DIAGNOSTIC AND PROGNOSTIC BIOMARKERS IN PEDIATRIC MULTIPLE SCLEROSIS AND RELATED DEMYELINATING DISORDERS

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1. Summary

Multiple sclerosis (MS) is a chronic inflammatory disease characterized by demyelination and axonal degeneration, with a first phase in which accumulation of disability is associated with relapses, resulting from multifocal inflammatory lesions, subsequently followed by a progressive phase mainly driven by neurodegeneration. Pediatric MS affects 5%-10% of the MS population, and they present with different clinical features, MRI characteristics, laboratory findings, and courses of the disease. In comparison with adults, the diagnosis in children is more difficult because different pathogenetically demyelinating syndromes may present with similar clinical features. In children, autoantibodies are more frequent and the repertoire more extensive than in adults. Therefore, a careful collection of clinical and MRI data and the use of appropriate strategies for the identification of antibodies may help to develop biomarkers capable of improving the diagnosis, and the prognosis of patients with a first demyelinating event. This is important because the initiation of immunomodulatory therapy is crucial for those children who will ultimately develop a relapsing disease but could be unnecessary or even harmful in those who will have a monophasic disease.

Objectives

1. To evaluate clinical and biological features that make it possible to establish a more accurate diagnosis and prognosis in pediatric patients with a first demyelinating event.

1.1 To apply the current diagnostic criteria

1.2 To analyze several biomarkers: magnetic resonance imaging (MRI); oligoclonal bands; and antibodies against glial antigens.

2. To evaluate the demyelination/axonal injury induced by the antibodies detected in the previous objective.

2. Results

1. The application of the 2017 McDonald criteria in children with a first episode is feasible and allows an earlier diagnosis of multiple sclerosis. Oligoclonal bands (OB) and antibodies to myelin oligodendrocyte glycoprotein

(MOG-IgG) are the most useful biomarkers for assessing the risk of developing multiple sclerosis.

From January 2014 to October 2018, we collected a cohort of 281 patients with a first demyelinating event from 40 participating centers. A total 186 patients were assessed after excluding those who were diagnosed with other disorders. For the comparative study of application of the criteria, we analyzed the 55 patients who had full clinical information, sample collected at the time of the acute episode, and appropriate MRI to be assessed blinding to the clinical and immunological data. The cohort of 55 children (45% female) had a median age of 6.2 years (IQR 3.5-13.6 years; 67% < 12 years). The diagnosis at onset (2010 McDonald criteria, and IPMSSG) was acute disseminated encephalomyelitis (ADEM) (28); MS (3); CIS (17); RIS (1); and other (6; ADEM without encephalopathy). After a median follow-up of 16 months (IQR 7-26 months), the diagnosis changed in 10 patients: 7 converted to MS, 1 to recurrent optic neuritis (ON), 1 to ADEM-ON, and 1 to neuromyelitis optica spectrum disorder (NMOSD). We observed than none of the 7 patients who converted to MS had MOG-IgG antibodies, in comparison with 22/38 (58%) of the patients who did not convert (p=0.01). In contrast, 5/7 (71%) of the patients with MS had positive OB, in comparison with 1/26 (4%) of the patients who did not convert (p< 0.001). AQP4-IgG were detected in none of the patients included in the study. After applying the 2017 McDonald criteria we did not observe differences in the number of patients diagnosed with MS at the last follow-up (10 patients); however, at onset only 3/10 fulfilled the 2010 McDonald criteria, while applying the 2017 McDonald criteria the patients were 7/10. Thus, the new criteria were able to identify 4 additional patients at onset, and all of them due to the OB. In summary, our study shows that the presence of OB in pediatric patients with a first demyelinating episode associates with risk of developing MS, and the presence of MOG-IgG with risk of developing recurrent non-MS. Finally, despite the limited number of patients, our study suggest that the current criteria can be applied in children < 10 years as long as they present with a typical clinic and radiological syndrome ***(Reference 1)***.

2. Acute disseminated encephalomyelitis (ADEM) is the most frequent presentation of children with a first demyelinating episode, and up to 50% of them harbor MOG-IgG antibodies

Up to 40% of the pediatric patients present with ADEM at the time of first demyelinating event, and 57% of them have MOG-IgG. The presence of MOG-IgG

associates with recurrent non-multiple sclerosis course, and most of the patients will remain as monophasic forms ***(Reference 2)*;** however, a small percentage of the patients will have a recurrent course and will ultimately be diagnosed with ADEM-ON. The latter associates with a severe course, and most of the patients will have visual and cognitive impairment, and will be refractory for immunosuppressive therapy ***(Reference 3)***.

3. Low frequency of neuromyelitis optica spectrum disorder (NMOSD) in the pediatric population.

An epidemiological study on neuromyelitis optica spectrum disorder (NMOSD) in Catalonia showed that the incidence and prevalence estimates were 1.5-fold higher with the new 2015 criteria compared to those of the 2006 ones. The prevalence in pediatric population was 0.22/100,000 and that of incidence 0.35/1,000,000 person-year, and that meant 4 and 2 fold lower than that observed in the overall population, respectively. Although AQP4-IgG cases were more incident and prevalent, the female predominance was lost in pediatric patients seronegative for AQP4-IgG ***(Reference 5)***. We demonstrated that optical coherence tomography (OCT) in patients with NMOSD made it possible to distinguish optic neuritis associated with AQP4-IgG or with MOG-IgG; the findings of the latter were quite similar to those found in multiple sclerosis patients ***(Reference 6)***. The paraneoplastic cause of NMOSD, although rare in adults, was not observed in pediatric population ***(Reference 7)***.

4 The clinical spectrum associated with MOG-IgG in pediatric population differs from that observed in adult patients.

In contrast with pediatric patients, 60% of adult patients with MOG-IgG present with optic neuritis, and only 4% of them with ADEM ***(Reference 8)***. We analyzed whether the presence of additional IgA or IgM antibodies to MOG could contribute to the clinical and outcome heterogeneity observed in patients with MOG-IgG. The study showed antibodies IgA or IgM against MOG in 24.5% of the children, and 15% of the adults. The clinical syndrome at onset in pediatric patients was ADEM (80%), and optic neuritis (70%) in adults. However, the coexistence of different classes of Ig (IgA or igM) anti-MOG did not confer any differential characteristic when they were compared to those pediatric or adult patients with only MOG-IgG ***(Reference 9)***.

5. The clinical spectrum associated with MOG-IgG in pediatric population is wider than expected. The importance of providing recommendations for the diagnosis and antibody determination

We have identified that the pathology of the brain inflammatory process associated with MOG-IgG can be misdiagnosed with small vessel CNS vasculitis. To be aware of this misdiagnosis is relevant because it has important diagnostic and therapeutic implications ***(Reference 10)***. The latter emphasizes the importance of providing recommendations for the diagnosis of the disorders associated with MOG-IgG, and the diagnostic approach in cases of suspected autoimmune encephalitis ***(Reference 12, 13)***

6. MOG-IgG antibodies seem to participate in the physiopathological mechanisms involved in the immune response: an experimental approach.

It has been demonstrated in an "in vivo" model that the antibodies MOG-IgG are involved through cooperation with reactive T cells, and by opsonization of endogenous CNS antigens, in the initiation and propagation of the disease ***(References 14, 15)***. And by an "ex vivo" animal model, a complement-mediated demyelination is induced by a subset of human MOG-IgG antibodies ***(Reference 16).*** Finally, the analysis of markers of astrocyte (GFAP) or myelin (MBP) damage in the CSF of patients with demyelinating disorders showed increased levels of MBP in patients with MOG-IgG and AQP4-IgG, in comparison with patients with multiple sclerosis. However, increased levels of GFAP were exclusively observed in patients with AQP4-IgG; altogether indicative of the different physiopathology involved in both settings ***(Reference 17)***.

3. Relevance and possible implications

1**.** We have demonstrated that the application of the revised 2017 McDonald criteria for the diagnosis of multiple sclerosis in pediatric population (children and adolescents) is feasible, and makes possible an earlier diagnosis of multiple sclerosis.
Although limited by the small sample size, our study also suggests that the criteria can be applied in children < 10 years, as long as they present with a typical clinical and radiological syndrome.

2. The determination of oligoclonal bands (OB), and MOG-IgG are the most useful biomarkers for assessing the risk of developing multiple sclerosis:

a) The presence of OB associates with the risk of developing multiple sclerosis.
b) The presence of MOG-IgG associates with the risk of developing a recurrent non-multiple sclerosis disorder.

3. MOG-IgG antibodies seem to participate in the physiopathological mechanisms involved in the immune response.
a) In an "in vivo" model, the MOG-IgG antibodies are involved through cooperation with reactive T cells, and by opsonization of endogenous CNS antigens in the initiation and propagation of the disease.
b) In an "ex vivo" model, a complement-mediated demyelination is induced by a subset of human MOG-IgG antibodies.

4. References

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