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Tratamento das doenças do espetro da neuromielite óptica em idade pediátrica

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Treatment of pediatric neuromyelitis optica spectrum disorders

Tratamento das doenças do espetro da neuromielite óptica em idade pediátrica

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Index

Abstract

Neuromyelitis optica spectrum disorders (NMOSD) are a group of autoimmune inflammatory and demyelinating disorders of the central nervous system. They are predominantly mediated by an autoantibody targeting the Aquaporin-4 channel (AQP4-IgG). However, some patients are positive for myelin-oligodendrocyte glycoprotein antibodies (MOG-IgG), and others are negative for both antibodies. This is an aggressive disease that follows a relapse-remitting course with a relapse-dependent disability, that can be extremely severe. It may lead to blindness, paraplegia, quadriplegia, and even life-threatening respiratory failure. Characteristic clinical manifestations are optic neuritis, longitudinally extensive transverse myelitis and area postrema syndrome, though others may be present.

As few studies have been conducted in children, the diagnostic criteria and the treatment approaches are inferred based on adult experience. Thus, this review aims to analyze and summarize all reports on this subject, so that the management of the patients is more evidence-based. We searched through the PubMed database with the MeSH term “Neuromyelitis Optica” and “drug therapy”, “prevention and control” and “therapy” as subheadings. We restricted our search to publications from the past 5 years, human species, ages from birth to 18 years and articles available in English, Spanish, French and Portuguese. All types of articles were included.

Treatment of relapses is, almost consensually, initiated with intravenous methylprednisolone (IVMP), and, in refractory patients, intravenous immunoglobulin (IVIG) or plasma exchange (PLEX) are tried. Some reports show that using IVMP+PLEX as initial therapy presents good results. First-line drugs for maintenance treatment are mycophenolate mofetil, rituximab, and azathioprine. There is contradictory evidence on which one should be the first choice. Nevertheless, before resorting to second-line drugs, treatment may be switched between these three drugs. Recently, new drugs have been approved for treatment of NMOSD in adults and may be a promising new line of therapy for children. MOG-IgG positive patients show good results in acute relapse treatment with IVMP+IVIG and maintenance treatment with IVIG.

Though it seems that age does not bring significant differences in disease features, this review pointed out that extrapolating adult evidence to children, in terms of therapeutic approaches, might not be as straightforward as it is believed. With this review, we highlight the importance of further research. Since this is a very rare disease, the best way to study its features and treatment efficacy and safety is through multicenter studies. Hence, in order to develop those, an additional effort to share the information of these cases is crucial.

Keywords: Neuromyelitis optica spectrum disorders; child; adolescent; therapeutics; AQP4-IgG; MOG-IgG.

Resumo

As doenças do espetro da neuromielite óptica (DENMO) são um grupo de doenças autoimunes, inflamatórias e desmielinizantes do sistema nervoso central. São mediadas, predominantemente, por um auto-anticorpo contra o canal da Aquaporina 4 (AQP4-IgG). No entanto, alguns doentes são positivos para o anticorpo contra a glicoproteína oligodendrocítica da mielina (MOG-IgG) e outros são negativos para ambos os anticorpos. Esta é uma doença agressiva, que segue um padrão de surtos e remissões, com consequente incapacidade neurológica dependente dos surtos, a qual pode ser extremamente grave. Pode conduzir a cegueira, paraplegia, tetraplegia e, ainda, falência respiratória potencialmente fatal. As manifestações clínicas características desta doença são a nevrite óptica, a mielite transversa longitudinalmente extensa e a síndrome da área postrema, apesar de outros quadros clínicos poderem estar presentes.

Tendo em conta o limitado número de estudos realizados em crianças, os critérios de diagnóstico e as estratégias de tratamento são inferidas da experiência adquirida em adultos. Assim, esta revisão visa analisar e sumariar os artigos disponíveis sobre esta matéria, de forma a que o tratamento destes doentes seja baseado na evidência. Realizámos uma pesquisa através da PubMed, usando o termo MeSH "Neuromyelitis Optica" e adicionando os subheadings "drug therapy", "prevention and control" e "therapy". De seguida, filtrámos a pesquisa a artigos publicados nos últimos 5 anos, sobre humanos, em idades até aos 18 anos e disponíveis em inglês, espanhol, francês e português. Todos os tipos de artigos foram incluídos.

De um modo quase consensual, o tratamento dos surtos faz-se com metilprednisolona intravenosa (MPIV) e, nos casos refratários, usa-se a imunoglobulina intravenosa (IGIV) ou a plasmaferese. Alguns trabalhos demonstram que o uso inicial de MPIV+plasmaferese conduz a bons resultados. Os fármacos utilizados como primeira linha na terapêutica de manutenção são o micofenolato de mofetil, o rituximab e a azatioprina. Estes três fármacos devem ser experimentados antes de recorrer aos de segunda linha. Foram recentemente aprovados novos fármacos para o tratamento das DENMO em adultos, que podem ser promissores para uso em crianças. Por outro lado, os doentes positivos para MOG-IgG demonstram bons resultados com MPIV+IGIV no controlo dos surtos e com IGIV no tratamento de manutenção.

Apesar de não haver uma aparente influência significativa da idade nas características da doença, este trabalho revelou que a extrapolação de dados de adultos para crianças, em termos terapêuticos, pode não ser tão simples quanto seria expectável. Com este trabalho, destaca-se a importância de se realizarem novos estudos. Visto tratar-se de uma doença muito rara, a melhor abordagem para estudar as suas características e a eficácia e segurança da terapêutica seria através de estudos multicêntricos. Portanto, uma divulgação mais alargada destes casos é essencial para que estes possam ser desenvolvidos.

Palavras-chave: Doenças do espetro da neuromielite óptica; criança; adolescente; tratamento farmacológico; AQP4-IgG; MOG-IgG.

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are a group of autoimmune inflammatory and demyelinating disorders of the central nervous system (CNS) that can be classified as seropositive or seronegative, according to the presence or absence, respectively, of Aquaporin 4-IgG antibodies (AQP4-IgG) in serum and/or cerebrospinal fluid (CSF).[1] This autoantibody targets the AQP4 channel, which is found in astrocytes foot processes and represents the most abundant water channel in the CNS, being responsible for water balance. The areas rich in this protein, and therefore most involved in the pathologic processes leading to disease, are mainly located in circumventricular and ependymal regions, contributing to define the location of lesions as a critical element for the diagnosis.[2]

AQP4-IgG has its genesis in peripheral B cells, circulates in the blood and reaches the blood-brain barrier (BBB), thus targeting the AQP4 channel and causing the activation of complement, inflammatory demyelination, and ultimately necrosis, both in the brain and spinal cord's white and grey matter. It also incites the down-regulation of surface AQP4 through endocytosis.[3, 4] This autoantibody, together with B and T lymphocytes, leads to disruption of the BBB, allowing this continuous inflammatory process through neutrophil and macrophage infiltration.[3] It is an important biomarker in NMOSD, since it can be identified in around 80% of the pediatric patients[5] and with a confirmed specificity of 98.3%.[6] However, caution is needed when interpreting the results, because the seropositivity can occur up to 4-5 years after disease onset.[7]

Recently, an association was made between clinically diagnosed NMOSD and the positivity to myelin-oligodendrocyte glycoprotein (MOG) antibodies, found in 20% to 40% of the pediatric patients.[8] These are predominantly of the IgG1 subtype and also mediate complement-dependent cytotoxicity.[9] However, it does not represent a specific diagnostic biomarker for NMOSD, as it has been reported in a variety of demyelinating diseases besides this condition, such as acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS), especially in children.[9] The suggestion that these MOG antibody-positive patients are part of the spectrum of the NMOSD or if they constitute a different entity of demyelinating diseases is still being discussed.

Histopathological features found in NMOSD lesions consist of a pronounced loss of oligodendrocytes, thickened and hyalinized penetrating spinal vessels, immunoglobulin and complement components deposition in a perivascular rim and rosette pattern and an inflammatory infiltrate of macrophages, eosinophils, and neutrophils.[10] During the chronic phase, spinal cord lesions appear like longitudinally extensive cord atrophy.[2] All these features make this clinical condition an extremely diverse spectrum, with clear therapeutic repercussions, since the pharmacological approach will have to take into account all these immunopathological variables. In children, the challenge is even greater, since the intervention possibilities described in the literature are very diverse and not very consistent. In this sense, this work was designed with the objective of reviewing which therapeutic options for pediatric NMOSD have been described and which is the rationale for their use.

NMOSD – state of the art

1. Epidemiology

Pediatric-onset NMOSD is relatively rare, being responsible for 4% of all seropositive cases.[2] The first demyelinating episode occurs on average at 13 years[5] and the female:male ratio is 3:1, holding a less substantial female preponderance when compared to adult-onset disease (up to 9:1).[1] Adult-based studies found a higher prevalence of NMOSD in non-white populations, with an apparent worse outcome.[11, 12] Regarding these epidemiologic features, there are some differences in the seronegative group, including a higher prevalence of caucasians and a more equitable sex distribution, though the same age at onset.[13, 14]

NMOSD's clinical course may follow a monophasic path or, as 93 to 95% of patients do, a relapsing one.[7] Nonetheless, it does not evolve with progressive neurologic deterioration, but instead through sequelae that are the outcome of the aggressive relapses that do not completely recover.[8]

2. Clinical manifestations

Clinically, NMOSD presents predominantly by optic neuritis (ON), transverse myelitis (TM) and by an area postrema syndrome. The typical ON is bilateral, resulting in ocular pain and visual loss.[4] The TM is usually longitudinally extensive (LETM) and expresses through severe symmetric paraplegia, sensory loss below the lesion and bladder dysfunction.[4] The area postrema syndrome consists of intractable hiccups, nausea, and vomiting.[1] There are some reports on diencephalic and brainstem syndromes, presenting as narcolepsy, hypersomnolence, and endocrine dysfunction.[7] Diplopia, facial palsy, vestibular ataxia, dysarthria, oscillopsia, nystagmus, and neurogenic respiratory dysfunction as a result of brainstem involvement are also frequently described.[2] If a large cerebral hemispheric lesion is present, the patient may develop hemiparesis, visual field defects or encephalopathy.[2] A study[15] stated that 75% of children presented ON at onset and 30% TM. Besides, over half had a brain syndrome episode during the follow-up and 95% had LETM.

3. Diagnosis

The evaluation of these patients requires brain and full-spine with contrast magnetic resonance imaging (MRI), serology for AQP4-IgG and, in some cases, CSF analysis (cell count, protein, glucose, oligoclonal bands, gram stain and culture). There are no definitive radiological criteria for diagnosing NMOSD in children, though there are some suggestive features.[7] Typical lesions involving the optic nerve, the spinal cord, or the brain appear on MRI as a hyperintensity in fat-suppressed T2 weighted sequences and as a hypointensity with enhancement after intravenous (IV) gadolinium administration in fat-suppressed T1 weighted sequences.[1, 2, 15] A bilateral involvement of the optic nerve with commitment of the chiasm and extensive lesions of more than half of optic nerve's length are characteristic of NMOSD.[1, 7, 13] A TM can affect both white and gray matter[2] and cord swelling may also be present.[1] These lesions typically affect more than 3 vertebral segments representing an LETM, which can fragment into discontinuous atrophic lesions during clinical remission.[1] Brain lesions affect more than 50% of children and are usually in the white matter, large (>2cm) and the acute ones frequently

resolve on control imaging.[1, 15, 16] Brain involvement is more common in children and AQP4-IgG positive patients.[2]

Table I. NMOSD diagnostic criteria

Diagnostic criteria for NMOSD with AQP4-IgG	At least 1 core clinical characteristic Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended) Exclusion of alternative diagnoses
Diagnostic criteria for NMOSD without AQP4-IgG or unknown AQP4-IgG status	At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements: 1. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome 2. Dissemination in space (2 or more different core clinical characteristics) 3. Fulfillment of additional MRI requirements, as applicable Negative tests for AQP4-IgG using best available detection method, or testing unavailable Exclusion of alternative diagnoses
Core clinical characteristics	Optic neuritis Acute myelitis Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting Acute brainstem syndrome Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions Symptomatic cerebral syndrome with NMOSD-typical brain lesions
Additional MRI requirements	
Acute optic neuritis	Requires brain MRI showing, either 1. normal findings or only nonspecific white matter lesions 2. optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium- enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm
Acute myelitis	Requires either 1. associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) 2. ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis
Area postrema syndrome	Requires associated dorsal medulla/area postrema lesions
Acute brainstem syndrome	Requires associated periependymal brainstem lesions

Abbreviations: AQP4-IgG = aquaporin 4-IgG; LETM = longitudinally extensive transverse myelitis; NMOSD = neuromyelitis optica spectrum disorders

NMOSD diagnostic criteria according to Wingerchuk et al., 2015[1]

Table II. Red flags for an alternative diagnosis

Clinical / Laboratory	
Clinical features and laboratory findings	Neurologic deterioration unrelated to attacks: consider MS Atypical time to attack nadir: 1. <4h consider cord ischemia / infarction 2. continual worsening for >4 weeks from attack onset consider sarcoidosis or neoplasm Partial transverse myelitis: consider MS Presence of CSF oligoclonal bands: consider MS
Comorbidities associated with neurologic syndromes that mimic NMOSD	Sarcoidosis Cancer: consider lymphoma or paraneoplastic disease Chronic infection
Conventional neuroimaging	
Brain	Imaging features MS-typical (T2-weighted MRI) 1. Lesions perpendicular to a lateral ventricular face (Dawson fingers) 2. Lesions adjacent to lateral ventricle in the inferior temporal lobe 3. Juxtacortical lesions involving subcortical U-fibers 4. Cortical lesions Imaging features suggestive of diseases other than MS and NMOSD 1. Lesions with persistent (> 3 months) gadolinium enhancement
Spinal cord	Characteristics more suggestive of MS than NMOSD 1. Lesions affecting < 3 complete vertebral segments on sagittal T2-weighted sequences 2. > 70% of lesions located in the peripheral cord on axial T2-weighted sequences 3. Diffuse, indistinct signal change on T2-weighted sequences

Abbreviations: CSF = cerebrospinal fluid; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorders

NMOSD red flags for an alternative diagnosis according to Wingerchuk et al., 2015[1]

The International Panel for Neuromyelitis Optica Diagnosis (IPND)[1] advises testing the AQP4-IgG with cell-based serum assays (microscopy or flow cytometry), since they have a better sensitivity (76.7%). The titles of this autoantibody increase before a relapse and decrease after remission and treatment.[2] Though routine CSF testing in AQP4-IgG seronegative patients is not recommended by the IPND, it can be useful for differential diagnosis in particular cases. The absence of oligoclonal bands is considered supportive evidence and pleocytosis may be observed, especially from neutrophils and eosinophils. The glial fibrillary acidic protein (GFAP) is increased merely for days to weeks after a relapse, nevertheless, it can be used as a diagnostic and prognostic biomarker.[1] No difference was found in the CSF analysis of seropositive and seronegative patients.[9] Similarly, the IPND does not recommend CNS biopsy, but assumes it can be suitable in atypical cases.[1]

As most clinical, neuroimaging and laboratory findings are similar to those of adult-onset disease, the IPND[1] concluded that the diagnosis criteria for adults (Table I) could be used, prudently, for pediatric patients. According to these criteria, clinical manifestations are mandatory. However, it is possible to have asymptomatic AQP4-IgG positive status for years, as it is to have asymptomatic

NMOSD-compatible MRI lesions, but these situations are poorly understood. Additionally, no clinical feature is pathognomonic as none is exclusionary, though some are considered red flags for an alternative diagnosis (Table II).[1] An assertive diagnosis is critical, since some drugs used in MS may worsen NMOSD.[1, 17]

4. Differential diagnosis and exams to be performed

Although the referred criteria (Table I) have proven to be 97% sensitive (opposing to the 49% sensitivity of the previous 2006 criteria),[7, 13, 14] some caution is needed when it comes to children, since bilateral ON in this group is more likely to be related to a post-infectious cause.[2] Besides, MS and ADEM often present with LETM in children, so this clinical finding is less specific and, therefore, implies a lower predictive value than in adults.[2] Thus, when managing a patient with clinical manifestations resembling NMOSD, infection, MS, and ADEM have also to be considered as probable diagnoses. To acknowledge one over the others, further evaluation should be conducted through MRI and CSF analysis.[18]

As suggested by the red flags, the main differential diagnosis to be considered is MS. A continuous inflammation and progressive degeneration are the key features of MS, opposing to the relapse-dependent disability of NMOSD.[8] When the patient's clinic does not allow the differentiation between these conditions, some exams should be performed. The most reliable exam to distinguish NMOSD from MS is the MRI, as there are some characteristic patterns described for NMOSD that are considered exceptional in MS. Likewise, the CSF analysis may help make the diagnosis. When oligoclonal bands are present, it strengthens MS diagnosis.[1] Seroconversion of an AQP4-IgG seronegative patient can occur. For that reason, it is advised to keep a longitudinal observation of the clinical course and to repeat the serologic tests before any B-cell or antibody-targeted therapy is initiated, in seronegative patients with NMOSD-suggestive clinical features.[1, 7, 13] The CSF AQP4-IgG and MOG-IgG, if available, could also be tested in pertinent cases.[7] Nevertheless, concomitant NMOSD should be considered in any pediatric autoimmune neurologic manifestation.[2]

5. Prognosis

A patient suffering from NMOSD can undergo severe neurologic disabilities, as blindness, paraplegia, quadriplegia, and even respiratory failure, if the lesion extends to the medullary respiratory center (located in the brainstem).[2] This disease-related disability depends on the number and aggressiveness of relapses, but has no association with the disease duration, hence the younger age of initial event does not necessarily mean poorer prognosis.[5] In fact, pediatric NMOSD is considered to have a better prognosis than in adults.[15] Usually, to enable comparison between different phases and simplify the follow-up, physicians use the Expanded Disability Status Scale (EDSS) (Table IV in Appendix). This scale was created for use in MS, but is suitable for NMOSD. It ranges between 0 and 10 and correlates with patient's prognosis.

A study with pediatric patients[15] showed that the mean time to relapse was 0.76 years for AQP4-IgG positive comparing to 2.4 years for AQP4-IgG negative cases. Moreover, the annualized relapse rate (ARR) was 0.70/year versus 0.38/year in the first and second groups, respectively. Thus, seronegative patients frequently follow a monophasic course[16] and any seropositive patient should be

considered at risk for relapse and preventive treatment should be pondered.[1] To claim a relapse, an interval longer than 4 weeks between attacks is needed and for assuming a monophasic course at least 5 years of a relapse-free period should be observed.[1] It has been noticed that AQP4-IgG seropositive cases frequently lead to visual impairment, and AQP4-IgG seronegative cases to motor disability.[15] Patients positive for MOG-IgG are considered to have a less aggressive form of the disease.[8, 16]

6. Treatment – why is this thesis relevant?

The existent knowledge of NMOSD and its particularities are recent and there are still a few gaps in the understanding of this disease. Nevertheless, we know it can be an aggressive disease following a relapse-remitting course with a relapse-dependent disability. It is fundamental to obtain an early-stage diagnosis and prompt treatment of acute attacks plus prevention of recurrences, as relapses are unpredictable and can be severe or even life-threatening. However, there are no randomized clinical trials for the treatment of NMOSD in children. So, pediatric patients are being treated based on adult experience. Additionally, reports about treatment on children are scarce, or have a small sample.

Currently, the management of acute attacks is achieved by the administration of intravenous (IV) high-dose-corticosteroids, IV immunoglobulins, and plasma exchange. Maintenance therapy is based on immunosuppressive agents, including azathioprine, rituximab, mycophenolate mofetil, methotrexate, cyclophosphamide, mitoxantrone, and ciclosporin.[19] Considering there is limited information on how to treat pediatric NMOSD, this review aims to analyze and summarize all reports on this subject, gathering every aspect available to enable a better understanding of how to manage these patients.

Methods

We conducted an online search in the PubMed database, on 02/12/2019, using the MeSH term “Neuromyelitis Optica” and adding the subheadings “drug therapy”, “prevention and control” and “therapy”. Then, we restricted our search to publications from the past 5 years, human species, ages from birth to 18 years and articles available in English, Spanish, French and Portuguese. There was no restriction on the article types. This search presented 82 results. Once the screening of title and abstract was complete, 23 articles were excluded for non-relevant study purpose, target population not of interest, duplicates and full-text not available. After full-text analysis, 40 articles were rejected due to non-relevant study purpose, evaluation only on adult population, insufficient information and the incapability to extract children’s information from the population results. From the 19 articles selected, screening of bibliography was performed, and 6 more articles were included. Therefore, 25 articles were used to complete this review (Fig. 1).

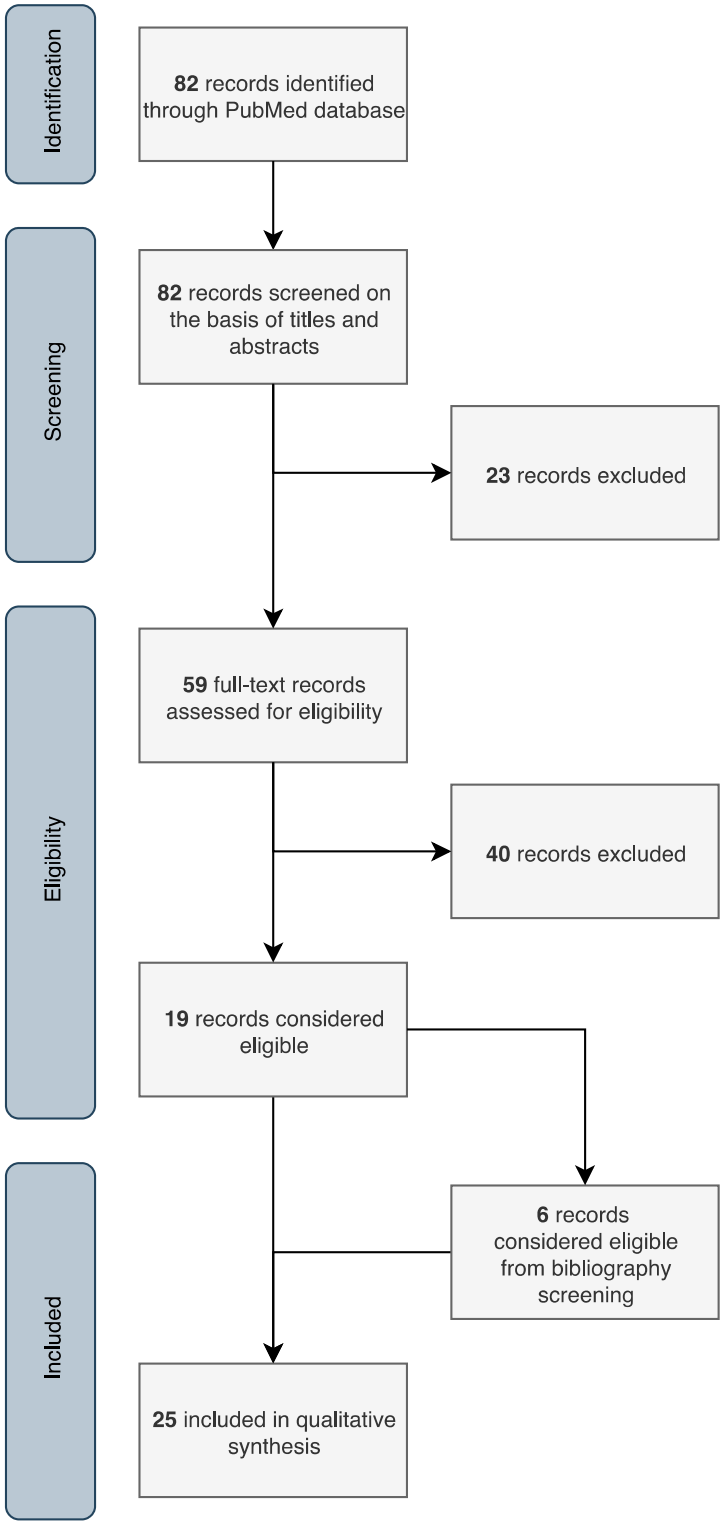

Figure 1. Flowchart of literature search.

Treatment of NMOSD in children

NMOSD patients' management should comprise treatment of acute relapses, maintenance therapy, and symptomatic relieving. As AQP4-IgG positivity predicts a relapsing course of the disease with severe disability, it is advised to start treatment as soon as the diagnosis is made and to prolong it indefinitely.[20] Additionally, high levels of AQP4-IgG is thought to be a predictor of treatment failure.[21] As seronegative patients' disease course is not fully understood, they are treated similarly to seropositive patients. They also respond well to rituximab. In MOG-IgG positive patients, treatment choice might be slightly different. There is some adult-based evidence that acute exacerbations will respond more favorably if the patient is on preventative medication.[7]

1. Treatment strategies

1.1. Treatment of relapses

The main goals of relapses treatment are to minimize irreversible damage and to restore neurologic function. As no definite guidelines for the treatment of NMOSD in children are available, recommendations widely vary depending on the author. However, the most accepted approach is to start with intravenous methylprednisolone (IVMP) and, in refractory patients, try either plasma exchange (PLEX) or intravenous immunoglobulin (IVIG).

Bradshaw et al.[7] strongly recommend using PLEX in addition to IVMP as first-line therapy, instead of using IVMP alone, since there is evidence of improved outcomes with that combined strategy.

1.1.1. Intravenous methylprednisolone (IVMP)

Intravenous methylprednisolone is widely considered the best option to start treatment. It is recommended to rule out any infections before methylprednisolone is initiated.[2] The recommended daily dose for children is 30 mg/kg/day to a maximum of 1000 mg, for 5 days (it is acceptable to extend the treatment up to 7 days).[2, 22, 23] However, some other authors recommend 20 mg/kg/day.[7]

1.1.2. Plasma exchange (PLEX)

This technique, with some modifications from the adult procedures, was considered to be safe to perform in most children. A specialized center and an experienced technician should be preferred. Indication for PLEX usually includes patients that are refractory to steroids.[24, 25]

Unclear indications and technical difficulties are limitations when choosing PLEX in children. Besides, it can cause complications such as pain, bleeding, thrombosis, infection, electrolyte abnormalities, coagulopathy, severe allergic reaction, liver and renal dysfunction, and, consequently to venous access, pneumothorax, hemothorax, cardiac arrhythmias, and central vein stenosis. Especially in children, anemia, hypotension, and citrate-related hypocalcemia can occur.[7, 24, 26]

Immunoadsorption (IA) is a similar technique that allows the elimination of pathogenic antibodies while sparing other plasma proteins. Despite being associated with fewer

adverse effects, its effectiveness in NMOSD is not yet established, and no study comparing it with PLEX is available.[26]

In a retrospective study,[26] 9 steroid-resistant patients (8 adults and 1 child) received apheresis (PLEX and/or IA) showing a rapid improvement of visual acuity, except for the only child of the group, that showed a slight and slow improvement, under PLEX.

1.1.3. Intravenous immunoglobulin (IVIG)

These immunoglobulins will inhibit the B-cell mediated antigen presentation and T-cells proliferation.[27] Despite being well-tolerated in children, IVIG's effectiveness has not yet been proven. Common complications associated to the drug include nausea, headache, and fever, while aseptic meningitis and anaphylactic reaction are rare ones.[2]

1.2. Maintenance therapy

The main goal of preventive therapy is to decrease risk of relapses and disability. Most physicians opt to concomitantly administer oral prednisolone for better outcomes, but this is not consensual. First-line drugs are mycophenolate mofetil (MM), rituximab (RTX) and azathioprine (AZA). Before resorting to second-line drugs due to adverse effects or poor response, treatment may be switched between these three drugs and then combining chronic intermittent PLEX could be considered. If immunosuppression is contraindicated, IVIG may be used as initial therapy.[23] Zhou et al.[28] compared the results of children and adults treated with AZA, MM, and RTX. They concluded that AZA had a less favorable progression, with a decrease of 48% in ARR after treatment, compared to a decrease of 87% and 100% with MM and RTX, respectively. However, all three drugs produced a good response in adults. Hereupon, AZA, although indicated in adults, does not seem to produce equally satisfactory results in children. For this reason, those authors recommend starting aggressive treatment from the beginning with MM or RTX.

New drugs, such as Inebilizumab,[29] Satralizumab[30] and Eculizumab[31], have recently been studied in adults, showing good results.[22] They may be a promising new line of therapy. However, it is still necessary to study their use in children.

Monitoring patients' blood and liver functions is important throughout treatment, as a screen for infections.[22, 23]

1.2.1. Mycophenolate mofetil (MM)

It is an inhibitor of the inosine monophosphate dehydrogenase, that subsequently inhibits B and T cells proliferation and antibody production.[2] The dosing of MM is not consensual. Baghbanian et al.[2] claim that it should be 2-3 g/day in a divided dose, while Gombolay et al.[22] say that the goal dose is 600 mg/m^2 twice a day, with a maximum of 1000 mg twice a day. Slower uptitration is associated with better tolerability, so Gombolay et al. propose to start at a quarter dose up to 250 mg twice a day for 14 days, then increase to half a dose up to 500 mg twice a day for the next 14 days, and finally the goal dose after that.

However, Zhou et al.[28] showed that 1 g/day was tolerable and effective for children. Its' effects will only begin 6 months after starting MM administration, so it should be considered continuing to administer steroids during this period.[2]

Although it is well-tolerated, constipation, headache, leukopenia, hair loss, anxiety, diarrhea, and bruising are common adverse effects.[2]

1.2.2. Rituximab (RTX)

This is a chimeric monoclonal antibody that targets B-cells surface protein CD20, decreasing B-cell activity and mediated autoimmunity.[2]

A study[21] including pediatric patients treated with RTX revealed a decrease in relapse frequency of 56% (p=0.0005), an improvement of 1.1 in the EDSS score (p=0.03) and a regression of inflammatory parameters on MRI. Evidence shows that starting RTX earlier in the disease course may lead to better outcomes.[32]

According to Gombolay et al., treatment with RTX should start at an induction dose of 375 mg/m^2 weekly for 4 weeks, and after that, the same dose every 6 months. However, many other protocols are proposed: 375 mg/m^2 every 4 weeks,[2] 1 g 2 weeks apart and then every 6 months,[2] induction dose of 375 mg/m^2 weekly for 4 weeks and once the CD19$^+$ B-cells reach 1% of circulating mononuclear cells start maintenance therapy with 2 infusions of 1 g every 15 days (Cabre et al.)[21], or reinfusion depending on CD19$^+$ B-cells count.[21, 23, 33] This last strategy of reinfusion according to B-cell repopulation prevents relapse in those who repopulate early and hypogammaglobulinemia with severe infections in those who have a late repopulation.[34] The interval for B-cells monitoring widely depends on opinions. Formerly, a 6 months interval was the most accepted one, based on the finding that B-cells depletion last on average 6 months.[34] However, some studies have recently proven that the interindividual variability is too important and that 6 months might be too long.[35, 36]

Since the delay between RTX administration and its therapeutic action can be 1 month, concomitant steroid administration should be an option. It can cause adverse events, like headache, rash, flu-like syndrome, nausea, fatigue, and infections, especially of the upper respiratory tract.[2] For this reason, it is advised regular questioning on infectious respiratory symptoms.[34] In an attempt to diminish adverse effects and costs, a group[37] studied the effect of treatment with low-dose RTX (100 mg) on a non-pediatric population. However, 21.1% of patients did not respond well and some required higher frequency of reinfusion to keep B-cells at target levels (<1%). The same report demonstrated that patients with anti-RTX antibodies had higher frequencies of reinfusion, even though no significant difference was found in the improvement of EDSS and ARR.

There is no consensus on the duration of therapy with RTX nor if there is an appropriate time to discontinue it without risking relapses, so most patients remain on treatment for prolonged periods. However, a group[32] showed that, after discontinuation of RTX, patients can preserve a sustained response (absence of relapses or even complete remission),

suggesting long-term effects. If a patient is stable on RTX for several years, we can consider continuing it, switch to azathioprine or MM, or try to stop it. No data about the safety and efficacy of these choices are available to guide the decision.

A multicenter retrospective study[35] was conducted in 16 children to establish a relationship between RTX, B-cell repopulation (>10 x 10^6 cells/L), and relapses so that monitoring and redosing of RTX would be improved. Different protocols (dosages and frequency of administration) were used. Redosing was performed if a relapse or B-cell repopulation were detected, or, more rarely, in a planned schedule. Redosing occurred at a mean time of 7.9 months, though considerable variability was observed. RTX was proven to be relatively well-tolerated, showing mild adverse effects but no major complications. Efficacy was also satisfactory, with a significant reduction in ARR and 6 patients being relapse-free throughout treatment. This relapse-free course was not associated with other immunosuppressive therapies besides RTX. Among the relapsing patients, only one was due to RTX failure, and the rest to inadequate monitoring and delay in redosing. Moreover, they concluded that once B-cells repopulated there was no spontaneous redepletion. The association between B-cells repopulation and relapses was also confirmed. However, significant interpatient variability in repopulation time was noticeable, ranging between 2.7 and 8.7 months after RTX infusion. A shorter time to repopulate correlated with lower RTX doses and younger patients, as a longer time correlated with higher doses and older patients. Nonetheless, intrapatient variability was smaller, implying relative predictability of repopulation, which would help monitorization. For these reasons, the authors propose every month B-cells monitoring and rapid redosing when repopulation is detected. If a regular interval for redosing is preferred, it should be done at shorter intervals (3-4 months), but this will increase costs and adverse effects.

Another retrospective study[36] in 5 children with NMOSD also proved that RTX is well-tolerated and stabilizes or even improves neurologic disability. In these 5 children, the EDSS decreased from 3.0 to 0.8, 12 months after treatment onset. Only 2 patients had permanent neurologic deficits and none showed extension of lesions after B-cell depletion was achieved. No significant adverse effects were reported. The authors found that B-cells count control at 6 months interval was not sufficient and proposed a more frequent assessment and a more individualized approach. Besides, they fight the tendency to reserve RTX to treatment-refractory cases in seropositive patients. It is possible that patients who undergo other immunosuppressive drugs before RTX have a higher risk of secondary antibody deficiency.[34]

1.2.3. Azathioprine (AZA)

This drug inhibits T and B cells proliferation through inhibition of purines' synthesis. It is advised to measure the thiopurine methyltransferase (TPMT) activity before starting AZA administration. This is because a patient with low TPMT activity is at a higher risk of toxicity (gastrointestinal symptoms and myelosuppression) and another immunosuppressive drug

should be proposed. Adverse effects that frequently follow AZA are fever, malaise, myalgia, hepatoxicity, thrombocytopenia, leukopenia, and infections. AZA should be used in a dose of 2-3 mg/kg/day, and its' effects take 6 months to develop.[2, 22] For this reason, some physicians choose to concomitantly use oral steroids.

In a Brazilian study[38] with 10 pediatric patients, treatment with AZA at a mean dose of 1.9 (0.5-3) mg/kg/day with or without prednisone at a mean dose of 0.4 (0.2-1) mg/kg/day was implemented. The ARR decreased from 1.26 to 0.41, though not reaching a significant level (p=0.093). The progression index (EDSS on last follow-up divided by years of disease course) significantly decreased, from 1.04 to 0 (p=0.028). No severe adverse effects were observed. They concluded that AZA was effective, as it was safe and well tolerated.

1.2.4. Second-line drugs

If the methods described above fail or cannot be applied, there are other alternatives, namely methotrexate, mitoxantrone, cyclosporine, and cyclophosphamide. However, their use in pediatric patients is unusual and information on their efficacy and adverse effects are limited. Alemtuzumab is an anti-CD52 humanized monoclonal antibody that is used in relapsing-remitting MS. It has been tested in some NMOSD cases before, but results showed no improvement or even worsening. Therefore, this drug is not recommended in this condition.[17] Interferon-β, natalizumab, and fingolimod are other drugs to avoid in NMOSD.[23]

1.3. Treatment of MOG-IgG positive patients

A case series report[39] about five MOG-IgG positive patients with CNS demyelinating disorders, demonstrated that acute relapses treatment with 5 days of 1 g IVMP and 2 days of IVIG (2g/kg) and subsequent maintenance treatment with IVIG led to satisfactory results with no further relapses (10months-4.5years follow-up). The maintenance IVIG followed different protocols: monthly infusions; monthly infusions for 1 or 2 years and then bi-monthly; and 5 or 7 monthly infusions.

2. Case reports

Much of the available information is recorded in the report of some clinical cases. A summary of the total number of cases found in the literature is presented (also in Table III), according to the research methods mentioned above.

2.1. A 9-year-old female patient[34] with intractable vomiting and optic neuritis was initially diagnosed with MS and had 1 year of interferon-β therapy, followed by IV steroids after each acute relapse of optic neuritis and myelitis, but with poor recovery. She was only diagnosed with NMOSD at the age of 29, when she tested positive for the AQP4-IgG. At that time, she was already blind and with an EDSS of 6.0. NMOSD-aimed therapy was initiated thereafter.

2.2. A 9-year-old female patient[17] with long-term vomiting, developed transverse myelitis, two relapses of bilateral ON, and two episodes of brainstem syndrome with nystagmus, ataxia, and facial sensory disorder. The MRI exposed one lower medullary lesion and several LETM. She underwent several preventative treatments, as 20 mg/day of prednisolone, IVIG for 5 days, 2 mg/kg/day of AZA, 500 mg/m^2 of cyclophosphamide for 6 sessions and 100 mg/day of ciclosporin. Despite all therapies, she remained significantly visually impaired and with spastic paraparesis. Her EDSS was 6.0 and the ARR was 4. Within 15 months of disease onset, she started alemtuzumab. She completed 2 cycles 12 months apart. Initially, this showed an apparent good outcome, but she relapsed, rendering her wheelchair dependent and blind by the age of 12. After one year of alemtuzumab, she had an EDSS of 8.0. She was diagnosed with NMO at the age of 16 and received PLEX, but inevitably died at the age of 18. Testing for AQP4-IgG was not available at that time.

2.3. An 18-year-old female patient[40] showed no perception of light in the left eye and 6/36 visual acuity in the right eye. She had a 1-month history of sudden onset painful visual loss of the left eye. She was AQP4-IgG positive. She started 1 g IVMP for 5 days, but had no significant improvement. Afterward, she underwent 5 sessions of PLEX and then started oral prednisolone and AZA. In 2 weeks, her visual acuity was 1/60 in the left eye and 6/9 in the right eye. She was discharged on AZA with steroids and kept close follow-up.

2.4. A 14-year-old male patient[2] with a history of optic neuritis, from which he recovered after IV steroids, presented 5 months later with myelitis symptoms. He tested positive for AQP4-IgG and started AZA. After 3 years of follow-up, there were no relapses.

2.5. A 10-year-old male patient[41] presented with a 10-days history of fever, back pain, inability to walk, urinary retention, constipation, and abdominal distension. In the previous 2 days, he started complaining of blurred vision in the left eye, until only light perception was present. The spinal MRI showed lesions compatible with TM throughout almost the entire spinal cord, though no alterations were found in the optic nerves. He was diagnosed with NMOSD and started on IVMP 30 mg/kg/day for 5 days, followed by oral tapering. As his condition did not improve, PLEX was performed for 5 days and then AZA 2 mg/kg/day was started, alongside physiotherapy. Though the left eye vision was lost, he significantly improved the strength and function of the limbs.

2.6. A 3-year-old female patient[7] had 4 days of progressive bilateral vision loss. The MRI confirmed bilateral optic neuritis. On the day of the presentation, she started empiric treatment for NMOSD with PLEX and IVMP 20 mg/kg/day. After 5 sessions of PLEX/IVMP, her vision improved significantly and was discharged with oral prednisolone. She was then found to be AQP4-IgG positive and started on 375 mg/m^2 of RTX 2 weeks apart and each 3 months thereafter. After the first cycle, her vision subjectively improved.

2.7. A 2 years prospective multicenter study[21] with two pediatric patients who were treated with the RTX protocol proposed by Cabre et al. showed the following data:

2.7.1. A 16-year-old female patient with one episode of optic neuritis and negative for AQP4-IgG that had been treated with cyclosporine, showed, before treatment with RTX, an ARR of 0.5 and an EDSS score of 3.5. At the last follow-up, she presented an ARR of 0.5 and an EDSS of 5.0.

2.7.2. A 14-year-old female patient with one episode of optic neuritis and one episode of LETM was positive for AQP4-IgG and had no previous immunosuppressant treatment. She had an ARR of 1.0 and an EDSS of 8.5. After treatment with RTX her ARR was 0 and her EDSS was 0.0.

2.8. A 17-year-old female patient[27] developed subacute blindness in the right eye, subsequently starting 1 g/day of IVMP for 7 days followed by oral tapering. After 3 weeks, she recovered her visual acuity. A month later, she presented with vomiting, painful feet dysesthesias followed by progressive quadriplegia with sensory level C2, painful left eye, respiratory distress, and hypotonic voice. At this moment she had an EDSS of 9.0. The MRI showed left ON and LETM from C1 to D10. The CSF analysis revealed an increased IgG index of 0.84 (normal < 0.70) and a positive AQP4-IgG, found in serum as well. She was treated with 1 g/day of IVMP for 5 days but without improvement, so she continued with 500 mg/day alongside PLEX for 5 more days. Her respiratory capacity slightly improved 2 days after the last PLEX session. A new CSF analysis was performed showing an IgG index of 1.48 and positive AQP4-IgG, which was negative in serum. Thus, 1 month into this ongoing relapse, 400 mg/kg of IVIG was initiated for 5 days, and on the third day, an additional 375 mg/m^2/week of RTX for 2 weeks. The IgG index was then normal in the CSF analysis and the AQP4-IgG was negative both in CSF and serum. Four months later, the neurologic exam and the control MRI were both normal. Thereafter, she kept 2 annual sessions of RTX for the prevention of relapses. Until a follow-up of 4 years, she was relapse-free with low titers of AQP4-IgG.

2.9. A 7-year-old female patient[42] complained of cervical back pain, followed by paraparesis. The MRI exposed two spinal lesions, from C2 to D5 and from D8 to D10. She was found positive for AQP4-IgG. IVMP 500 mg daily was administered for 5 days, resulting in complete remission. She maintained preventative treatment with oral steroids and 50 mg/day of AZA, but relapsed twice with acute paraparesis at 8 years of age and again at 9. The lesions in MRI were in C6-D5 and D7-D9 territories on the first relapse, and in C7-D4 and D7-D9 on the second one. Both relapses were successfully managed with IVMP. Preventative therapy was started at the age of 9 with 375 mg/m^2 of RTX weekly for 3 weeks and repeated after 6 months. There were no further relapses in a follow-up until 12-years-old.

2.10. A 9-year-old female patient[43] presented with severe and progressive loss of strength, limb and joint pain, axial rigidity, neck stiffness, and urinary retention. She rapidly became quadriplegic with complete sensory loss and developed respiratory distress that required mechanical ventilation. The MRI showed LETM in C5-D10 and the AQP4-IgG was positive. She initiated treatment with IVMP 30 mg/kg/day for 5 days followed by 5 days of 0.4 g/kg/day of IVIG. With no improvement observed, she underwent 5 PLEX sessions, with good outcomes. However,

one month later she developed spastic paraplegia with bilateral clonus and a sensory level at D12. This time, RTX 375 mg/m^2 weekly for 4 weeks was started. During a follow-up of 9 months, she was completely recovered and had no further relapses. Every 3 months, CD19$^+$ B-cell count was performed, and it remained low. The authors support using RTX as first-line therapy.

2.11. A set of three pediatric case reports[32] demonstrated that treatment with RTX and subsequent discontinuation leads to prolonged periods of disease inactivity:

2.11.1. A 15-year-old male patient that had been diagnosed at the age of 10, with a positive AQP4-IgG test, presented with acute dysphagia, dysarthria, diplopia, and impaired coordination. His MRI showed lesions around the third ventricle, interhemispheric fissure, caudate nuclei, and brainstem. Treatment with prednisone for 2 weeks led to good recovery, except for prior subclinical optic neuropathy. Four months later the patient developed TM at C1-C3 levels, treated with 600 mg IVMP for 5 days followed by a 2-week oral taper, and, two months later, with two infusions of 200 mg/m^2 of RTX two weeks apart. It resulted in CD19$^+$ B-cells <1% for three months, until they returned to 23%. He received two more infusions of 350 mg/m^2 two weeks apart, followed by four more infusions at the same dose every 6 months, after which he discontinued RTX. He remained stable for 4.5 years, including 3 years without any medication. The ARR before and after RTX therapy was 2.67 and 0, respectively. His last EDSS was 1.0.

2.11.2. A 16-year-old female patient was diagnosed at the age of 4, being AQP4-IgG seropositive. She experienced 10 episodes of TM over 5 years, despite treatment with AZA, MM, IVIG, and PLEX. At the age of 9, she received infusions of 375 mg/m2 of RTX every 4 weeks, alongside IVIG for 6 months. A total of 5 cycles of RTX were administered at 6 to 12 months interval, being the last two cycles at 750 mg/m^2 2 weeks apart. Every infusion resulted in CD19$^+$ B-cell depletion <1% that lasted 6 to 7 months. She remained stable for 6 years, including 3 years without any medication. She had a mild relapse of TM that responded well to IVMP and RTX 375 mg/m^2. The ARR before and after RTX therapy was 2.67 and 0.38, respectively. Her last EDSS was 4.0, the result of complete bilateral loss of vision from the first episode.

2.11.3. A 15-year-old girl, AQP4-IgG positive, that had her first brainstem episode at the age of 2 years and 6 months, with subsequent optic neuritis episodes at ages of 4 and 6, was successfully treated with IVMP after every attack. When she was 6 years old, she started on RTX 375 mg/m^2 4-weekly, attaining CD19$^+$ B-cell depletion <1%, that lasted 5 months, after the first cycle. Thereafter, she received 5 cycles at 6 months interval, showing no further relapses. RTX was discontinued when she was 9. She remained relapse-free for 8 years, including 5 years without any medication. She relapsed with optic neuritis at 13 years-old and was treated with IVMP and PLEX, with good results, starting on AZA. The ARR before and after RTX therapy was 0.75 and 0.2, respectively. Her last EDSS was 3.0, from her first optic neuritis episode.

2.12. A 15-year-old female patient[34] developed optic neuritis and further relapses of optic neuritis and myelitis. At 16 she started azathioprine, switching to MM at 17 and then to a 6-monthly infusion of rituximab at 18. Rituximab was given alongside daily prednisolone for 3 years. When these last drugs were started, she had an EDSS of 4 and her serum Igs were normal. However, at 21 she developed hypogammaglobulinemia that led to severe pneumonia. After this episode she changed her rituximab schedule to retreatment according to B-cell repopulation, remaining stable thereafter.

2.13. A 12-year-old female patient[44] presented with sudden paresis of the left arm and progressive paresis of the left leg. The MRI showed LETM in C2-T2. She was treated with 1 g IVMP for 10 days and continued oral tapering for the following 3 months. Cefotaxime and acyclovir were also tried over 10 days. She experienced complete remission, but also a Cushing syndrome. She was relapse-free for 4 years until a sudden vision loss of the left eye appeared, and the MRI revealed optic nerve lesions. Testing for AQP4-IgG was positive. After being administrated a pulse of 1 g IVMP for 7 days, and another of 2 g for 7 more days, followed by 8 cycles of PLEX, there were no significant improvements. AZA at 2 mg/kg with oral steroids was started, but was discontinued after 2 months because of adverse effects (neutropenia and pancreatitis). Ultimately, rituximab was tried with 1 g on days 1 and 14 and then yearly for 3 years, depending on B-cell counts. Monthly monitoring of $CD19^+$ B-cells was performed. The first infusion provided a good response with significant depletion of $CD19^+$ lymphocytes. She was stable with residual neurological deficits and no further lesions appeared in the MRI for a follow-up of 3 years. Authors found this case supportive of the association between sufficient B-cell depletion and lower risk of relapse. They also propose monitoring of $CD19^+$ B-cells on a 3 months interval.

2.14. A 16-year-old female patient[37] positive for AQP4-IgG started having NMOSD symptoms in the past 10 months, with 4 exacerbations during that period. Control of acute relapses with IVMP and IVIG was achieved. She then started treatment with low-dose RTX at 100 mg weekly for 3 weeks, followed by measurement of $CD19^+$ B-cells at intervals of 12 weeks or less. Once the concentration of these cells was higher than 1% of mononuclear cells, 100 mg of RTX was reinfused. In the first year of treatment, she needed 3 re-infusions, but had no relapses. Her ARR decreased from 4.69 to 0.0, though it was a very short follow-up (1.4 years), and after 1 year her EDSS decreased from 2.0 to 1.0.

2.15. A 10-year-old male patient[39], positive for MOG-IgG, presented with a 13-days history of severe bilateral vision loss. Five weeks earlier, he had been treated with steroids for Henoch-Schonlein purpura. The MRI showed abnormalities in the thalami, brainstem and optic nerves. He received 5 days of 1 g IVMP and 2 days of IVIG (2 g/kg), with good results after one week and complete recovery after 2 months. He received thereafter 5-monthly IVIG infusions, showing no relapses in a 16 months follow-up.

Table III. Case Reports

Case	Age, Sex	Antibody	Clinical Manifestations	Treatment	Outcome
1	9, F	AQP4-IgG +	BS, ON	Interferon-ß + IVMP	No improvement EDSS 6
2	9, F	Unknown	BS, LETM, Bilateral ON ARR 4, EDSS 6.0	IVMP, IVIG, AZA, CYCL, Ciclosporin	No improvement
				Alemtuzumab	Worsening EDSS 8.0
3	18, F	AQP4-IgG+	ON	1g IVMP	No improvement
				PLEX + Oral prednisolone + AZA	Improvement
4	14, M	AQP4-IgG +	ON, Myelitis	AZA	Stable (3 y)
5	10, M	Unknow	LETM	30mg/kg/d IVMP	No improvement
				PLEX, AZA + physiotherapy	Improvement
6	3, F	AQP4-IgG +	Bilateral ON	PLEX + 20mg/kg/d IVMP	Improvement
				RTX 2w apart, then every 3mo	No information
7.1	16, F	AQP4-IgG -	ON ARR 0.5, EDSS 3.5	RTX weekly for 4w, then 2x 1g every 15d	Worsening ARR 0.5, EDSS 5.0
7.2	14, F	AQP4-IgG +	ON, LETM ARR 1, EDSS 8.5	RTX weekly for 4w, then 2x 1g every 15d	Improvement ARR 0, EDSS 0.0
8	17, F	AQP4-IgG +	ON, LETM EDSS 9.0	1g IVMP	No improvement
				500mg IVMP + PLEX	Slight improvement
				400mg/kg IVIG + RTX 2w apart, then 2-annualy	Full recovery and stable (4y)
9	7, F	AQP4-IgG +	LETM	500mg IVMP	Complete remission
				Oral steroid + AZA	2 relapses
				RTX weekly for 3w and after 6mo	Stable (3y)

10	9, F	AQP4-IgG +	LETM	30mg/kg/d IVMP, IVIG	No improvement
				PLEX	Improvement
				RTX weekly for 4w	Full remission and stable (9mo)
11.1	15, M	AQP4-IgG +	Cerebral syndrome, TM ARR 2.67	600mg IVMP + RTX 2w apart, then 4 more doses every 6mo	Stable (4.5y) ARR 0
11.2	16, F	AQP4-IgG +	TM ARR 2.67	AZA, MM, IVIG, PLEX	Relapsed
				RTX 4-weekly + IVIG 6mo	Stable (6y) ARR 0.38
11.3	15, F	AQP4-IgG +	BS, ON ARR 0.75	RTX 4-weekly, then 6-monthly	Stable (8y) ARR 0.2
12	15, F	Unknown	ON, Myelitis EDSS 4.0	RTX 6-monthly + Daily prednisolone	Hypogammaglobulinemia- Severe pneumonia
				RTX depending on B-cells count	Stable
13	12, F	AQP4-IgG +	LETM, ON	IVMP, PLEX	No improvement
				AZA + Oral steroids	Severe adverse effects
				RTX 2w apart, then depending on B-cells count	Stable (3y)
14	16, F	AQP4-IgG +	NMOSD symptoms ARR 4.69, EDSS 2	Low-dose RTX weekly for 3w, then depending on B-cells count	Stable ARR 0, EDSS 1
15	10, M	MOG-IgG +	ON	IVMP + IVIG	Full remission
				IVIG 5-monthly	Stable (16mo)

Abbreviations: AQP4-IgG = aquaporin 4-IgG; ARR = annualized relapse rate; AZA = azathioprine; BS = brainstem syndrome; CYCL = cyclosporin; d = day; EDSS = expanded disability status scale; F = female; IVIG = intravenous immunoglobulin; IVMP = intravenous methylprednisolone; LETM = longitudinally extensive transverse myelitis; M = male; MM = mycophenolate mofetil; mo = month; MOG-IgG = myelin-oligodendrocyte glycoprotein-IgG; NMOSD = neuromyelitis optica spectrum disorders; ON = optic neuritis; PLEX = plasma exchange; RTX = rituximab; TM = transverse myelitis; w = week; y = year

Summary of the Case Reports described above (age of patients in years).

Discussion

Treatment of NMOSD in children holds little consensus. Different protocols of dosages, treatment duration, and intervals between administrations are used and highly depend on the physician's opinion. Thus, comparing results becomes challenging and brings little clinical value. However, this review of the literature gathers enough information to support some decisions, as to propose future research.

Regarding the acute treatment, most physicians use IVMP as it shows good results. Though other options are available, they have not yet been studied in children. However, Bradshaw et al.[7] suggestion of using IVMP+PLEX from the beginning should be tested, mainly in aggressive cases, in which IVMP alone does not control symptoms evolution. Case reports 6 and 8 represent two situations where this strategy was applied and had good results. Case report 2.3, in a retrospective analysis, is an example of a patient who could have beneficiated from this strategy from the beginning, due to her prolonged and advanced disease. Studies on the efficacy of IVIG, PLEX and IA are essential for a more informed decision, regarding these therapeutic strategies. While they are not available, IVMP and IVMP+PLEX seem to be the most acceptable choices.

Maintenance treatment has more divergent opinions. There is a study that proves that AZA has less beneficial effects and that MM and RTX should be the first choices.[28] Though another study attests AZA's tolerability and efficacy in reducing EDSS (not ARR).[38] Case reports 4 and 5 show good response, while 9 and 13 have a bad response and adverse effects. There is no solid opinion on AZA, but, if used, oral steroids should be added in the first 6 months.

Several recommendations on MM dosing are described, but there is evidence that 1 g/day is tolerable and effective.[28] Though it is recommended a slower up-titration of MM, we found no reports describing this method. So, there is a need for confirmatory tests. Similarly to AZA, this drug needs to be accompanied by oral steroids for the first 6 months of treatment.

In this review we found several reports describing RTX as an effective and tolerable drug. Patients from case reports 7.2, 8, 9, 10, 11, 13 and 14 responded well to RTX, opposing to the one patient from case report 7.1 that showed no response to the drug. However, it may be related to the delay in starting therapy with RTX, or to the negativity for AQP4-IgG, since every patient that responded well was AQP4-IgG positive. To achieve better results, RTX should be initiated as soon as possible and, currently, more specialists advocate the use of RTX as first-line therapy. The expensive cost restrains its large-scale use. In an attempt to work around this problem, the effect of low-dose rituximab (100 mg) was studied in an adult population, though not showing satisfactory results.[37] However, the patient from case report 14 was treated with the same dose and progressed well. With the same goal, some authors infused patients according to $CD19^+$ B-cell repopulation, proving it is safer, more economical, and equally effective. This is patent in case reports 12, 13 and 14. Though the repopulation time has a marked interindividual variability, the intraindividual variability appears less pronounced. In the case series 11, we verify that RTX leads to prolonged periods of disease inactivity. Thus, it may be reasonable to discontinue this drug in selected cases. We find this of utter importance, and research on this subject could create opportunities for RTX, as it would be more cost-effective. Nevertheless, information on RTX's long-term effects are scarce and should be further evaluated, in order to assess its tolerability.

In MOG-IgG positive patients, treatment approaches are different. Exacerbations should be managed with IVMP and IVIG, while maintenance treatment is based on IVIG alone. The patient from case report 15 underwent this strategy and presented good results.

We underline the importance of an assertive and prompt diagnosis, so that targeted therapy is initiated. We present cases 1 and 2 in which patients were treated erroneously with Interferon-β and Alemtuzumab due to the delay in diagnosing NMOSD. These patients suffered a severe and irreversible disability. Some drugs should be utterly avoided in NMOSD, as Interferon-β, Alemtuzumab, Natalizumab and Fingolimod (all of them are currently approved for MS treatment).

Currently, NMOSD treatment in children is based on adult evidence. Though it seems that age does not bring significant differences in disease features and that treatment can be extrapolated from adults to children, this review pointed some caveats to this. A report on the use of PLEX showed that the only patient not improving was the only child of the group.[26] Another report proved that AZA in children does not have as beneficial results as in adults.[28] The article that claims that low-dose RTX has no satisfactory effect on adults[37] argues against the case report 14, in which a 16-year-old patient responded well to this dose. Although this is a small sample and conclusions cannot be hastily drawn, this should alert for the fact that extrapolating adult evidence to children might not be as straightforward as it is believed.

Conclusion

Pediatric-onset NMOSD is a very rare disease. For this reason, few reports on its treatment are available, and the ones that exist have small samples. In addition, as there is no consensus on how to treat patients, each physician uses a different protocol, which hinders results comparison. After this review, the importance of further research on this subject should be highlighted.

The use of monoclonal antibodies as maintenance treatment may be a mainstay of future therapeutic intervention in this clinical conditions (even due to the recent approval of 3 more drugs in this category, in adults), but this will only increase the difficulty of pharmacological management of children with this disease. The effort, on a global scale, to share the information of these cases is crucial, in order to achieve the objective of having multicentric studies done with children (given the rarity of the disease). And this is true both in terms of efficacy and safety of drugs.

Appendix

Table IV. Expanded Disability Status Scale – EDSS

Score	Description
0.0	Normal neurological exam, no disability in any FS
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Moderate disability in one FS and more than minimal disability in several others. Fully ambulatory
4.0	Self-sufficient and up and about some 12 hours a day despite relatively severe disability. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Ambulatory without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Ambulatory without aid or rest for 100m
6.0	Requires intermittent or unilateral constant assistance to walk about 100m with or without resting
6.5	Requires constant bilateral assistance to walk about 20m without resting
7.0	Unable to walk beyond about 5m even with aid. Essentially restricted to wheelchair. Wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Wheels self but cannot carry on in standard wheelchair for a full day. May require a motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms. Retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS
Functional systems: Pyramidal, Cerebellar, Brainstem, Sensory, Bowel and bladder, Visual, Cerebral, and Other functions	

Abbreviations: FS = functional system; MS = multiple sclerosis

Expanded Disability Status Scale according to Kurtzke et al., 1983[45]

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