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SPECTRUM OF ANTI-MOG ASSOCIATED DEMYELINATING DISEASES IN CHILDREN

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Spectrum of anti-MOG-associated demyelinating diseases in children

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Abstract

Antibodies against myelin oligodendrocyte glycoprotein (anti-MOG) are associated to a wide spectrum of demyelinating diseases of the Central Nervous System (CNS), particularly in paediatric ages. On contrary to what was initially thought, anti-MOG antibodies are less prevalent in Multiple Sclerosis (MS) and more often associated with less prevalent demyelinating diseases in children, such as Acute Disseminated Encephalomyelitis (ADEM), Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Diseases (NMOSD), Optic Neuritis (ON) and Transverse Myelitis (TM). Though the exact mechanism through which anti-MOG antibodies are pathogenic is still unclear, further investigation is necessary in order to clarify it and to propose children diagnosed with these conditions innovative therapeutic approaches.

This review article has the main purpose of summarizing the most recent literature about the spectrum of anti-MOG-associated diseases in children. A bibliographic review was conducted, searching for articles written in English and published in the last 10 years (2008-2018), available in Pubmed platform.

Studies until now revealed that anti-MOG antibodies are related with an earlier age at disease onset. Seropositive patients are often younger than seronegative ones. Children with Acquired Demyelinating Syndromes (ADS) had higher titers of these antibodies when compared with adults with the same diseases, highlighting the fact that anti-MOG antibodies have a particular role in demyelinating events in children.

Anti-MOG antibodies are observed transiently in monophasic diseases such as ADEM and their decline after the acute event is associated with a better prognosis. On the other hand, when they remain detectable for longer periods, even after the first treatment, the disease typically develops a relapsing course as, for example, ADEM followed by ON (ADEM-ON), multiphasic ADEM, recurrent ON, or MS. According to recent data, near 50% of anti-MOG

positive patients relapse. These multiphasic entities affect specially adolescents and adults, being ON the most common clinical presentation.

Anti-MOG positive patients have prominent inflammation presenting very high inflammatory markers, in general. Comparing with seronegative patients, they have higher cerebrospinal fluid (CSF) cell counting, higher CSF protein levels and higher neutrophil-related cytokines. The knowledge of these cells and cytokine profiles may improve our ability to monitor inflammation and response to treatment. In addition, some of these molecules may represent potential immunomodulatory targets for new therapies.

In conclusion, anti-MOG antibodies are associated with a very heterogeneous clinical spectrum and with a young age at disease onset. It is not yet possible to delineate a common clinical phenotype. There is a lot of ongoing research, with fruitful results expected in the short, medium and long term.

Keywords: Anti-MOG, spectrum, acquired demyelinating syndromes, paediatric ages.

Introduction

This review article has the purpose of summarizing the most recent information about anti-MOG-associated diseases in children. Myelin oligodendrocyte glycoprotein (MOG) is a glycoprotein exclusively expressed in the Central Nervous System (CNS) and its location in myelin outermost surface and oligodendrocytes' membrane makes it a potential target for cellular and humoral autoimmune phenomena (1).

The enormous interest in these autoantibodies is related with the fact that they may represent important diagnostic and prognostic biomarkers as, for example, anti-aquaporin-4 (anti-AQP4) in Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Diseases (NMOSD), as it has been since its identification in the early 2000s (2).

Anti-MOG antibodies can be associated to a large spectrum of acquired demyelinating diseases, predominantly, in paediatric ages. Using cell-based assays (CBA), anti-MOG antibodies have been identified in children with Acute Disseminated Encephalomyelitis (ADEM), Optic Neuritis (ON), NMO/NMOSD and Transverse Myelitis (TM) but rarely in patients with Multiple Sclerosis (MS) and in older ages. The spectrum of anti-MOG-associated conditions is still under construction and this aspect may raise a relevant discussion. Recently, different clinical phenotypes have been described and related with these antibodies (3,4).

The specific mechanism through which anti-MOG antibodies are pathogenic is not yet fully understood, and that is why they cannot be considered so far biomarkers in the diagnosis criteria (5).

Methods

This review is based in data collected from articles published in the PubMed platform in the last 10 years (2008-2018), focusing on antibodies anti-myelin oligodendrocyte glycoprotein and on the spectrum of associated diseases, in children and adolescents (age between 0 and 17 years and 364 days). The keywords used for the selection of the articles were "anti-MOG", "spectrum", "acquired demyelinating syndromes" and "paediatric ages" alone and in combination. All articles identified were written in English and only items for which the full text was available were considered. For each of them, we also searched the reference list for further relevant papers. Figure 1 outlines the criteria used for the research.

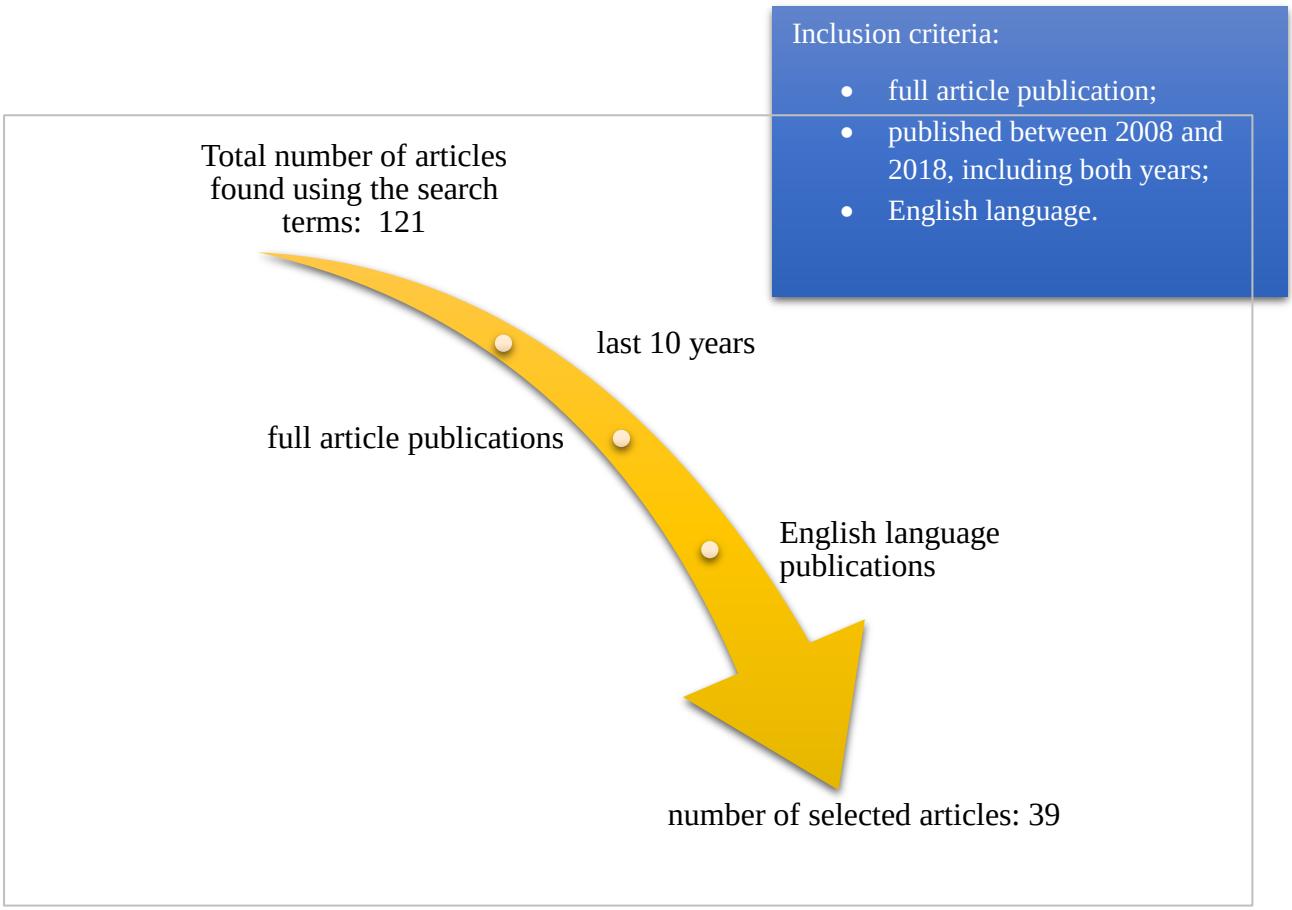

Figure 1 - *Methods: inclusion criteria and article selection.*

The target protein

Myelin Oligodendrocyte Glycoprotein (MOG) belongs to the immunoglobulin superfamily. This full-length protein is composed by 218 amino acids. It is exclusively expressed on the outermost lamellae of the myelin sheath and on the surface of oligodendrocytes in CNS. MOG represents less than 0.05% of myelin proteins. Although its slight concentration, it plays an important role as a surface biomarker of oligodendrocyte maturation, once it is relatively late expressed in neural development. It is also relevant for myelin integrity, adhesion and in cell surface interactions. Its location in the external surface of myelin sheath makes it a putative target for autoimmune mechanisms that result in CNS inflammation and demyelination (4-8).

MOG was identified for the first time 30 years ago, in an animal model of multiple sclerosis (MS) named Experimental Autoimmune Encephalomyelitis (EAE), which has shown that antibodies against MOG can increase demyelination, inducing both cell-mediated cytotoxicity and humoral immune response. However, the pathophysiological mechanisms mediated by these antibodies remain not totally clear (8,9).

Antibody detection

After finding the correlation between anti-MOG seropositivity and demyelination in CNS (firstly in animal models), the detection of these antibodies has gained interest in the last decades, as well as the way it can contribute to the diagnosis and prognosis of some demyelinating diseases of the CNS (5,8).

First experimental studies used mainly animal models, specifically the aforementioned EAE model, an important laboratorial tool that produces MS features by the immunization of animals CNS tissue or purified myelin components. Through these experimental assays,

MOG has been identified as an important CNS specific target for primary demyelination in autoimmune diseases like MS. There are different types of anti-MOG antibodies, but only those against conformational epitopes on the extracellular domain are pathogenic. Nevertheless, initial studies using animal models have produced controversial results, because of the use of inappropriate methods such as Enzyme-Linked Immunosorbent Assay (ELISA) and Western blot, leading to the conclusion that the detection method is crucial for the study of the immunopathology associated with these antibodies (5,8).

When using animal models, it is important to consider that the predicted sequence of the mature MOG protein is conserved among mammalian species, but certain epitopes are length or species dependent, which means that the applicability of the knowledge obtained with animal models to humans needs to be carefully evaluated (10). Nevertheless, with the development of CBA using correctly folded and glycosylated MOG protein, anti-MOG antibodies were found predominantly in paediatric patients with ADEM, AQP4-seronegative NMO/NMOSD, monophasic or recurrent isolated ON, in TM and in childhood MS. The majority of studies confirmed that both prevalence and titers of anti-MOG antibodies are higher in children with CNS demyelination than in adults. Higher antibody titres are consistently associated with younger age at disease onset (11,12).

In contrast to previous studies, using ELISA or Western blot in CBA, anti-MOG antibodies were rarely found on healthy controls or in patients with other inflammatory neurological diseases, like viral encephalitis, neither on immune systemic diseases, such as type 1 diabetes mellitus, this suggests that anti-MOG antibodies are specific for CNS demyelination (7,9,13-15).

Anti-MOG immunopathogenesis

In recent years, autoantibodies emerged as important biomarkers in neurological autoimmune diseases and have even contributed to a paradigm shift in the approach to neurological conditions. There is a growing evidence that B cells and antibodies have a central role in inflammatory and demyelinating events in the CNS and some specific antibodies have been already associated to certain diseases, such as anti-AQP4 in NMO/NMOSD and anti-N-methyl-D-aspartate (NMDA) receptor in limbic encephalitis (9, 16).

The role of anti-MOG antibodies in the pathogenesis of demyelinating diseases of the CNS remains to be completely clarified. It is not yet known if anti-MOG antibodies have an active role in demyelinating diseases or if their presence is only an epiphenomenon, secondary to myelin destruction and antigen spreading (5). First studies using animal models (EAE) argue in favour of a secondary immune reaction such as an antibody-dependent cellular mediated cytotoxicity. They also revealed that the susceptibility to anti-MOG antibodies is determined by Major Histocompatibility Complex (MHC) and non-MHC genes (1).

One study has shown that MOG IgG from paediatric patients induce natural killer (NK) cells, causing the death of cells expressing MOG, emphasising a cell-mediated toxicity effect. The same study also evidenced that there is a correlation between antibody titers and the extension of antibody dependent cell-mediated cytotoxicity, leading to the conclusion that higher titers are associated with higher levels of cytotoxicity (5,9).

Anti-MOG antibodies are mainly produced out of the CNS, at the periphery, and their detection is more sensitive in the serum than in the cerebrospinal fluid (CSF). Probably for this reason, they are less likely associated to the presence of intrathecal oligoclonal bands.

Though, one important question arises: how can peripheral antibodies gain access to the CNS? To be pathogenic in human CNS, an antibody needs either to be produced within or pass through the blood-brain barrier (BBB). The most reasonable hypothesis suggests that reactive T cells, activated during infections, damage the BBB, allowing pathogenic antibodies to access to the CNS. Another possible theory is that direct infection of the brain parenchyma exposes CNS antigens to the immune system, affecting BBB and triggering autoimmune diseases (5,17).

The majority of anti-MOG antibodies are IgG 1 isotype, which are able to fix complement and bind Fc receptors. There is an emerging evidence that complement component C5a is involved in Fc receptor regulation and sensing. Fc receptor (FcR) and complement interact with each other at the level of C5a at sites of inflammation (18). This connecting pathway may represent a new therapeutic target (18,19).

A recent research about cytokines profile in anti-MOG positive patients verified that B cell-related cytokines in CSF were much higher in an anti-MOG positive group, when compared with the anti-MOG negative group. Cytokines are intercellular messengers with pleiotropic effects on a variety of cell types. Thus, they can lead to immune system activation, inducing proliferation, differentiation and recruitment of immune cells to the site of inflammation, contributing to the immunopathogenesis. Specifically, CXCL13 is increased in anti-MOG positive patients. This cytokine facilitates Th17 cells migration into the CNS. In turn, Th17-related cytokines, such as IL-6, correlate with monophasic acquired demyelination syndromes, work as critical switch factors to activate naive T cells towards pro-inflammatory Th17 lymphocytes. In addition, granulocyte colony-stimulating factor (G-CSF) also induced by Th17 cells, stimulates survival, proliferation and differentiation of neutrophils (20). This cytokine profile may be useful to improve the ability to monitor inflammation and response to

treatment. Some of these molecules may also represent potential immunomodulatory targets (20).

This same study revealed that anti-MOG antibody positive patients had higher systemic inflammatory markers, in general. Higher CSF cell count, CSF proteins, CSF IgG levels, higher lesion load on MRI and, more often, had relapses and minor neurological deficits at follow-up, suggesting that MOG antibodies-associated demyelination can be connected with a higher inflammatory burden inside the CNS, but also with probably better clinical outcomes (20).

The histopathology associated with MOG antibodies shows demyelinating lesions with features of MS pattern II, highlighting the relevance on inflammation in these processes, with well demarcated confluent plaques, numerous macrophages containing myelin debris and deposition of complement, suggesting complement cytotoxicity (1). Anti-MOG antibodies cause disruption of oligodendrocyte cytoskeleton with loss of the organization of the thin filaments and of the architecture of microtubules of oligodendrocytes (21,22).

To sum up, both cellular and humoral mechanisms are involved in anti-MOG immunopathogenesis. Several studies have shown that anti-MOG response implicates complement fixing antibodies of IgG1 subtype and B cells that are antibody dependent and antibody independent, both mechanisms causing tissue damage (8,23).

Acquired Demyelinating Syndromes in children and anti-MOG antibodies

Acquired Demyelinating Syndromes (ADS) in children are complex diseases resulting from an interaction between a genetic susceptibility profile and environmental risk factors of multiple natures, characterized by the occurrence of immune-mediated demyelinating events

inside the CNS. The clinical spectrum is very heterogeneous, comprising MS, ADEM, NMO, NMOSD, ON, TM and clinically isolated syndrome (CIS) (12).

MS, idiopathic ON and ADEM represent the most common inflammatory and demyelinating diseases of CNS among all ages. The distinction between these entities may be challenging due to their similar clinical, radiological and immunopathological features, especially at disease onset. On the other hand, disease course and severity are largely variable. It is important to mention that all these different types of ADS can represent a first episode of MS or rare variants of this condition, such as Marburg disease or Baló concentric sclerosis (8).

It is fundamental to distinguish monophasic diseases like ADEM from chronic relapsing diseases, such as NMO and MS, once there is a disease-modifying therapy recommended for children with MS, which may have an important impact in the natural history of the condition. In addition, demyelinating diseases are considered an important cause of neurological disability in children and young adults. The relationship with anti-MOG antibodies may be of relevance, since they can contribute to identify specific forms of these diseases, with possibly different response profiles to the treatments and also with potentially different prognoses (8).

Acute disseminated encephalomyelitis

ADEM is a well-characterized acquired demyelinating syndrome defined by multifocal involvement of CNS and encephalopathy that triggers consciousness alteration and behavioural changes. Brain Magnetic Resonance Imaging (MRI) typically shows diffuse and poorly demarcated, bilateral lesions involving most predominantly the cerebral white matter

and the spinal cord. This clinical entity affects mainly children and young adults. It may be preceded by infectious diseases or, more rarely, by vaccination (24,25).

ADEM has usually a monophasic presentation, especially if it is early diagnosed and adequately treated, providing a favourable clinical prognosis. Anti-MOG antibodies are present in approximately 50% of children with ADEM, this being the most frequent clinical syndrome associated with their presence in serum. Patients have frequently very high titers of these antibodies in the first episode (25).

Nevertheless, a subgroup of children with ADEM develops a relapsing disease course, a chronic disorder that often leads to the diagnosis of MS or NMOSD. More recently, a distinct clinical phenotype has been recognised with patients presenting ADEM followed by a single or recurrent episode of ON (4,17,26,27). Despite the slight prevalence of children with ADEM followed by ON (ADEM-ON) in the ADS spectrum, the majority of them are positive for anti-MOG antibodies. ADEM-ON has been the final diagnosis in near 40% of anti-MOG positive patients who initially presented ADEM. Children with ADEM-ON can have a very heterogeneous disease course. They are frequently corticosteroid-dependent and need immunosuppression for maintenance, also because episodes of ON, in this context, are usually severe and very disabling (26).

Optic neuritis

ON is characterized by oculodynia aggravated with eye movement and visual loss due to the inflammation of the optic nerve. It is often associated with the diagnosis of MS or NMOSD, being one of their most typical manifestations (28,29).

Recent data suggest that anti-MOG antibodies are present in certain forms of ON. There is a strong association between anti-MOG antibodies and simultaneous bilateral and/or recurrent ON among all ages. This particular subgroup of patients has multiple episodes that involve one or both optic nerves, occurring during weeks or months (29).

ON imaging frequently shows bilateral and longitudinally extensive involvement of the optic nerves, affecting especially the anterior visual pathway, with optic nerve head swelling and retrobulbar optic nerve involvement. Optic disc swelling is very suggestive of anti-MOG-positive ON (29).

The entity defined as recurrent ON is typically corticosteroid-responsive and corticosteroid-dependent, requiring immune suppressive therapy for a steroid-sparing effect (28,29).

ON is the second most prevalent demyelinating manifestation associated to anti-MOG antibodies. Patients usually have a relapsing disease course. For this reason, it seems reasonable to organize early secondary prevention strategies such as corticosteroids maintenance, intravenous Ig or chronic immunosuppression with mycophenolate mofetil or rituximab (30).

Transverse myelitis

TM is caused by inflammation of spinal cord and it is characterized by an acute onset of motor, sensory and autonomic dysfunction. This clinic entity is rare nowadays, mainly because the diagnosis of myelitis rarely appears isolated, being a typical manifestation of several ADS in children. As other demyelinating events mentioned before, also TM may represent the first episode of MS. Correct diagnosis and rapid initiation of treatment are fundamental to achieve a favourable prognosis. The treatment includes immunomodulatory therapy, using intravenous corticosteroids or plasma exchange (31).

Considering TM low prevalence, there is lack of information about its relationship with anti-MOG antibodies (31).

Neuromyelitis optica and neuromyelitis optica spectrum disorders

NMO is an autoimmune demyelinating disorder that selectively targets optic nerves and spinal cord. It is characterized by episodes of recurrent unilateral or bilateral ON and longitudinal extensive transverse myelitis (LETM) (32). Complementary diagnostic criteria include spinal cord lesion extending over three or more vertebral segments on MRI, a brain MRI that does not match with the criteria for MS and seropositivity for anti-AQP4 antibodies (19). Atypical forms of the disease are included in the designation of NMOSD, which comprises patients with single or recurrent events of LETM or recurrent or simultaneous bilateral ON. Both entities are associated with a poor prognosis (32).

NMO pathogenesis is well demonstrated to be related to aquaporin 4 (AQP4) antibody (33). AQP4 is a water channel protein essentially expressed by astrocytes, in the CNS. The antibody can damage those cells causing CNS inflammation. Anti-AQP4 is a highly sensitive

and specific biomarker for NMO and for this reason it has been included in the diagnostic criteria for this entity (8,34).

Near 90% of the patients with NMO and more than half of the patients with NMOSD are positive for anti-AQP4. Nevertheless, a subgroup of patients (12-30%), especially children with NMO/NMOSD is seronegative for AQP4 antibodies (5), suggesting that other autoantibodies might be involved in the pathophysiology of these conditions. Several recent studies revealed the presence of anti-MOG antibodies in patients seronegative for anti-AQP4 (19,29,32,34,35).

Anti-MOG positive patients frequently have younger age at onset and present a clinical phenotype of recurrent ON or LETM. There is also a strong association between anti-MOG antibodies and simultaneous bilateral ON. Some patients present the classic simultaneous or rapidly sequential ON and TM, which is rarely associated with anti-AQP4 antibodies. Nevertheless, anti-MOG positive patients frequently have a favourable prognosis with mild residual disability (34,35).

Recent data suggest that there is a minority of patients that are positive for both antibodies (double positives). These cases are associated with worst prognosis, usually presenting a multiphase disease with high annual relapse rates and severe residual disability. This latest study suggested that positive patients for both autoantibodies combined features of prototypic NMO and relapsing-remitting MS (28). MRI imaging findings and optical coherence tomography (OCT) are indispensable in the diagnosis and evaluation of NMOSD (34).

Multiple sclerosis

MS is the most common demyelinating disease of CNS among all age groups though is relatively uncommon in childhood, representing near 5% of the total MS population. It is presumed to be caused by an autoimmune attack to myelin sheaths, leading to demyelination and axonal loss. The clinical diagnosis of MS is based on the evidence of demyelinating lesions disseminated in time and space. The diagnosis requires neurologic symptoms and MRI findings consistent with MS lesions, demonstration of intrathecal oligoclonal bands and/or detection of abnormal visual evoked potentials, depending on the clinical phenotype of the disease (7,25).

As mentioned before, anti-MOG antibodies are present in a slight percentage of children with MS and within MS patients, these antibodies are found predominantly in paediatric ages. Studies in MS patients did not use a very high titer for the cut off, being possible to conclude that anti-MOG antibodies are rare in MS and may represent a negative biomarker. Even children with MS positive for anti-MOG antibodies have a different clinical phenotype, presenting more evident pleocytosis, rare intrathecal oligoclonal bands and atypical MRI lesions, confluent and asymmetrical. This is why anti-MOG antibodies positivity may represent a negative predictor for the diagnosis of MS, in association with atypical MRI features and absence of oligoclonal bands. On the other hand, if anti-MOG titers are persistently elevated, there is trivial possibility that MS is the final diagnosis (4,17,24,27, 36).

Clinical relevance of anti-MOG antibodies spectrum diseases

Try to define the spectrum of anti-MOG associated demyelinating diseases in children would be the main goal of this article. However, after researching on this topic, it remains difficult to establish a straightforward and clean spectrum, given until now different demyelinating events are being associated to the presence of these autoantibodies in serum (Figure 2).

Fernandez-Carbonell et al. recognized a bimodal distribution of MOG seropositive patients by age of onset, with a distinct younger group (4-8 years) having a high prevalence of ADEM and an older group (13-18 years) having predominantly ON. The same study verified that there is not a significant difference between patient gender or race and the family history of MS or other autoimmune diseases seemed to be irrelevant. When considering symptoms, seropositive patients were more likely to have encephalopathy as the first symptom, suggesting a strong association of anti-MOG antibodies to ADEM (16).

Anti-MOG antibodies were found in 1/3 of children with ADS, 57% presented an ADEM-like first episode, 25% recurrent ON, 25% anti-AQP4 seronegative NMO/NMOSD and a lower percentage (8%) was found in children with MS with early onset, before 10 years of age (3,16). Recently, new subgroups of anti-MOG positive children have been identified including children with multiphasic ADEM and ADEM followed by monophasic or recurrent ON (ADEM-ON), emphasising that there are a variety of phenotypes associated with these autoantibodies (32).

Initially, anti-MOG antibodies were thought to be associated with a benign disease course, but nowadays it is known that they are found in a substantial proportion of children with relapsing episodes (some of them clinically severe) associated with high persisting titers (32). As an example, anti-MOG antibodies were persistently elevated in children with ADEM

followed by ON. The first episode is usually characterised by acute and severe clinical symptoms with neurological manifestations comprising bowel dysfunction and visual loss. Sometimes it is preceded by prominent prodromal phase with headache and nausea some weeks before the demyelinating event. The first episode appears to be worse than future relapses (3). This condition seems to be very sensitive to corticosteroids, but the relapses may be extremely disabling.

Laboratory and imaging findings have also revealed some particularities in anti-MOG positive cases. MOG seropositivity is associated to elevated levels of white blood cells, pleocytosis in CSF and to the absence of intrathecal IgG oligoclonal bands, suggesting a different profile from what is considered to be classic in MS (16). Around 1/3 of anti-MOG positive patients have abnormal CNS imaging. MRI findings include large lesions typical of ADEM, widespread cortical lesions and deep grey matter involvement, comprising bilateral thalamic, basal ganglia lesions and longitudinally extensive spinal cord lesions, involving principally the cervicothoracic region and the conus medullaris (4). Analysis of qualitative MRI features showed that corpus callosum lesions are absent in MOG seropositive patients, as well as thoracic cord lesions, in opposition of what happens in MS patients, suggesting different targets in the demyelination process (16).

In conclusion, it seems reasonable to perform an anti-MOG test in all childhood-onset demyelinating diseases, once these antibodies are specific for ADS among paediatric ages and an early diagnosis may have a favourable impact in the prognosis, especially in diseases with relapsing courses (30,37).

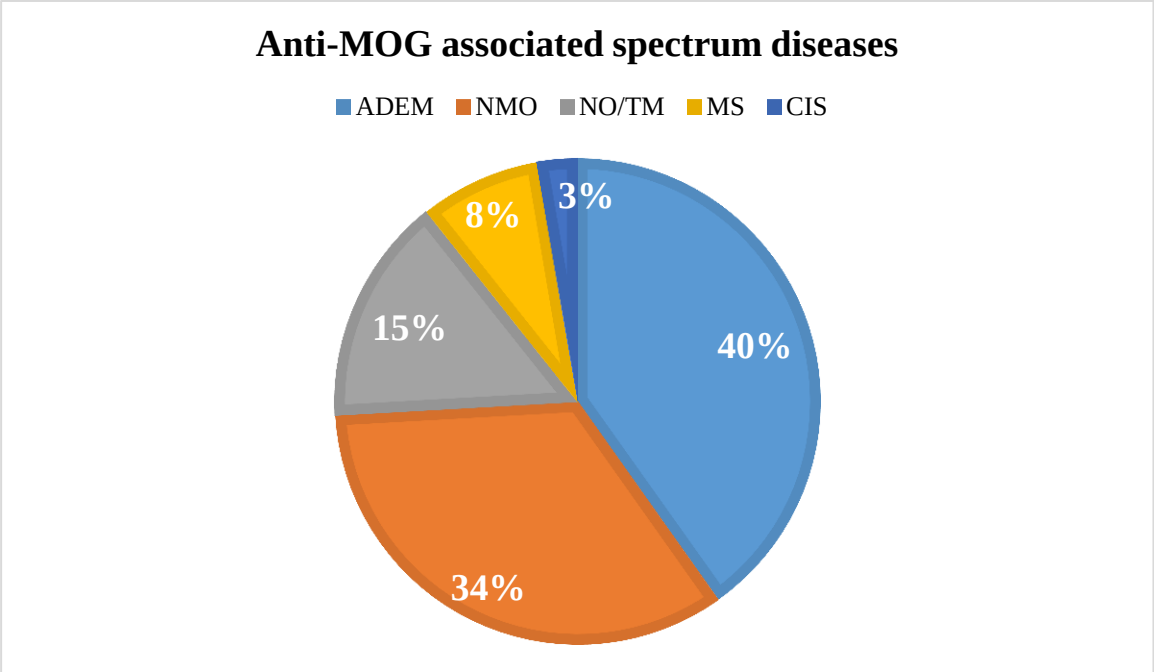

Figure 2 - Anti-MOG-associated spectrum of diseases. Based in Rostásy et al. study (2012).

Therapeutic approach

Considering anti-MOG antibodies and their pathogenic potential, it seems reasonable to treat MOG-associated demyelinating diseases with immune suppression, including corticosteroids, intravenous Ig, plasma exchange or B-cell-directed therapies, such as rituximab. It is fundamental to do a correct diagnosis at the beginning of the disease, once there are different therapeutic options, as for example, between MS and other demyelinating conditions. MS is typically treated with disease modifying immunomodulatory therapy which may have a detrimental impact in anti-MOG positive patients (38).

Current therapeutics for anti-MOG-associated diseases include high doses of intravenous/oral steroids, intravenous Ig or plasma exchange and, as second line agents, mycophenolate mofetil or azathioprine, followed in refractory cases by rituximab. Considering that patients may have different immunopathogenic responses to the presence of the antibodies, particularly children, there is a variability of possible outcomes associated to these treatments (4).

Anti-MOG seropositive patients respond rapidly to steroids and plasma exchange. However, in recurrent cases, it is necessary to initiate a maintenance therapy with, as an example, daily doses of prednisone. In some cases, patients are corticodependent, relapsing with steroids reduction or cessation (29). Because of that, steroid-sparing therapies such as azathioprine and mycophenolate mofetil could be very useful, for those patients who are in risk of frequent and severe relapses. However, second line therapies, such as these oral immunossupressive drugs, may take some months to reach total efficacy. For this reason, steroids treatment should not be rapidly interrupted when adding or switching to new drugs.

Treatment failure rates were lower when patients were in maintenance with steroids compared with those on non-steroidal maintenance immunotherapy. In patients presenting ADEM-ON, one study verified that no relapses occurred while using a prednisone dose >10 mg per day. But corticosteroids' side effects and the unpredictable disease course of ADEM-ON do not allow their use as long-term therapy (26).

It seems useful to have a relapse plan, allowing some patients to have a rapid access to steroids at the beginning of the relapse. After the acute treatment with high doses of steroids (usually intravenous methylprednisolone in doses of 1000 mg/day, during 3-7 days; in children with less than 30 kg of weight, the recommended dose is of 30 mg/kg/day during the same period of time), a new event may be prevented by low doses of oral prednisone (or prednisolone) or monthly intravenous Ig, being mycophenolate mofetil or rituximab a further step (39).

At follow-up near 71% of patients had residual deficits, as visual impairments, cognitive impairments, behavioural problems, bowel dysfunction and motor deficits. Frequent relapses were found to lead to sustained disability, particularly when affecting the optic nerve (39). Anti-MOG antibodies serostatus (absence/presence and titers) should be used in

conjunction with clinical information to guide maintenance therapy. However, there are no formal recommendations related to this aspect, so it should be approached with caution.

Conclusion

Anti-MOG antibodies are highly related with ADS in children, representing a possible biomarker for the diagnosis of these demyelinating diseases among paediatric ages. ADS include a large spectrum of clinical entities and some of them can have a relapsing course.

Some important key-ideas emerged from this review: anti-MOG antibodies are associated with an earlier disease onset, being more prevalent among paediatric patients; clinical presentation at onset is age-dependent, with a younger subgroup having mainly ADEM and an older group presenting predominantly ON with high risk of future relapses, that may be quite disabling; the spectrum of diseases mediated by anti-MOG antibodies are particularly steroid-responsive and this characteristic may justify long-term immunosuppression, since the risk of recurrence could be high. In fact, there is growing evidence that a substantial proportion of children relapse after the first episode (near 50%). Relapsing disease course is associated with high persistent titers and ON is the most common clinical manifestation associated with that risk of recurrence.

Recent years have been profitable in new knowledge related to pathophysiology, immunopathogenesis and clinical manifestations associated with the presence of anti-MOG antibodies. Still, many gaps in knowledge exist, especially considering the paediatric population. In fact, paediatric neuroimmunology is an area of knowledge that is rapidly expanding and the future will surely bring a wealth of scientific knowledge that may allow us to change the face of many of these immune-mediated conditions.

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References

1. Peschl P, Bradl M, Hoftberger R, Berger T, Reindl M. Myelin Oligodendrocyte Glycoprotein: Deciphering a Target in Inflammatory Demyelinating Diseases. Frontiers in immunology. 2017;8:529.

2. Reindl M, Jarius S, Rostasy K, Berger T. Myelin oligodendrocyte glycoprotein antibodies: How clinically useful are they? Current opinion in neurology. 2017;30(3):295-301.

3. Hennes EM, Baumann M, Lechner C, Rostasy K. MOG Spectrum Disorders and Role of MOG-Antibodies in Clinical Practice. Neuropediatrics. 2018;49(1):3-11.

4. Thulasirajah S, Pohl D, Davila-Acosta J, Venkateswaran S. Myelin Oligodendrocyte Glycoprotein-Associated Pediatric Central Nervous System Demyelination: Clinical Course, Neuroimaging Findings, and Response to Therapy. Neuropediatrics. 2016;47(4):245-52.

5. Ramanathan S, Dale RC, Brilot F. Anti-MOG antibody: The history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. Autoimmunity reviews. 2016;15(4):307-24.

6. Adoni T. Anti-MOG syndrome: a road to be paved. Arquivos de neuro-psiquiatria. 2017;75(10):685-6.

7. Di Pauli F, Mader S, Rostasy K, Schanda K, Bajer-Kornek B, Ehling R, et al. Temporal dynamics of anti-MOG antibodies in CNS demyelinating diseases. Clinical immunology. 2011;138(3):247-54.

8. Reindl M, Di Pauli F, Rostasy K, Berger T. The spectrum of MOG autoantibody-associated demyelinating diseases. Nat Rev Neurol. 2013;9(8):455-61.

9. Brilot F, Dale RC, Selter RC, Grummel V, Kalluri SR, Aslam M, et al. Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease. Annals of neurology. 2009;66(6):833-42.

10. Menge T, Lalive PH, von Budingen HC, Genain CP. Conformational epitopes of myelin oligodendrocyte glycoprotein are targets of potentially pathogenic antibody responses in multiple sclerosis. Journal of neuroinflammation. 2011;8:161.

11. Nakashima I. [Anti-MOG Antibody Associated Diseases]. Brain and nerve = Shinkei kenkyu no shinpo. 2017;69(11):1331-6.

12. Ketelslegers IA, Van Pelt DE, Bryde S, Neuteboom RF, Catsman-Berrevoets CE, Hamann D, et al. Anti-MOG antibodies plead against MS diagnosis in an Acquired Demyelinating Syndromes cohort. Multiple sclerosis. 2015;21(12):1513-20.

13. Lalive PH, Menge T, Delarasse C, Della Gaspera B, Pham-Dinh D, Villoslada P, et al. Antibodies to native myelin oligodendrocyte glycoprotein are serologic markers of early inflammation in multiple sclerosis. Proc Natl Acad Sci U S A. 2006;103(7):2280-5.

14. McLaughlin KA, Chitnis T, Newcombe J, Franz B, Kennedy J, McArdel S, et al. Age-dependent B cell autoimmunity to a myelin surface antigen in pediatric multiple sclerosis. J Immunol. 2009;183(6):4067-76.

15. O'Connor KC, McLaughlin KA, De Jager PL, Chitnis T, Bettelli E, Xu C, et al. Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein. Nat Med. 2007;13(2):211-7.

16. Fernandez-Carbonell C, Vargas-Lowy D, Musallam A, Healy B, McLaughlin K, Wucherpfennig KW, et al. Clinical and MRI phenotype of children with MOG antibodies. Multiple sclerosis. 2016;22(2):174-84.

17. Polat I, Yis U, Karaoglu P, Ayanoglu M, Ozturk T, Guleryuz H, et al. Myelin Oligodendrocyte Glycoprotein Antibody Persistency in a Steroid-Dependent ADEM Case. Pediatrics. 2016;137(5).

18. Schmidt RE, Gessner JE. Fc receptors and their interaction with complement in autoimmunity. Immunol Lett. 2005;100(1):56-67.

19. Lechner C, Baumann M, Hennes EM, Schanda K, Marquard K, Karenfort M, et al. Antibodies to MOG and AQP4 in children with neuromyelitis optica and limited forms of the disease. Journal of neurology, neurosurgery, and psychiatry. 2016;87(8):897-905.

20. Kothur K, Wienholt L, Tantsis EM, Earl J, Bandodkar S, Prelog K, et al. B Cell, Th17, and Neutrophil Related Cerebrospinal Fluid Cytokine/Chemokines Are Elevated in MOG Antibody Associated Demyelination. PloS one. 2016;11(2):e0149411.

21. Berg CT, Khorooshi R, Asgari N, Owens T. Influence of type I IFN signaling on anti-MOG antibody-mediated demyelination. Journal of neuroinflammation. 2017;14(1):127.

22. Dale RC, Tantsis EM, Merheb V, Kumaran RY, Sinmaz N, Pathmanandavel K, et al. Antibodies to MOG have a demyelination phenotype and affect oligodendrocyte cytoskeleton. Neurology(R) neuroimmunology & neuroinflammation. 2014;1(1):e12.

23. Mayer MC, Meinl E. Glycoproteins as targets of autoantibodies in CNS inflammation: MOG and more. Therapeutic advances in neurological disorders. 2012;5(3):147-59.

24. Baumann M, Sahin K, Lechner C, Hennes EM, Schanda K, Mader S, et al. Clinical and neuroradiological differences of paediatric acute disseminating encephalomyelitis with and without antibodies to the myelin oligodendrocyte glycoprotein. Journal of neurology, neurosurgery, and psychiatry. 2015;86(3):265-72.

25. Hoftberger R, Lassmann H. Inflammatory demyelinating diseases of the central nervous system. Handbook of clinical neurology. 2017;145:263-83.

26. Wong YYM, Hacohen Y, Armangue T, Wassmer E, Verhelst H, Hemingway C, et al. Paediatric acute disseminated encephalomyelitis followed by optic neuritis: disease course, treatment response and outcome. European journal of neurology. 2018.

27. Miyauchi A, Monden Y, Watanabe M, Sugie H, Morita M, Kezuka T, et al. Persistent presence of the anti-myelin oligodendrocyte glycoprotein autoantibody in a pediatric case of

acute disseminated encephalomyelitis followed by optic neuritis. Neuropediatrics. 2014;45(3):196-9.

28. Chalmoukou K, Alexopoulos H, Akrivou S, Stathopoulos P, Reindl M, Dalakas MC. Anti-MOG antibodies are frequently associated with steroid-sensitive recurrent optic neuritis. Neurology(R) neuroimmunology & neuroinflammation. 2015;2(4):e131.

29. Ramanathan S, Prelog K, Barnes EH, Tantsis EM, Reddel SW, Henderson AP, et al. Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis. Multiple sclerosis. 2016;22(4):470-82.

30. Ramanathan S, Mohammad S, Tantsis E, Nguyen TK, Merheb V, Fung VSC, et al. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. Journal of neurology, neurosurgery, and psychiatry. 2018;89(2):127-37.

31. Wolf VL, Lupo PJ, Lotze TE. Pediatric acute transverse myelitis overview and differential diagnosis. J Child Neurol. 2012;27(11):1426-36.

32. Sato DK, Callegaro D, Lana-Peixoto MA, Waters PJ, de Haidar Jorge FM, Takahashi T, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. Neurology. 2014;82(6):474-81.

33. Zhou L, Huang Y, Li H, Fan J, Zhangbao J, Yu H, et al. MOG-antibody associated demyelinating disease of the CNS: A clinical and pathological study in Chinese Han patients. Journal of neuroimmunology. 2017;305:19-28.

34. Yan Y, Li Y, Fu Y, Yang L, Su L, Shi K, et al. Autoantibody to MOG suggests two distinct clinical subtypes of NMOSD. Science China Life sciences. 2016;59(12):1270-81.

35. Jasiak-Zatonska M, Kalinowska-Lyszczarz A, Michalak S, Kozubski W. The Immunology of Neuromyelitis Optica-Current Knowledge, Clinical Implications,

Controversies and Future Perspectives. International journal of molecular sciences. 2016;17(3):273.

36. Probstel AK, Dornmair K, Bittner R, Sperl P, Jenne D, Magalhaes S, et al. Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis. Neurology. 2011;77(6):580-8.

37. Mariotto S, Ferrari S, Monaco S, Benedetti MD, Schanda K, Alberti D, et al. Clinical spectrum and IgG subclass analysis of anti-myelin oligodendrocyte glycoprotein antibody-associated syndromes: a multicenter study. Journal of neurology. 2017;264(12):2420-30.

38. Hacohen Y, Wong YY, Lechner C, Jurynczyk M, Wright S, Konuskan B, et al. Disease Course and Treatment Responses in Children With Relapsing Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease. JAMA neurology. 2018.

39. Reindl M. Clinical course of MOG antibody-associated recurrent demyelinating diseases. Journal of neurology, neurosurgery, and psychiatry. 2018;89(2):118.