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Diagnosis and management of neuromyelitis optica spectrum disorders - An update

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ABSTRACT

Neuromyelitis optica (NMO) and Neuromyelitis optica spectrum disorders (NMOSD) are a group of autoimmune conditions characterized by inflammatory involvement of the optic nerve, spinal cord and central nervous system. Novel evidence showed a key role of autoantibodies against aquaporin-4 immunoglobulin G (AQP4 IgG) in the pathogenesis of NMOSD and, recently, new classification and diagnostic criteria have been adopted to facilitate an earlier identification and improve the management of these conditions. Diagnosis of NMOSD is currently based on clinical, neuroimaging and laboratory features. Standard treatment is based on the use of steroids and immunosuppressive drugs and aims to control the severity of acute attacks and to prevent relapses of the disease. This review gives an update of latest knowledge of NMOSD and NMO, emphasizing the novel diagnostic criteria and both current and future therapeutic approaches.

Contents

Abbreviations: AQP4, aquaporin-4; AQP4 IgG, immunoglobulin G against aquaporin-4; ARR, Annualized Relapse Rates; AZT, azathioprine; BBB, blood-brain barrier; CNS, central nervous system; EDSS, Expanded Disability Status Scale; GFAP, glial fibrillary acid protein; ICAM1, intercellular adhesion molecule-1; LETM, longitudinally extensive transverse myelitis; MM, mycophenolate mofetil; MOG, myelin oligodendrocytes glycoprotein; MS, multiple sclerosis; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorders; OCT, ocular coherence tomography; ON, optic neuritis; PLEX, plasma exchange; PNS, peripheral nervous system; VEP, visual evoked potential; VCAM1, vascular adhesion molecule-1; VEGF A, endothelial growth factor-A.

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1. Introduction

Neuromyelitis optica spectrum disorders (NMOSD), that include the neuromyelitis optica (NMO), previously known as Devic's syndrome, are a group of inflammatory disorders of the central nervous system (CNS) characterized by episodes of immune-mediated demyelination and axonal damage mainly involving optic nerves and spinal cord.

The term "NMO spectrum disorders" (NMOSD) has been recently introduced to expand the definition of NMO and to include a wider spectrum of clinical manifestations [1,2]. In fact, the increasing understanding of the pathogenesis of these disorders, the identification of disease-specific serum NMO-IgG antibodies, that selectively bind aquaporin-4 (AQP4), and the definition of specific neuroimaging features of NMO resulted in the revision of the previous classification of NMO, redefined as NMOSD, with more specific diagnostic criteria and an update in the guidelines for disease management [3–6]. These clinical, immunological and radiological features allow a proper differential diagnosis between NMO and multiple sclerosis (MS), or autoimmune diseases [7–9]. Beside NMOSD with AQP4-IgG (NMOSD-AQP4), the novel classification has defined a group of NMOSD without AQP4-IgG or with unknown AQP4-IgG status that includes patients with atypical manifestations such as unilateral optic neuritis (ON), isolated or recurrent transverse myelitis, or isolated brain lesions with or without detectable anti AQP4-IgG autoantibody [10].

NMO is usually sporadic but a few familial cases have been described [11]. NMO is a rare disease (ORPHA:71211) that affects all ethnicities in different socio-economic environments, with a prevalence in ranging from 0.52 to 4.4/100000 in different studies [12–16]. Overall, the wide range of prevalence reported for NMO is due to variability in the source data, as well as to the different diagnostic criteria and assay used to test the AQP4-IgG.

The aim of the present review is to describe clinical features of NMO and NMOSD and to provide an update on the novel classification, diagnostic criteria, and the current therapeutic approach.

2. Immunopathogenesis

The causes of NMO and NMODS are still unknown, but it is widely recognized that these conditions are primarily antibody-mediated disorders with the main role played by the humoral immune system that targets astrocytes [17,18].

Several immune pathogenic targets have been described in NMOSD, including aquaporin (AQP), myelin oligodendrocytes glycoprotein (MOG), glial fibrillary acid protein (GFAP), S100 protein, metalloprotease-9, VEGF A, ICAM1 and VCAM1 [10,19,20]. Of note, the recent discovery of the aquaporin involvement in NMO increased the understanding of its pathogenic mechanisms, allowing a novel classification and opening novel perspectives in terms of therapeutic approach [2].

Aquaporins constitute a family of water channels that regulate the transport of water in many organs including the nervous system, eye, kidney, gastrointestinal tract, secretory glands, inner ear and muscles [21–25]. Aquaporin-4 (AQP4), the main target in NMO pathogenesis, is an integral protein of astrocytes and ependymal in the nervous system, of Müller cells in the retina and of Hensen's and inner sulcus cells in the ear [24,26]. In the mammalian brain, aquaporins are concentrated at the blood-brain barrier (BBB), anchored in the astrocytic foot process membrane by the dystroglycan complex [27]. Immunopathological studies have shown that AQP4 immunoreactivity is localized in a perivascular rim and rosette pattern, which matches the pattern of IgG and activated complement components deposition in NMO lesions [25]. Changes of the perivascular region with macrophage infiltration, complement and immunoglobulin deposition, and vascular hyalinization suggest that the perivascular space is the primary target site of the NMO inflammatory process [25]. The selective IgGs binding to aquaporin-4 down-regulates the AQP4 surface expression, causing the increased BBB permeability in NMO. Moreover, the IgG-AQP4 complex binding to astrocytes activates the complement, with subsequent tissue infiltration of leucocytes (eosinophils and neutrophils), T lymphocytes (CD3+ and CD8+) and NK cells [18,26,28,29]. The resulting inflammatory process leads to astrocyte damage and death, and secondary oligodendrocyte and neuron involvement [25].

Two types of inflammatory demyelinating or non-demyelinating lesions have been described in NMO. The classic acute NMO lesion is characterized by confluent and/or focal perivascular demyelination, infiltration of inflammatory cells, severe axonal loss, necrosis of both the gray and white matter of the spinal cord, loss of astrocytes and oligodendrocytes [30]. The second type of NMO lesion, that is not characterized by demyelination, typically presents granulocytic inflammation, astrocyte and microglial activation, axonal damage and apoptosis of oligodendrocytes [31]. This last type of lesion can potentially be reversible.

In the late and chronic stages, NMO lesions present gliosis, cavitation, cystic and atrophic degeneration of the optic nerves and spinal cord. An increasing number of blood vessels – with the walls thickening – within the necrotic lesion are a common histopathological feature [18].

In light of the wide spectrum of both demyelinating and non-demyelinating components in NMO, it is difficult to stage the disease based on lesions and according to classification schemes similar to those used to stage the demyelinating activity of multiple sclerosis (MS) plaques.

3. Clinical manifestation and diagnostic criteria

NMO generally affects young adults (mean age 32.6–45.7 years) with a predominance in females (ranges from 68% to 88% of the affected population) [13,32]. However, cases of disease onset in the elderly and during childhood have been described [17]. The most typical clinical presentation of NMO is with acute optic neuritis (bilateral or rapidly sequential) or longitudinally extensive transverse myelitis (LETM) [33]. Optic neuritis (ON) is an inflammation of the optic nerve with a severe impairment of visual acuity that can lead to blindness associated to ocular pain. Transverse myelitis is an inflammatory disease involving three or more contiguous vertebral segments, also called longitudinally extensive transverse myelitis (LETM), that typically presents with several symptoms including paraplegia, bladder dysfunction and sensory loss [1–4,34]. The relapsing course of the disease is the most typical presentation, representing approximately 90% of NMOSD [33]. On the other hand, the monophasic course (representing the remaining 10% of cases) is uncommon and characterized by simultaneous ON and LETM severe attack with acute impairment and poorer prognosis of recovery if untreated [4]. The monophasic course does generally affects a younger population and does not appear to have gender differences in terms of prevalence; it has a less frequent association with other autoimmune diseases and a lower prevalence of AQP4IgG-serum antibodies [33]. The consensus panel who set up the new diagnostic criteria for NMOSD recommends that 5 years or longer of relapse-free time is necessary before making a monophasic course diagnosis. In patients with a relapsing course, after the first occurrence of NMO, the relapses may occur within one year (60% of patients) or up to three (90% patients) or more years, and presents a typically progressive course that leads to the development of persistent disabilities [4,8].

These typical and common clinical features are observed in most NMO patients, and great efforts have been made to identify diagnostic criteria that can allow a prompt and timely diagnosis of all cases, including those with partial or uncommon manifestations. These criteria are based on medical history, clinical manifestations, laboratory tests and MRI features, and have significantly evolved over the years in parallel to the increased understanding of NMO pathogenic mechanisms [34].

The basis for a consensus over NMO diagnostic criteria was set back in 1999 and revised in 2006, and the first actual international consensus