INTRODUCTION

Neuromyelitis optica (NMO) or Devic's syndrome, classically defined as the occurrence of optic neuritis (NO) and longitudinally extended transverse myelitis (MTEL), is currently considered as a broad spectrum of autoimmune disorders that cause inflammation and demyelination on the optic nerves and the spinal cord. However, it can also affect other brain areas, such as the area postrema in the medulla oblongata, other areas in the brain stem, the diencephalon, and specific brain areas such as periependymal surfaces of the third and fourth ventricles, the corpus callosum, and the subcortical white matter.\(^1\)

Its prevalence has been estimated at 0.3 to 4.4 cases per 100,000 individuals\(^2\), while its incidence is less than 1 per 100,000 individuals in Western countries\(^3\). It is less frequent in Caucasians than in Asians and Africans\(^4,5\), and its average age of onset is 39 years of age.\(^2\)

Regarding its clinical presentation, symptoms are varied, for they may originate from the involvement of various areas of the CNS. The most common and classic symptom is...
bilateral optic neuritis, which can develop into blindness and transverse myelitis. However, other clinical manifestations are Area Postrema Syndrome, which consists of intractable vomit or hiccups,\textsuperscript{1,6} or symptoms derived from brain stem impairment such as vertigo, sensorineural hearing loss, facial paralysis, trigeminal neuralgia, diplopia, ptosis, and nystagmus.\textsuperscript{7,8}

Originally, NMO was conceived as a variant of Multiple Sclerosis (MS), since both syndromes were associated with inflammatory and demyelinating lesions of the CNS. However, current and clear evidence allows us to identify NMOSD as a different pathological entity due to its distinctive pathophysiological characteristics, clinical manifestations, response to treatment, and prognosis.\textsuperscript{2,9-11}

In 2004, the link between NMOSD and the water channel aquaporin 4 (AQP4-IgG) antibody was published. It is detected in 60 to 90\% of patients affected by this condition.\textsuperscript{10,11} In light of current knowledge, it has been established that AQP4-IgG has a pathogenic role in the syndrome, probably via an astrocyte cytotoxicity mechanism dependent on complement activation.\textsuperscript{12}

The main recognized effector in the pathogenesis of NMOSD is the anti-AQP4 antibody (AQP4-IgG), which is self-reactive and complement-activating\textsuperscript{15}. The direct evidence that this antibody is pathogenic in vivo comes from the intracerebral injection of AQP4-IgG and human complement in mice. This reproduces the histological characteristics of lesions seen in NMOSD, such as loss of AQP4 and GFAP (glial fibrillary acidic protein), inflammatory cell infiltrate, loss of myelin, and perivascular deposition of activated complement\textsuperscript{12}. However, today, it is known that up to 25\% of patients are seronegative for AQP4-IgG and that it is important to detect another antibody, which is targeted against myelin, called anti-MOG (myelin oligodendrocyte glycoprotein).\textsuperscript{16,17}

Even though, to date, the pathogenesis by which anti-MOG triggers the syndrome has not been clarified, its capacity to cause typical NMO spectrum lesions has been demonstrated in experimental studies with mice\textsuperscript{18}. However, the syndrome phenotype linked to this antibody is more restricted to optic nerve syndrome than to the spinal cord, and the clinical course is less severe than that of AQP4-IgG seropositive patients, with fewer attacks and better functional recovery after them.\textsuperscript{16,17}

Hereinafter, we will review the latest advances regarding the understanding of the NMOSD pathophysiology in AQP4-IgG seropositive patients.

**NMO ETIOPATHOGENESIS**

The etiology of NMOSD remains poorly understood. The classical etiopathogenic theory of autoimmunity has recently been proposed to explain how lesions in this syndrome are caused. According to this theory, an initially mild and polyclonal B-cell disorder leads to the formation of antibodies in a genetically susceptible individual, which, by not being naturally suppressed, prompt the progressive appearance of autoimmune and inflammatory tissue lesions to which those autoantibodies are targeted--thus causing the clinically defined syndrome and dysfunction.

In the initial stages of NMOSD, environmental factors, which have not yet been described, play a role in the perpetuation and reinforcement of autoimmunity.\textsuperscript{13,14}

The focus of this review is to detail the cascade of pathophysiological events resulting from the binding of the AQP4-IgG antibody to the AQP4 water channel and its relevance in the spectrum of neuromyelitis optica pathogenesis.

**Predisposing factors and relationship with other syndromes.**

Genetic factor: most cases of NMOSD are sporadic; the familial pattern is identified in only 3\% of patients. Current evidence identifies NMOSD as a spectrum of syndromes more consistently related with a non-Mendelian polygenic inheritance pattern.\textsuperscript{19}

NMOSD is related with HLA-DRB1*03, an allele linked to other autoimmune syndromes such as Systemic Lupus Erythematosus.\textsuperscript{20} However, it is not related-- or perhaps has a negative association--with HLA-DRB1*1501, the allele most strongly associated with EM.\textsuperscript{19,20}

Moreover, a study that examined the association of 35 single nucleotide polymorphism (SNP) of the minor histocompatibility complex (which increase the susceptibility to MS) found that
none of them were associated with NMOSD. All these findings support the hypothesis that NMOSD is a different pathological entity from MS instead of being a variant of it, as initially proposed.

Autoimmunity: NMOSD is associated with other autoimmune syndromes. The most frequent co-associations are with thyroid autoimmunity, SLE, Sjogren's syndrome, myasthenia gravis, and celiac disease.

Paraneoplastic syndrome: a small percentage of patients with NMOSD also develop cancers of various types, and on rare occasions, the expression of AQP4 has been documented in the tumor and associated with inflammatory changes. These cancers could initiate the humoral autoimmune response and foster the development of NMOSD. However, the specificity of the paraneoplastic expression of AQP4 for NMOSD has not yet been established.

Structure, function and cellular location of the AQP4 channel
AQP4 is the most strongly expressed water channel in the central nervous system, but it is also present in renal epithelial cells (of collecting tubules), parietal cells of gastric mucosa, the respiratory tract, glands, skeletal muscle, and supporting cells of the retina (known as Müller cells).

In the central nervous system, the AQP4 channel is expressed in the end-feet processes of astrocytes that are in contact with the small blood vessels which are part of the blood-brain barrier (BBB). It is also found in the spinal cord, optic nerve, pia mater, and ependymal surfaces in contact with cerebrospinal fluid (CSF). AQP4 is a transmembrane protein channel that assembles in a heterotetrameric configuration. Each monomer is made up of six transmembrane helical domains and two short helical segments that are arranged around the narrow aqueous pore of the channel. There are two main channel isoforms, transcribed from the same gene and generated by alternative splicing. They differ by 22 N-terminal amino acids present in isoform M1 (whose translation initiation is Met-1 amino aid) and absent in isoform M23 (whose translation initiation is Met-23 amino acid). Both isoforms are expressed in astrocytes and form heterotetramers. However, only the M23 isoform channel can associate, at the plasma membrane level, in large supramolecular aggregates called orthogonal arrays of particles (OAPs). Current evidence shows that AQP4-IgG binds with greater affinity to the M23 isoform of the AQP4 channel than to the M1 isoform. Thus, there is a preferential antibody binding due to the conformation in the channel OAPs. A rational explanation for the lesional selectivity of the optic nerve and the spinal cord regarding the other tissues that express AQP4 could be the substantial difference in the expression levels of both isoforms and in the degree of supramolecular aggregation that has been observed in the former.

Channel AQP4 function is to facilitate the bidirectional movement of water between the brain and the blood, and between the brain and the CSD compartment. Furthermore, AQP4 is implied in other functions such as neuroexcitation, astrocyte migration, and neuroinflammation. The role of the complement-mediated cytotoxicity mechanism in the pathogenesis of NMOSD.
The available scientific evidence proposes that the primary pathophysiological mechanism in the development of typical NMOIDS lesions is complement-mediated cytotoxicity.

The AQP4-IgG autoantibody involved in the NMOIDS pathogenesis is predominantly of the IgG1 subtype, which effectively activates complement proteins such as C1q. The primary source of its synthesis is the plasmablasts cell subpopulation. The pathophysiological mechanism involves, as an initial step, the binding of the AQP4-IgG autoantibody to the AQP4 channel in the astrocytes end-feet processes that are part of the BBB in the CNS. The aforementioned conditions the complement-activation with subsequent formation of membrane attack complexes (MACs), which generates a primary injury in the astrocytes. This initial event is followed by the recruitment of inflammatory cells to the injury site. First, granulocytes (neutrophils and eosinophils) and then macrophages, which determines a greater damage to the BBB. The
primary astrocyte injury and the initiation of an inflammatory response with cytokine release cause secondary damage to oligodendrocytes, loss of myelin, and neuronal death with subsequent clinical neurological deficit.\textsuperscript{12,45}

An interesting question that has arisen regarding the NMOSD pathogenic process and that is currently partly answered, is why peripheral organs that express the AQP4 water channel are not damaged by the syndrome. In this context, a current study by Saadoun et al. found that the SNC astrocytic tissue has a lower level of expression and colocalization of complement inhibitor proteins and AQP4 compared to tissues located outside the CNS, which make it more susceptible to damage by complement-mediated lysis compared to the latter.\textsuperscript{46}

The role of the antibody-mediated cytotoxicity mechanism in the pathogenesis of NMOSD.

This antibody-mediated astrocyte mechanism, whose role in the pathogenesis of NMOSD is still not entirely clear, initially requires the binding of NK cells to the Fc region of the AQP4-IgG antibody. This conditions the degranulation of these effector cells and the release of perforins and granzymes that cause catastrophic astrocyte injuries but does not cause loss of myelin.\textsuperscript{47} Various types of leukocytes, in addition to NK cells, express Fc receptors and can mediate this mechanism, including macrophages, neutrophils, and eosinophils, which are cell types frequently found in NMOSD lesions.\textsuperscript{41} Definitive quantification of the role of the antibody-dependent cytotoxicity in human NMOSD lesions will require further investigation.

The role of eosinophils, macrophages, and regulatory T cells

Studies in humans support the critical role of the neutrophil and eosinophil populations in the NMOSD pathogenesis.\textsuperscript{45,48} In this syndrome, eosinophils can stimulate the humoral immune response by producing type 2 cytokines. Furthermore, they can contribute to the destructive inflammatory process at the CNS through protein secretion such as neutrotoxin, and the generation of free radicals.\textsuperscript{49} The role of macrophages in NMO is still not entirely clear. It is believed that they could contribute to the cleaning of cellular debris produced by astrocytic cytotoxicity and granulocyte infiltration.\textsuperscript{50} On the other hand, natalizumab, a monoclonal anti-integrin α-4 antibody (a protein expressed in human macrophages), has a harmful effect in some NMO patients\textsuperscript{51} which suggests a potentially beneficial role of this cell type for this condition. In relation to T cells role in the NMO development, recent studies show that Th17, a subgroup of T helper cells, is involved in the BBB disruption, which allows the extravasation of the AQP4-IgG antibody and complement, together with the recruitment of polymorphonuclear cells to injury sites.\textsuperscript{52,53}

The role of Cytokines

IL 6 is an important trophic factor for plasmablasts. This cytokine has been consistently overexpressed in NMOSD and is associated with the syndrome activity. Moreover, it can foster B cell survival, among other pathogenic mechanisms. Another cytokine that has been found to be overexpressed in NMOSD is the activating factor of B cells.\textsuperscript{44,54}

Non-lytic changes in NMOSD

The main effector mechanism identified in NMO attacks is the complement-mediated inflammation and its pathophysiological consequences. The latter include the chemokine generation, secondary neutrophil, and eosinophil toxicity, and, ultimately, cell lysis. However, non-lytic changes have been observed in certain brain areas, particularly in the area postrema and in the floor of the fourth ventricle. This would translate a different underlying pathogenesis from the classically observed in the optic nerve and spinal cord, which has not been clarified.\textsuperscript{55}

PENDING QUESTIONS AND FUTURE PERSPECTIVES

Although, in recent years, substantial progress has been made in understanding the NMO spectrum etiopathogenesis, relevant questions remain to be answered. In this context, future efforts should be aimed at clarifying, for example, the exact mechanism by which AQP4-IgG (which is known to be peripherally
produced manages to enter the CNS. Another question of interest is why neurohistological changes are generated in the area postrema in contrast to classic lytic lesions observed in the optic nerve and spinal cord, and whether this would have any differences in the phenotypic expression of the syndrome. Finally, it would be advantageous to clarify the role of many other cytokines and specific cell types, such as macrophages, involved in the NMOSD pathogenesis, due to their implication in the development of new therapeutic strategies.

**BIBLIOGRAPHY**


Correspondence to:
Dr. Claudio Meza Poblete
Contact number: 997906815
E-mail: claudiomeducm@gmail.com