy, polyfocal clinical presentation favoring demyelination must be considered for an NMOSD diagnosis [104]; LETM MRI lesions are less specific in pediatric patients than in adults [1].

**Epidemiology:** According to a report from the US Network of Pediatric MS Centers, the youngest patient with NMOSD was 16 months old. Mean patient age (years) of pediatric NMOSD was 10.2 ± 4.7 at onset. Onset prior to age 11 years is less common in NMOSD. Female/male ratio was reported as 1.5/1 in patients less than 11 years of age and 3.25/1 in those more than 11 years. Non-white race is more common in NMOSD patients than MS and ADEM [8]. In the European pediatric population as reported by Huppke (ref), NMOSD seems to be rare. The median age at onset was 12 years (13-17 y), the female/male ratio was 42:76, and only 2 patients were seropositive [9]. In a Brazilian report of pediatric NMOSD, the median age at presentation was 13 years (5-17y), the reported female/male ratio was 2.6/1, and the majority of more patients were of mixed ethnicity (Caucasian and African) [10]. In a case note review of pediatric onset NMOSD from the UK national NMOSD service, the male/female ratio was 2:1. The median age at onset was 10.5 (2.9–16.8) years [11]. In a prospective multicenter study, the reported female/male ratio was 1.04/1. Median age at the first presentation was 9 years (0.75–17 years), and the most common ethnicity was Caucasian [12]. Then although NMOSD seems to be rare but might be presented before 17 years among different ethnicity and more common in female than male.

**Clinical features:**

Two important clinical presentations of NMOSD are optic neuritis (ON) and transverse myelitis (TM). ON is defined as an inflammatory process of the optic nerve. ON presents with acute reduction in visual acuity during hours to days, with color obscuration especially of red, and accompanying pain with eye movements. Unilateral or bilateral ON could be the first manifestation of MS or NMOSD. In more than 50% of adult NMOSD patients, ON was the first initial presentation [13]. Although unilateral ON is more common, bilateral ONwas the first presentation in 20% of patients. Compared with MS, visual loss is commonly more severe, and in 80% of patients a visual loss more severe than 20/200 was detected during acute attacks. Formally, unilateral or bilateral blindness at a median 7.7 years was reported in 60% of patients. Unilateral ON may be ignored by patients or parents and its diagnosis delayed [14]. Contrary to adults, bilateral ON in children is most often associated with post-infectious causes [15].

TM is defined as a spinal cord inflammation causing sensory, motor, and/or autonomic involvement. At the neurological examination, the patient is paraparetic with sphincter dysfunction. LETM presents as a sub-type of spinal cord lesion with the involvement of more than 3 vertebral segments.
In children, MS and acute demyelinating encephalomyelitis (ADEM) may present with LETM. Therefore detection of a LETM MRI lesion may be less specific for NMOSD in pediatric patients [16, 17].

**Area postrema syndrome:** Area postrema is a circumventricular organ, located in the dorsomedial part of the medulla oblongata and might be seen in the caudal part of the 4th ventricle as two projected areas [18]. Area postrema is exposed to factors from the circulation due to the lack of a blood brain barrier (BBB), which could modulate homeostatic responses [22]. One of the core criteria of NMOSD presentation is area postrema involvement syndrome and area postrema syndrome presenting with intractable vomiting and hiccups may be the initial presentation of fulminant NMOSD in adults [27][23]. In one review of NMOSD patients, 21% had hiccups and 17% had nausea [24]. Another study reported that 50% of patients presented with this syndrome [25]. In a neuropathological study, 40% of patients' specimens showed complement deposition, myelin preservation, and loss of AQP4 in area postrema [26]. It seems that the isolated area postrema syndrome is more specific for NMOSD than lesions extending to this area [28], but area postrema sole MRI involvement is not specific for an NMOSD diagnosis and should be related to the clinical presentation [29]. As a caveat, area postrema syndrome might be the first presentation of MS and thus is not specific for neuromyelitis optica [30].

**Acute brainstem syndromes:** Human caudal hindbrain consists of neural pathways and groups, which is named brainstem. If involved, it is defined as one of the NMOSD core criteria. Brainstem syndrome was reported as between 8% [31] to 39% [32] in different adult studies. One study reported 32.7% Abs in seropositive and 26% involvement in seronegative NMOSD adult patients. The type of involvement was not different between the two groups. Two or more brainstem involvements were reported in 41.3% of patients during the disease course. Vomiting and hiccups were the most common symptoms. In pediatric NMOSD patients, 40% manifested brainstem symptoms and 44% presented with intractable vomiting. Diplopia occurred in 16.7%, facial palsy in 11.1%, and vestibular ataxia and dysarthria was observed in 5.6%. This study [33] did not report any difference between adult and pediatric patients in distribution of brainstem symptoms. In this study, brainstem involvement occurred in the early stages of disease [33]. Neurogenic respiratory dysfunction due to medullary respiratory center dysfunction is a possible brainstem symptom [34]. Oscillopsia and different types of nystagmus and eye movement abnormality because of dysfunction of pons and medullar eye movement nuclei and tracts have been reported [35]. Trigeminal autonomic cephalalgia is a rare presentation in pediatric NMOSD [36].

**Acute diencephalic clinical syndrome:** The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a common presentation of NMOSD [37, 38, and 39]. It is sometimes relapsing [40], occasionally as a first presentation [41], and is not always associated with AQP4-IgG seropositivity [42]. Inappropriate antidiuretic hormone secretion (SIADH) with NMOSD association is important and AQP4-IgG testing has been suggested in any unexplained SIADH associated with unexplained progressive unconsciousness, especially with bilateral anterior thalamus and hypothalamus brain MRI involvement [43]. Hypotension, hypersomnia, hypothermia, behavioral changes, amenorrhea galactorrhea syndrome [44], and narcolepsy [45]. This syndrome have been reported in a 12-year-old girl with AQP4-IgG positive NMOSD three month after presenting paraparesis and lower cranial dysfunction [12].
Cerebral syndromes: This syndrome is not common in many NMOSD patients, but it is possible. AQP4 rich areas are located in circumventricular and ependymal ventricular areas and are considered to be highly susceptible for involvement. Large cerebral hemispheric lesions in NMOSD could cause hemiparesis, visual field involvement, and encephalopathy [46]. Yet, the most common brain lesions in NMOSD are small subcortical T2 lesions [46, 47, and 48]. Of course, this ADEM like syndrome have been reported in pediatric MOG antibody-positive and aquaporin-4 (AQP4) antibody-negative patients and have not been seen in aquaporin-4 (AQP4) antibody-positive pediatric NMOSD [12].

Rare neurological presentation:

It is possible that AQP-4 ab-related inflammation occludes the cerebral aqueduct and causes hydrocephalus. Another explanation is widespread ependymal/meningeal AQP4-IgG mediated inflammation. The prevalence of hydrocephalus in NMOSD was reported as low as 1%, but more than the general population prevalence expectation [49, 50]. Meningeal enhancement and conus medullaris inflammation was also reported in NMOSD patients [51, 52]. AQP4-IgG-mediated inflammation in the inner part of the conus medullaris explains the rare myeloradiculitis presented in NMOSD patients [52]. Above rare presentations have not reported in pediatric NMOSD patients yet.

Comorbid autoimmunity disorders:

A known Sjogren’s syndrome patient presented with ON and TM with positive Anti-SSA autoantibodies (Anti-Sjögren’s-syndrome-related antigen A). An MRI showed optic nerve involvement and longitudinal extensive transverse myelitis, but AQP4-IgG was negative [53]. Based on new NMOSD criteria, this patient’s condition was characterized as NMOSD without AQP4-IgG. A 10-year-old female patient presented with recurrent optic neuritis myelitis and MRI features of NMOSD disorders. AQP4-IgG was negative, but based on elevated ANA and Anti-RO and Anti-La (Anti-Sjögren’s-syndrome-related antigen B) levels, she was diagnosed with primary Sjogren’s syndrome [54].

Myasthenia gravis (MG) concomitant with NMOSD is frequently reported, and it seems it could cause a benign course of myasthenia [55, 56]. Usually, NMOSD presents after MG and has an aggressive course [56]. Optic neuritis and myelitis was reported in a known case of systemic lupus erythematosus (SLE) in a female patient; she was also AQP4-IgG positive [57]. In conclusion, in any pediatric autoimmune neurologic presentations, concomitant NMOSD is supposed to considered.

Comorbid cancer disorders:

The frequency of neoplastic disorders in NMOSD was more common than in MS [58, 59]. Actually on the other hand, NMOSD may present as a paraneoplastic disorder, and cancer treatment may cure NMOSD [60, 61, and 62]. Anyway these comorbid cancer disorders have not been reported in pediatric NMOSD yet.

Pathogenesis:

In 2004, an IgG antibody named NMO-IgG was identified for the first time in the serum of NMO patients by the Mayo Clinic group [63]. In 2005, a water channel on the astrocyte foot process
(AQP4) was shown to be explained as a target of this antibody [64]. All the current information about AQP4 has resulted from AQP4 knockout mice, because genetic mutation in AQP4 has not been reported in humans [65]. AQP4 aggregation in cell membranes forms a supramolecular protein structure named orthogonal arrays of particles (OAPs) [66]. AQP4 is generally expressed in the astrocyte foot process, gathers at the ependymal and pial surfaces in contact with blood vessels and cerebrospinal fluid [67, 68]. It acts as a water channel and prepares the possibility of water flow in response to osmotic gradients [69]. Although AQP4 is commonly expressed in the brain, spinal cord, and optic nerves, its expression in other organs, for example, in the collecting tubule of the kidney, skeletal muscles, glands, airways, and parietal cells of the stomach, has been documented [70]. However, pathologically autoimmune mediated abnormality in peripheral AQP4 has not been reported. AQP4-IgGs generally bind to CNS structures and start and complement fixation mediated autoimmunity in NMOSD [71]. AQP4 IgG is positive in 68-91% of NMOSD patients and is highly specific (85-99%) [72]. Before any NMOSD neurologic attack, AQP4-IgG levels increase, and after pulse, plasmapheresis, or attack remission, they decrease [72, 73]. AQP4-IgG concentration is 500 times more in serum than in CSF; thus, it seems that peripheral and secondary antibodies enter the CSF [74]. Nevertheless, lodged plasma cells defined in CSF seem to be a source of AQP4-IgG production [75]. In all circumstances, circulating AQP-IgG alone cannot completely explain the immunopathogenesis of NMO [72]. It seems that one important part of the continuing inflammatory process is disruption of the blood brain barrier, which is accompanied by neutrophil and macrophage infiltration [76]. In NMOSD, demyelination happens secondarily to astrocyte damage [77], and ultimately, axonal degeneration and neuronal necrosis occur [78].

Neuroimaging:

Magnetic resonance imaging plays a key role in the diagnosis and follow-up of NMOSD patients.

Optic nerve MR imaging:

During acute optic neuritis in the course of NMOSD, optic nerve MRI shows hyperintensity in fat suppression T2 weighted sequences and presents enhancement in fat suppressed T1 weighted with gadolinium in 94% patients [79]. This finding is not characteristic of NMOSD, however, and is also described in multiple sclerosis. More posterior involvement of the more posterior part, including chiasm, bilateral involvement, and involvement of more than half the optic nerve length, has been observed in NMOSD [80, 81]. Fig- 1

Spinal cord MR imaging:

Spinal cord inflammatory involvement in NMOSD usually shows hyperintensity in T2 weighted and hypointensity in T1 weighted MRI sequences. Cervical and upper thoracic spinal cord involvement is most common. Cord lesions usually extend to more than 3 complete vertebral segments, affecting both white and gray matter, mainly the central component, and is named LETM (longitudinally extensive transverse myelitis) [82, 83, and 84]. LETM in an MRI of the spinal cord with acute myelitis is a characteristic feature of NMOSD, which is rare in adult MS [85]. In children, however, LETM may be observed in MS and ADEM. One cohort study reported 14% LETM in pediatric MS patients [86]. Therefore, LETM does not rule out MS in pediatric patients and suggests a lower predictive value in
pediatric rather than adult NMOSD [86]. MS cord lesions extend about one vertebral segment, involve dorsolateral white matter, and might be asymptomatic. LETM in the acute phase may be enhanced in T1 weighted MRI with gadolinium. In the chronic phase, spinal cord lesions might be seen as longitudinally extensive cord atrophy. Meanwhile, short segment myelitis cannot rule out NMOSD [87]. On the other hand, many differential diagnoses may be entertained when LETM presents in a patient. For example, spinal cord infarction, neoplastic, granulomatosis, infective, and paraneoplastic etiologies [51]. Fig - 2

Brain MR imaging:

Before the discovery of AQP4-IgG, unexplained scattered white matter brain MRI abnormalities were defined in NMO patients [88, 89]. After the expression of AQP4-IgG, these lesions referred to an area with more expression of AQP4 [90, 91]. However, MRI abnormalities can occur in areas where AQP4 presentation is not high [92]. Actually, scattered dots and patches at T2 hyperintensity in deep and subcortical white matter are the most common brain MRI findings in NMOSD patients [94]. With the passage of time during the disease, the incidence of brain MRI abnormalities will increase. For this reason, the incidence of brain MRI abnormalities among various studies ranges between 50% and 89% [92, 93, and 94]. Periventricular areas of the third and fourth ventricles, midbrain, cerebellum, infratentorial, and supratentorial regions are the common sites of involvement [93]. Area involvement in adult and pediatric patients are similar, but one study reported that brain MRI involvement was more common in pediatric patients than in adults [95]. Conversely, MS-like lesions in are reportedly more common in pediatric NMOSD (25%) than adult cases (10%) [96].

NMOSD Brain MRI abnormality classification:

A. Periependymal ventricular lesions: A third ventricle and cerebral aqueduct lesion involving the hypothalamus, thalamus, and anterior border of the midbrain present in hypothalamic and behavioral syndromes [91, 92, and 93]. The dorsal brainstem near the 4th ventricle is one specific area where area postrema lesions are involved and could cause nausea, vomiting, and intractable hiccups [91, 92, and 93]. Linear-shaped cervical lesions extend to the dorsal brainstem.

B. Periependymal lateral ventricles lesions: Different callosal lesions have been described in NMOSD brain MRI. These lesions are near the corpus callosum and follow the ependymal lining with various shapes [92]. Heterogenous and edematous callosal lesions (having a marbled pattern) involve all thicknesses of the splenium (arch bridge pattern) and callosal lesions extending to the hemispheric cerebral white matter as confluent lesions have been defined in various case of NMOSD [92]. In the chronic phase, corpus callosum cystic lesions and atrophic change have been described [97].

C. Hemispheric lesions:

Large confluent white matter lesions more than 3 cm in diameter but without any mass effect on neighboring structures has been described in a brain MRI of NMOSD patients [92]. These lesions sometimes follow the white matter tract and form spindle- or radial-shaped lesions [92]. These lesions are more common in pediatric patients than in adults [99] and in AQP4-IgG positive patients than negative ones [99]. Furthermore, they may mimic Baló lesions, posterior reversible
encephalopathy syndrome [100], acute disseminated encephalomyelitis [101], and even tumoral lesions [102].

D. Lesions following corticospinal tracts:
Lesions involving the unilateral or bilateral corticospinal tract may follow the posterior limb of the internal capsule to end cerebral peduncles of the midbrain or pons [92].

E. Nonspecific lesions:
These scattered T2 hyperintense dots and patches are the most common brain MRI lesions in NMOSD patients and are frequently asymptomatic [91, 92].

F. Enhancing lesions:
Various forms of enhancement have been described in the neuroimaging of NMOSD patients. Cloud-like patterns [103] enhancement, a poorly marginated patchy pattern of enhancement, a pencil-thin linear pattern [98] of enhancement around the lateral ventricles, and nodular and meningeal patterns of enhancement [92] have been described in NMOSD patient brain MRIs with contrast; they are different from MS patterns of enhancement and useful for differentiation.

A case report of pediatric NMOSD:
A 14-year-old boy with a history of right optic neuritis from which he recovered by pulse therapy 5 months ago; was referred to the MS clinic with a history of numbness of both lower limbs since 3 weeks ago. Neurological examination showed paraparesis with sphincteric involvement and a T4 sensory level, which improved by pulse therapy. Vasculitis lab test was normal. CSF oligoclonal band and myelin oligodendrocyte glycoprotein antibody were negative and AQP4-IgG was positive. Brain and cervicothoracic MRI was performed. The brain MRI was normal but in the cervicothoracic MRI, a long cervicothoracic LETM was seen (fig 2-B). Based on imaging and criteria, NMO was diagnosed and azathioprine was administered. In the last 3 years, no new relapse has occurred.

Treatment:
Attack-associated disability is greater in NMOSD than in MS; it could even be life threatening according to adult experiences. In contrast to MS, attack in NMOSD is not classified as mild, moderate, or severe, because disability in NMOSD is exclusively associated with relapses. Thus, early treatment and prevention of attacks are crucial in NMOSD patients. Because of the lack of controlled studies in the pediatric group, treatment must be done based on adult experiences. The international consensus guidelines in adult NMOSD proposes a lifelong treatment approach for NMOSD with AQP4-IgG [1]. About 5-10% of adult NMOSD has presented as a monophasic disorder. Also, according to the last international consensus NMOSD guideline, at least 5 years after the first attack should be considered before assuming monophasic NMOSD. On the other hand, at least 4 weeks interval after the initial attack need to be considered for relapsing NMOSD. Otherwise, AQP4 IgG seropositivity is a crucial concern to the commencement of treatment, even in the apparently clinical remission setting [1].

1. Acute exacerbations:
Relapses must be treated as soon as possible after initial presentations, even with a mild presentation. Even a mild attack may result in devastating neurological disabilities similar to blindness, complete paraplegia, or even quadriplegia with respiratory insufficiency when an LETM extends to area postrema and involves the medullary respiratory center. As a first-line treatment, high-dose intravenous methylprednisolone (30 mg/kg/d for 5 days to a maximum of 1000 mg daily) is recommended [105]. Before starting methylprednisolone, any infection should be ruled out and a urinalysis should be performed. If significant improvement does not occur by day 5, plasma exchange (5 exchanges over 5–10 days) should be considered [106-113]. If plasma exchange is not accessible, intravenous immunoglobulin (a total dose of 2 g/kg) is recommended [114]. Some authorities would prefer to continue high-dose oral prednisolone, tapering down slowly over 2 to 6 months [115]. Others would suggest to continue longer-term maintenance corticosteroid therapy as an attack prevention strategy [116]. The guidelines of the American Society for Apheresis (ASFA) do not distinguish pediatric from adult indications of plasma exchange. Limitations of plasma exchange in the pediatric population are unclear indications and technical difficulties. Pain, thrombosis, bleeding, and infection are the major risks, and pneumothorax, cardiac arrhythmias, hemothorax and central vein stenosis are the important complications of venous access. In children, because of small blood volume intraprocedural anemia, iron deficiency anemia should be considered. Citrate-related hypocalcemia is a major concern in pediatric plasma exchange, and it is important to emphasize that hypocalcemia symptoms in children are hypotension, pallor, vomiting, and abdominal pain, which are different from adult symptoms. According to the American Society for Apheresis (ASFA), plasma exchange is included as a class II indication for acute steroid refractory pediatric CNS-, MS-, and NMOSD-associated demyelinating disorders [117]. Intravenous immune globulin is safe for use and well tolerated in the pediatric population. Nausea, headaches, and fever are common complications and aseptic meningitis or anaphylactic reaction is rare complications of intravenous immune globulin [118]. In contrast with plasma exchange, it’s the effectiveness of which has been confirmed in patients including pediatric patients [109], IVIG clinical effectiveness has not be proven in acute exacerbation of pediatric NMO [119].

2. Prevention of relapses:

Neuromyelitis optica spectrum disorders are rare in both adults and children, but they are potentially life threatening. There has been no randomized clinical trial for preventive therapy in NMOSD. Experiences of immunosuppressive therapy in adults, which confirmed that immunosuppressive therapy reduced mortality rates by reducing relapse rate and severity [120, 121], give rise to the immunosuppressive therapy rational in pediatric groups.

2.1. First line therapy:

2.1.1. Azathioprine:

A purine synthesis inhibitor inhibits cell proliferation, especially T and B cells with inhibition DNA synthesis. For renal transplantation and active rheumatoid arthritis, azathioprine received FDA approval as an adjunctive treatment. Its efficacy in adult NMO preventive therapy has been reported. Its use in a large group of pediatric NMO patients demonstrated its effect on reduced attack frequency [3]. The recommended dose of azathioprine is 2-3mg/kg, and its effects will start after 6 months. During this 6 months, especially if concomitant corticosteroid therapy continues at lower than 20 mg/d prednisolone, patients might experience a new relapse. Key laboratory findings
in favor of effective suppression of lymphocyte counts with azathioprine raises the mean corpuscular volume at least 5 points from the baseline [122]. Before starting azathioprine, thiopurine methyltransferase (TPMT) activity should be measured. In patients with low TPMT activity, the risk of azathioprine toxicity, which presents with gastrointestinal symptoms and myelosuppression, will increase. In patients with low TPMT activity, treatment may be switched to other immunosuppressive drugs. If that is not possible, then a 50% reduction in azathioprine dose should be considered. Common adverse events are fever, malaise, thrombocytopenia, hepatotoxicity, leukopenia, infections, and myalgia [123, 124].

2.1.2. Mycophenolate mofetil:

Mycophenolate mofetil inhibits the proliferation of T and B lymphocytes and B lymphocytes antibody production by inhibiting inosine monophosphate dehydrogenase which plays a key role in guanosine nucleotide synthesis. Practically, a prescription of 2–3 g/day in a divided dose, and similar to azathioprine, will begin taking effect after 6 months. Continuing a moderate dose of corticosteroid during this 6 months is supposed to be considered. Its therapeutic effect on bone marrow suppression should be monitored by measuring the absolute lymphocyte count; when absolute lymphocyte count is reduced to lower than 1500/µl, its effect is starting. Mycophenolate mofetil is commonly used in organ transplantation rejection prevention; it is increasingly being used in autoimmune diseases, like systemic lupus erythematosus, psoriasis, and myasthenia gravis. Limited adult case series have reported that mycophenolate mofetil can reduce the annual relapse rate of NMOSD patients [125, 126]. Mycophenolate mofetil in pediatric NMO case series has shown favorable clinical results [4]. Common adverse events of mycophenolate mofetil are constipation, leukopenia, headache, hair loss, anxiety, diarrhea, and bruising, but this drug is well tolerated [127].

2.1.3. Rituximab:

A chimeric monoclonal antibody against CD20, a membrane protein present on pre-B cells and matured B cells but not expressed on plasma cells or stem cells, reduces B-cell activity and mediated autoimmunity [128]. The recommended dose of rituximab is 375mg/m² every 4 weeks [129], but the most frequently followed regimen is 1 g by IV 2 weeks apart and then repeated every 6 months. An individualized alternative regimen is 1 g by IV, monthly CD19 lymphocyte monitoring by flow cytometry, and an alternate infusion of 1 g IV if CD19 lymphocytes increase more than 0.1% of total lymphocytes. The onset of Rituximab’s therapeutic action might be delayed 1 month because of plasma cell sparing of anti-CD20 therapy; relapse may occur within one week after the administration of rituximab. Co-administration of corticosteroid therapy at least 2 weeks after rituximab infusion may reduce this risk [130, 131]. Pre-treatment hepatitis B infection screening is recommended. As chimeric monoclonal antibodies, infusion-associated reaction present with rash, flu-like syndrome, headache, nausea, and fatigue, especially with the first infusion [132]. In such case, pre-treatment administration of acetaminophen (10–15 mg/kg oral dose), diphenhydramine (0.5 mg/kg oral dose), and methylprednisolone 125 mg intravenously 30 minutes before infusion is recommended [133]. The most common non-infusion-associated adverse event is infection, particularly in the upper respiratory tract [115]. Off-label studies have reported rituximab use in
pediatric NMOSD patients. It seems that rituximab was well tolerated and reduced the annual relapse rate of pediatric NMOSD significantly [3, 4, 13, and 134]. Although progressive multifocal leukoencephalopathy (PML) has been reported with rituximab use in other autoimmune diseases, no PML has been reported in NMOSD or MS [135].

2.2. Second line therapy:

2.2.1. Methotrexate:

An inhibitor of dihydrofolate reductase and inhibition purine synthesis was used for only one child in an adult case series of NMOSD, and 36 months of remission as a monotherapy was reported [3]. Hepatotoxicity is a major safety concern in treatment with methotrexate, especially in overweight patients. Methotrexate should be avoided in chronic viral hepatitis and hepatic transaminase derangement.

2.2.2. Mitoxantrone:

An inhibitor of topoisomerase II caused DNA intercalation has commonly been used for acute myeloid leukemia. Acute leukemia and cardiomyopathy are the major risks of mitoxantrone use which limits its use only in refractory cases. The only experience of mitoxantrone in pediatric NMO is related to a single refractory patient [136].

2.2.3. Cyclophosphamide:

Cyclophosphamide has usually been used as an induction therapy and administered in an intravenous dose of 1000 mg/m² monthly for 6 months. In such cases, treatment is usually switched to other immunosuppressive drugs [136].

Stop treatment:

NMOSD with positive AQP4-IgG should be treated with preventive therapy despite a prolonged clinical remission, because relapses in NMOSD are unpredictable and potentially life-threatening [1].

Avoided therapies:

Some MS immunomodulatory treatments such as interferon-β, fingolimod, natalizumab, and alemtuzumab have no place in NMOSD treatment and may exacerbate the course of the disease [137-140]. Catastrophic NMO relapses were reported with dimethyl fumarate, although the evidence favoring it is not enough [141, 142].

Treatment of NMOSD without Anti-AQP4 Ab:

With modern assays, NMOSD without AQP4-IgG is uncommon. It seems the annual relapse and disability rates of NMOSD without AQP4-IgG present similarly with NMOSD with AQP4-IgG [143]. For this reason, both positive AQP4-IgG and NMOSD without AQP4-IgG are treated in the same manner [1].
Pregnancy considerations:

In contrast to multiple sclerosis in which disease relapses decrease during pregnancy (especially in the third trimester), pregnancy imposes negative effects on the NMOSD course, and relapses increase in the first trimester [144, 145]. Nearly 50% of patients suffer a new exacerbation during this time [146]. A high number of relapses before pregnancy could be a marker for high attack possibility during pregnancy [146]. High miscarriage possibility in NMOSD patients with positive anti-AQP4 Ab was reported, and it seems that AQP4-IgG placental-induced inflammation plays a role in such circumstances [147]. Based on the increased possibility of a new attack during pregnancy that may result in severe neurological disability or even be life threatening, a treatment strategy should be considered during pregnancy. Corticosteroid at the lowest possible dose could be continued during pregnancy as a maintenance therapy [148]. Experiences of azathioprine treatment continuation during pregnancy in inflammatory bowel disease, renal disease, and connective tissue disease could suggest the continuation of azathioprine in pregnant NMO patients [149]. Nevertheless, the benefits of continuing azathioprine must be weighed against the risks of discontinuing it [150]. Azathioprine is safe during breastfeeding [151]. Mycophenolate mofetil and methotrexate are absolutely contraindicated during pregnancy [151]. According to the rituximab manufacturer’s recommendations, rituximab should be stopped 12 months before pregnancy, but in highly active pregnant NMO patients and especially during the first trimester it can be considered for treatment [152].

Baby care:

The coexistence of NMOSD and myasthenia gravis was reported [153,154]. Transient neonatal myasthenia gravis was reported in a baby born from an NMOSD mother [155]. Because of the possibility of respiratory problems, pediatric experts should consider respiratory neonatal respiratory resuscitation facilities for babies of NMOSD mothers [151].

MOG antibody syndrome:

Myelin oligodendrocyte glycoprotein (MOG) is a surface protein of oligodendrocytes and has been regarded as a target of autoantibody-mediated demyelination since 30 years ago. Animal and experimental demyelinating models have confirmed anti-MOG pathogenic roles in demyelination. Now, the international consensus guideline defines unique clinical and radiological presentations of anti-MOG antibody-associated demyelination in children (pediatric) and adults [156]. The anti-MOG syndrome might present encephalopathy in young children and optic neuritis in older children as a first symptom. In young children, the final diagnosis could be MS, ADEM or ADEM-ON but in old children, the final diagnosis might be CIS, MS or NMOSD. The involvement of the corpus callosum and thoracic LETM are not common in anti-MOG positive patients. The CSF WBC count was reported to be significantly high in anti-MOG seropositive patients[157]. Studies in pediatric NMOSD with both AQP4-IgG and anti-MOG seropositivity reported more bilateral optic neuritis and caudal myelitis but fewer attacks compared to patients with only AQP4-IgG positive or both antibodies negative patients. On the other hand, anti-MOG positive patients less often required treatment with immunosuppressive drugs [158]. Actually, MOG antibody seropositivity is not associated with the course of multiple sclerosis [158,159 and 160]. A large adult cohort study showed that anti-MOG
associated syndrome start and continue with its own rules. A characteristic clinical presentation with increase of antibody titer in the serum and CSF which cause complement fixation without existing anti-AQP4 ab has been defined for the anti-MOG syndrome [161]. On the other hand, this large study against previous reports showed that the long term course of the anti-MOG syndrome is similar with the anti-AQP4 syndrome and not so benign [162].

Conclusion:

Based on the similarity of clinical, neuroimaging, and laboratory characteristics of pediatric NMOSD to those of the adult form, the international panel suggested that adult criteria of NMOSD also are appropriate in pediatric patients. However, the proposed criteria need validation in pediatric patients. Because of the lack of controlled studies in the pediatric group, treatment must be given based on evidence obtained from the adult experiences. The use of immunosuppressive therapy in adults, which confirmed that immunosuppressive therapy reduced mortality rates, gives rise to a immunosuppressive therapy rationale in the pediatric groups. This strategy poses challenges to the study design in clinical trials in pediatric NMOSD patients.
References:


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### Table 1

<table>
<thead>
<tr>
<th>NMOSD diagnostic criteria for adult patients</th>
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<tbody>
<tr>
<td><strong>Diagnostic criteria for NMOSD with AQP4-IgG</strong></td>
</tr>
<tr>
<td>1. At least 1 core clinical characteristic</td>
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<td>2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)</td>
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<tr>
<td>3. Exclusion of alternative diagnoses</td>
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</table>

| **Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status** |
| 1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements: |
| a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome |
| b. Dissemination in space (2 or more different core clinical characteristics) |
| c. Fulfillment of additional MRI requirements, as applicable |
| 2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable |
| 3. Exclusion of alternative diagnoses |

| **Core clinical characteristics** |
| 1. Optic neuritis |
| 2. Acute myelitis |
| 3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting |

| **Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status** |
| 1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadoliniumenhancing lesion extending over ≥1/2 optic nerve length or involving optic chiasm |
| 2. Acute myelitis: requires associated intramedullary MRI lesion extending over >3 contiguous segments (LETM) OR >3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis |
| 3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions |
| 4. Acute brainstem syndrome: requires associated periependymal brainstem lesions |
fig – 1 A and C: 14 years old female anti-AQP4 Ab positive patients presented with recurrent optic neuritis and acute brain stem syndrome. B: 10 years old female anti-AQP4 Ab positive patients presented with recurrent optic neuritis and nonspecific brain lesions D: 12 years old female anti-AQP4 Ab positive patients presented with recurrent optic neuritis and transverse myelitis (Sahraeian et al. Sina hospital neuromyelitis optica spectrum disorders cohort program, with permission)
fig -2 A: 9 years male anti-AQP4 Ab positive patients presented with recurrent optic neuritis and cervical transverse myelitis B: 14 years male anti-AQP4 Ab positive patients presented with recurrent optic neuritis and transverse myelitis C: 15 years female anti-AQP4 Ab positive patients presented with recurrent optic neuritis and transverse myelitis D: 13 years old female anti-AQP4 Ab positive patients presented with transverse myelitis and one years ago acute brainstem syndrome

(Sahraeian et al. Sina hospital neuromyelitis optica spectrum disorders cohort program, with permission)

Highlights

- Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disorder of the central nervous system (CNS). Serum immunoglobulin G autoantibodies (NMO-IgG) are identified in the majority of NMOSD patients.
- The Pediatric form presents before 18 years.
- The international panel suggested that adult criteria of NMOSD also are appropriate in pediatric patients. However, the proposed criteria need validation in pediatric patients.
- Because of the lack of controlled studies in the pediatric group, treatment must be given based on evidence obtained from the adult experiences.
- The use of immunosuppressive therapy in adults, which confirmed that immunosuppressive therapy reduced mortality rates, gives rise to a immunosuppressive therapy rationale in the pediatric groups.