Pathophysiological Basis Of Neuromyelitis Optica Spectrum Disorders: What Do We Know?

Claudio Meza Poblete1, Pilar Canales Fernández2

Neuromyelitis Optica Spectrum Disorders (NMOSD) is a set of clinical manifestations derived from an inflammatory and demyelinating process of the central nervous system that causes lesions primarily in spinal cord and optic nerves but also in other regions such as the brainstem, diencephalon or specific brain areas. Most patients with NMOSD are seropositive for autoantibodies against AQP4, the major water channel of astrocytes, however, there is a non-negligible percentage of patients, close to 25%, who are seronegative for these antibodies and in whom the presence of antibodies directed against myelin (anti-MOG) could have a pathogenic role that to date has not been well elucidated. Current scientific evidence has allowed recognize that AQP4-IgG is pathogenic in NMOSD, probably by a mechanism involving complement-dependent cellular cytotoxicity, causing leucocyte infiltration, cytokine release and blood-brain barrier disruption, which leads to oligodendrocyte death, myelin loss and neuron death.

This article presents an evidence-based review, which emphasizes the main aspects in NMOSD pathogenesis.

Keywords: Neuromielytis optica, aquaporin-4, autoimmune syndrome.

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

The authors declare that they have no conflicts of interest with respect to this study.

Accepted: 2020/04/14
Received: 2019/01/13

1 Surgeon, Universidad Católica del Maule
2 Neurologist, Medical Service, Talca Regional Hospital.

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,[1,6] or symptoms derived from brain stem impairment such as vertigo, sensorineural hearing loss, facial paralysis, trigeminal neuralgia, diplopia, ptosis, and nystagmus.[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.[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 [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.[12]

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.

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.[13,14]

The main recognized effector in the pathogenesis of NMOSD is the anti-AQP4 antibody (AQP4-IgG), which is self-reactive and complement-activating[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[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).[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[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.[16,17]

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

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.[19]

NMOSD is related with HLA-DRB1*03, an allele linked to other autoimmune syndromes such as Systemic Lupus Erythematosus[20]. However, it is not related-- or perhaps has a negative association--with HLA-DRB1*1501, the allele most strongly associated with EM[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[21]. 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.[22-24]

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.[25-27]

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).[28,29]

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)[30,31]

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[32]. 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)[33,34]. 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.[35,36]. 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.[37]

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[38], astrocyte migration[39], and neuroinflammation[40].

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 NMODS lesions is complement-mediated cytotoxicity.[41]

The AQP4-IgG autoantibody involved in the NMOSD pathogenesis is predominantly of the IgG1 subtype, which effectively activates complement proteins such as C1q[42,43]. The primary source of its synthesis is the plasmablasts cell subpopulation[44]. 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 oligodentrocytes, loss of myelin, and neuronal death with subsequent clinical neurological deficit.[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.[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.[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.[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.[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 neurotoxin, and the generation of free radicals.[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.[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[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.[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.[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.[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[56] 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

1. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015; 85:177-89.

2. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet Neurol 2007; 6:805-15.

3. Sellner J, Boggild M, Clanet M, et al. EFNS guidelines on diagnosis and management of neuromyelitis Optica. Eur J Neurol 2010; 17:1019-1032.

4. Jarius S, Wildemann B. AQP4 antibodies in neuromyelitis optica: diagnostic and pathogenetic relevance. Nat Rev Neurol 2010; 6:383-92.

5. El Otmani H, Rafai MA, Moutaouakil F, El Moutawakkil B, Boulaajaj FZ, Moudden M, et al. Devic's neuromyelitis optica in Morocco. A study of 9-cases. Rev Neurol 2005; 161:1191-6.

6. Misu T, Fujihara K, Nakashima L, Sato S, Itoyama Y. Intractable hiccup and nausea with periaqueductal lesions in neuromyelitis optica. Neurology 2005; 65:1479-82.

7. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999; 53:1107-14.

8. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006; 66:1485-9.

9. Pittock SJ. Neuromyelitis optica: a new perspective. Semin Neurol 2008; 28: 95-104.

10. Weinshenker BG, Wingerchuk DM. Neuromyelitis optica: clinical syndrome and the NMO- IgG autoantibody marker. Curr Top Microbiol Immunol 2008; 318:343-56.

11. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004; 364: 2106-12.

12. Saadoun S, Waters P, Bell BA, Vincent A, Verkman AS, Papadopoulos MC. Intracerebral injection of neuromyelitis óptica immunoglobulin G and human complement produces neuromyelitis optica lesions in mice. Brain 2010; 133: 349–61.

13. Yoshimura S, Isobe N, Matsushita T, et al. Distinct genetic and infectious profiles in Japanese neuromyelitis optica patients according to anti-aquaporin 4 antibody status. J Neurol Neurosurg Psychiatry 2013; 84 (1): 29-34.

14. Chiquete E, Navarro-Bonnet J, Ayala-Armas R, Gutiérrez-Gutiérrez N, Solórzano-Melendez A, Rodriguez Tapia D, et al. Neuromielitis óptica: actualización clínica. Rev Neurol 2010; 51(5):289-294.

15. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med 2005; 202 (4):473-477.

16. Kitley J, Woodhall M, Waters P, Leite MI, Devenney E, Craig J, et al. Myelin oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis ópticaphenotype. Neurology 2012; 79:1273-77.

17. Sato D, Callegaro D, Lana-Peixoto M, Waters PJ, De Haidar FM, Takahashi T, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. Neurology 2014; 82:1-8.

18. Saadoun S, Waters P, Owens GP, Bennett JL, Vincent A, Papadopoulos MC. Neuromyelitis optica MOG-IgG causes reversible lesions in mouse brain. Acta Neuropathol Commun. 2014; 2:35.

19. Matiello M, Kim HJ, Kim W, et al. Familial neuromyelitis optica. Neurology.2010; 75(4):310-315.

20. Brum DG, Barreira AA, dos Santos AC, et al. HLA-DRB association in neuromyelitis optica is different from that observed in multiple sclerosis. Mult Scler. 2010;16(1):21-29.

21. Liu Q-B, Li Z-X, Zhao G-X, Yu H, Wu Z-Y. No association between identified multiple sclerosis non-MHC risk loci and neuromyelitis optica. Neurosci Bull. 2014; 30(6):1036-1044.

22. Pittock SJ, Lennon VA, de Seze J, et al. Neuromyelitis óptica and non-organ-specific autoimmunity. Arch Neurol. 2008; 65(1):78-83.

23. Iyer A, Elsone L, Appleton R, Jacob A. A review of the current literature and aguide to the early diagnosis of autoimmune disorders associated with neuromyelitis optica. Autoimmunity 2014; 47: 154-61.

24. Wingerchuk DM, Weinshenker BG. The emerging relationship between neuromyelitis optica and systemic rheumatologic autoimmune disease. Mult Scler 2012; 18: 5-10.

25. Figueroa M, Guo Y, Tselis A, et al. Paraneoplastic neuromyelitis optica spectrum disorder associated with metastatic carcinoid expressing aquaporin-4. JAMA Neurol. 2014; 71(4):495-498.

26. Yang HK, Woo SJ, Park WY, Hwang JM. Paraneoplastic neuromyelitis optica associated with ANNA-1 antibodies in invasive thymoma. BMC Ophthalmol. 2014; 14:106.

27. Verschuur CV, Kooi AJ, Troost D. Anti-aquaporin 4 related paraneoplastic neuromyelitis optica in the presence of adenocarcinoma of the lung. Clin Neuropathol. 2015; 34(4):232-236.

28. Verkman AS. Aquaporins in clinical medicine. Annu Rev Med 2012; 63:303-16.

29. Li J, Patil RV, Verkman AS. Mildly abnormal retinal function in transgenic mice without Muller cell aquaporin-4 water channels. Invest Ophthalmol Vis Sci 2002; 43: 573-79.

30. Rash JE, Yasumura T, Hudson CS, Agre P, Nielsen S. Direct immunogold labeling of aquaporin-4 in square arrays of astrocyte and ependymocyte plasma membranes in rat brain and spinal cord. Proc Natl Acad Sci USA 1998; 95: 11981–86.

31. Nielsen S, Nagelhus EA, Amiry-Moghaddam M, Bourque C, Agre P, Ottersen OP. Specialized membrane domains for water transport in glial cells: high-resolution immunogold cytochemistry of aquaporin-4 in rat brain. J Neurosci 1997; 17:171-80.

32. Ho JD, Yeh R, Sandstrom A, Chorny I, Harries WE, Robbins RA, et al. Crystal structure of human aquaporin 4 at 1.8A and its mechanism of conductance. Proc Natl Acad Sci USA 2009; 106:7437-42.

33. Lu M, Lee MD, Smith BL, Jung JS, Agre P, Verdijk MA, et al. The human AQP4 gene: definition of the locus encoding two water channel polypeptides in brain. Proc Natl Acad Sci USA 1996; 93:10908-12.

34. Crane JM, Bennett JL, Verkman AS. Live cell analysis of aquaporin-4 M1/M23 interactions and regulated orthogonal array assembly in glial cells. J Biol Chem 2009; 284:35850-60.

35. Crane JM, Lam C, Rossi A, Gupta T, Bennett JL, Verkman AS. Binding affinity and specificity of neuromyelitis optica autoantibodies to aquaporin-4 M1/M23 isoforms and orthogonal arrays. J Biol Chem 2011; 286:16516–24.

36. Phuan P-W, Ratelade J, Rossi A, Tradtrantip L, Verkman AS. Complement-dependent cytotoxicity in neuromyelitis óptica requires aquaporin-4 protein assembly in orthogonal arrays. J Biol Chem. 2012; 287(17):13829-13839.

37. Matiello M, Schaefer-Klein J, Sun D, Weinshenker BG. Aquaporin 4 expression and tissue susceptibility to neuromyelitis optica. JAMA Neurol. 2013; 70(9):1118-1125.

38. Lu DC, Zhang H, Zador Z, Verkman AS. Impaired olfaction in mice lacking aquaporin-4 water channels. FASEB J 2008; 22:3216–23.

39. Auguste KI, Jin S, Uchida K, Yan D, Manley GT, Papadopoulos MC, et al. Greatly impaired migration of implanted aquaporin-4-deficient astroglial cells in mouse brain toward a site of injury. FASEB J 2007; 21:108–16.

40. Li L, Zhang H, Varrin-Doyer M, Zamvil SS, Verkman AS. Proinflammatory role of aquaporin-4 in autoimmune neuroinflammation. FASEB J 2011; 25:1556–66.

41. Ratelade J, Verkman AS. Neuromyelitis optica: Aquaporin-4 based pathogenesis mechanisms and new therapies. Int J Biochem Cell Biol 2012; 44: 1519-30.

42. Isobe N, Yonekawa T, Matsushita T, Kawano Y, Masaki K, Yoshimura S, et al. Quantitative assays for anti-aquaporin-4 antibody with subclass analysis in neuromyelitis optica. Mult Scler 2012; 18(11):1541-51

43. Capel PJ, Van De Winkel JG, Van Den Herik-Oudijk IE, Verbeek JS. Heterogeneity of human IgG Fc receptors. Immunomethods 1994; 4:25–34.

44. Chihara N, Aranami T, Sato W, et al. Interleukin 6 signaling promotes anti-aquaporin 4 autoantibody production from plasmablasts in neuromyelitis optica. Proc Natl Acad Sci USA. 2011; 108(9):3701-3706.

45. Misu T, Fujihara K, Kakita A, Konno H, Nakamura M, Watanabe S, et al. loss of aquaporin 4 in lesions of neuromyelitis optica: distinction from multiple sclerosis. Brain 2007; 130:1224–34.

46. Saadoun S, Papadopoulos MC. Role of membrane complement regulators in neuromyelitis optica. Mult Scler. 2015; 21(13):1644-1654.

47. Ratelade J, Zhang H, Saadoun S, Bennett JL, Papadopoulos MC, Verkman AS. Neuromyelitis optica IgG and natural killer cells produce NMO lesions in mice without myelin loss. Acta Neuropathol (Berl) 2012; 123:861-72.

48. Saadoun S, Waters P, Macdonald C, et al. Neutrophil protease inhibition reduces NMO-IgG-induced damage in mouse brain. Ann Neurol 2012; 71:323-33.

49. Kita H. Eosinophils: multifaceted biological properties and roles in health and disease. Immunol Rev 2011; 242:161-77.

50. Hendriks JJ, Teunissen CE, De Vries HE, Dijkstra CD. Macrophages and neurodegeneration. Brain Res Rev 2005; 48:185-95.

51. Barnett M, Prineas J, Buckland M, Parratt J, Pollard J. Massive astrocyte destruction in neuromyelitis optica despite natalizumab therapy. Mult Scler 2012; 18:108-12.

52. Herges K, De Jong BA, Kolkowitz I, et al. Protective effect of an elastase inhibitor in a neuromyelitis optica-like disease driven by a peptide of myelin oligodendroglial glycoprotein. Mult Scler 2012; 18:398-408.

53. Li Y, Wang H, Long Y, Lu Z, Hu X. Increased memory Th17 cells in patients with neuromyelitis optica and multiple sclerosis. Journal of Neuroimmunology 2011; 234:155-160.

54. Araki M, Matsuoka T, Miyamoto K, et al. Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica: a pilot

study. Neurology. 2014; 82(15):1302-1306.

55. Popescu BFG, Lennon VA, Parisi JE, et al. Neuromyelitis óptica unique area postrema lesions: nausea, vomiting, and pathogenic implications. Neurology. 2011; 76(14):1229-1237.

56. Jarius S, Franciotta D, Paul F, et al. Cerebrospinal fluid antibodies to aquaporin-4 in neuromyelitis optica and related disorders: frequency, origin, and diagnostic relevance. J Neuroinflammation 2010; 7: 52.

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