# Neuromyelitis optica spectrum disorder diagnostic-therapeutic update. Systematic review

*Actualización diagnóstica-terapéutica de la neuromielitis óptica. Revisión sistemática*

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Received: 02/26/2021 Accepted: 05/15/2022 Published: 05/25/2022 DOI: https://doi.org/10.5281/zenodo.7135584

## Abstract

Neuromyelitis Optica spectrum disorder (NMOSD) is a rare pathology characterized by recurrent inflammatory crises of the central nervous system focused on the level of the spinal cord and the optic chiasm. This disease can alter other regions of the CNS and its pathophysiology is immunologic and heterogeneous, which makes us think of a spectrum of the disease. It is believed that NMOSD is caused by the presence of two classes of antibodies called: Anti-aquaporin 4 NMO IgG and Anti-MOG-IgG, the disease can present with one of the antibodies or with both, in this last case the severity of the disease increases exponentially. The pathophysiology of this condition is not completely clear since it is known that the mentioned antibodies trigger inflammatory processes and demyelination of astrocytic cells, but it is not known by what mechanisms they do it. However, MRI studies can adequately delimit the lesions in the areas mentioned earlier and immunohistochemically localize the antibodies. The initial clinical picture is characterized by simultaneous involvement of both the optic chiasm and the medulla in the early stage of the disease, although in most cases there is a variable period of months and years to evidence lesions in the involved structures. The manifestations are severe and are characterized by a progressive decrease in a vision leading to blindness and total flaccid paraplegia. The prognosis of this disease is not encouraging, since in 18% of cases sufferers lose sight in both eyes; irreversible motor disability occurs in 34% of patients, and in 23% of cases the use of a wheelchair is permanent. This disease has a mortality rate of 9%. We conducted a systematic review of the therapeutic and diagnostic advances in the pathology of neuromyelitis optica using complete, updated articles written in the last 5 years, which will be obtained from digital databases such as PubMed, Scopus, Chrocane Library, UpToDate, and Scielo.

**Keywords:** Neuromyelitis Optica, Anti-aquaporin 4, Anti-MOG-IgG, Devic's neuromyelitis optical treatment, Devic's neuromyelitis optica diagnosis, Rituximab

## Resumen

El trastorno del espectro de la neuromielitis optica (NMOSD) es una patología poco frecuente la cual se caracteriza por crisis inflamatorias recurrentes del sistema nervioso central que se focalizan a nivel de la medula espinal y el quiasma óptico. Esta enfermedad puede llegar a alterar otras regiones del SNC y su fisiopatología es netamente inmunológica y heterogénea lo que nos hace pensar en un espectro del padecimiento. Se cree que la NMOSD está causada por la presencia de dos clases de anticuerpos llamados: Anti-acuaporina 4 NMO IgG y Anti-MOG-IgG, la enfermedad puede presentarse con uno de los anticuerpos o con ambos, en este último caso la gravedad del padecimiento incrementa exponencialmente. La fisiopatología de este cuadro no es completamente clara ya que se sabe que los anticuerpos mencionados desencadenan procesos inflamatorios y desmielinización de las células astrociticas, pero no se conoce mediante que mecanismos lo hacen. Sin embargo, mediante estudios de resonancia magnética se puede delimitar adecuadamente las lesiones en las zonas mencionadas y mediante inmunohistoquímica localizar los anticuerpos. El cuadro clínico inicial se caracteriza por afecciones simultaneas tanto en el quiasma óptico como en la medula en el estadio temprano de la enfermedad, aunque en la mayoría de los casos existe un periodo de tiempo variable entre meses y años para evidenciar las lesiones de las estructuras involucradas. Las manifestaciones son graves y se caracterizan por disminución progresiva de la visión que termina en ceguera y paraplejia flácida total. El pronóstico de esta enfermedad no es alentador, ya que en el 18% de los casos quienes la padecen pierden la vista de ambos ojos; la incapacidad motora irreversible se presenta en el 34% de pacientes y en el 23% de casos el uso de silla de ruedas es permanente. Esta enfermedad tiene un porcentaje de mortalidad del 9%. Realizamos una revisión sistemática acerca de los avances terapéuticos y diagnósticos en la patología de neuromielitis optica utilizando artículos completos, actualizados y redactados en los últimos 5 años, los mismos que

serán obtenidos de bases digitales como: PubMed, Scopus, Chrocane Library, UpToDate y Scielo.

**Palabras clave:** Neuromielitis óptica, Anti-acuaporina 4, Anti-MOG-IgG, Tratamiento de la neuromielitis óptica de Devic, Diagnóstico de la neuromielitis óptica de Devic, Rituximab

## Introduction

Devic's disease is also known as neuromyelitis optic. It is a disease in which an inflammatory disorder causes chronic demyelination of the central nervous system (CNS). This triggers the well-known optic neuritis and attacks of myelitis that can be transverse and severe. This disease damages the spinal cord, especially the bursts and remissions of the optic nerve, known as monophasic form. The damage results in deficits in young and old. Some specialists also consider this disease as a variant of multiple sclerosis since demyelination and seizures are similar. However, it is currently considered a pathology not linked to multiple sclerosis. The pathophysiology of this clinical condition is based on B lymphocytes, which produce immunoglobulin G antibodies and attack the aquaporin 4 channels of astrocytes of the pedicle blood-brain barrier[1,2]

Neuromyelitis Optica spectrum disorder (NMOSD) being a pathology triggered by antigens against IgG immunoglobulin of aquaporin 4 (AQP4) is one of the main diagnoses that should be considered at the time of differential diagnosis with autoimmune multiple sclerosis. Another pathology that should also be considered ruled out is encephalomyelitis associated with myelin IgG immunoglobulin, this disease is also known as encephalomyelitis associated with MOG, MOGAD antibodies[1,2]

Aquaporin 4 is defined as a two-way osmotically flowing water channel that is impermeable to anions and glycerol. Most of these channels are located at the end feet of perivascular and peripapillary astrocytes which communicate directly with the basal lamina endothelia and pia mater, respectively. In addition to this localization, APQ4 is found in the membranes of ependymal cells and is absent in oligodendrocytes, neurons, and choroidal epithelial cells[1,2]

Aquaporins are proteins found in the brain and fluid compartments such as the blood-brain barrier. They are localizable in other sites such as astrocytes, ependymal cells, endothelial and supraoptic nucleus cells, and around neurons responsible for vasopressin secretion. These proteins are also present in potassium channels located in Müller cells at the renal level, forming the most important water channels of the central nervous system[1,2]

The localization and prognosis of the severity of the lesions in the presence of AQP4-IgG will depend on the level of expression of AQP4, i.e., the number of channels in each area, for example, they are found in greater quantities in the optic nerve, the area postrema, the spinal cord, and the diencephalon. The severity of the disease will also be influenced by the number of supramolecular aggregates of AQP4 which is much more profuse in the spinal cord and optic nerves, hence the explanation for the main clinical manifestations. The last influential factor is the permeability of the blood-brain barrier which is increased in the organs around the ventricles including the area postrema, thalamus, cerebellum, and hypothalamus[1,2]

Optic neuritis is initiated by the appearance of a relatively unknown antigen capable of stimulating the production of circulating IgG-NMO immunoglobulins. These antibodies penetrate the CNS when there is a deficit or a break in the permeability of the blood-brain barrier which facilitates the antibodies to recognize the antigen (AQP4) and bind to it, causing the activation of the complement system and the migration of cells such as macrophages, neutrophils ,and eosinophils which produce the local inflammatory cascade and subsequent demyelination of the optic nerve, the spinal cord and the structures of the central nervous system. This demyelination will cause loss of axons, necrotic processes, edema, and in chronic cases atrophy of tissues and cavitations. Within the mechanisms of the disease, we can say that it is characterized by the deposition of IgG and complement in the terminal ends of astrocytes (feet), the loss of these, and in some cases, secondary loss of neurons and oligodendrocyte cells. In the case of the complement system, this includes C9neo which demonstrates the activation of the complement deposition, i.e., the activation of the immune system that causes membrane-focused injury and causes the astrocyte to inadequately handle water in the cell which results in osmotic demyelination and inflammatory injury triggered by macrophages, eosinophils, neutrophils and B and T lymphocytes[1,2]

**DESIGN AND RESEARCH TYPE:** A systematic review of the descriptive-explanatory literature was carried out, following the PRISMA statement. The bibliography search and selection process took place using the following databases: SCIELO, SCOPUS, CHROCRANE LIBRARY, UP TO DATE, and PUBMED. Additionally, Spanish, and English articles published between 2016-2021 were included.

**INCLUSION AND EXCLUSION CRITERIA:** The inclusion criteria involved including fully available original English or Spanish articles, written either in English or Spanish and published between 2016 and 2021. The availability of the papers in the mentioned databases was also considered. The exclusion criteria consisted of eliminating the scientific publications that were not within the time limit determined; the incomplete or repeated studies and those not included in the databases mentioned were also excluded. Table 1 presents the information

**Table 1. Database searching strategies**

| # | Search Engine | Bibliographic Source | Year | Language | Document Type | Link |
|---|---|---|---|---|---|---|
| 1 | Scielo | Manejo del dolor en un caso de neuromielitis óptica (enfermedad de Devic) | 2016 | Spanish | Article | http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1134-80462016000400005 |
| | | Aspectos clínicos en el espectro de neuromielitis óptica: revisión de la literatura | 2016 | Spanish | Article | https://scielo.conicyt.cl/pdf/rchnp/v54n3/art07.pdf |
| | | Espectro de neuromielitis óptica en Colombia, primera caracterización clínico-imagenológica en tres centros de Bogotá | 2016 | Spanish | Article | http://www.scielo.org.co/pdf/anco/v32n3/v32n3a03.pdf |
| | | Neuromielitis óptica de Devic | 2016 | Spanish | Article | http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1699-695X2016000200009 |
| | | Neuromielitis óptica durante el embarazo. Reporte de caso | 2019 | Spanish | Article | http://www.scielo.org.pe/scielo.php?script=sci_arttext&pid=S2304-51322019000200012 |
| 2 | PubMed | Neuritis ópticas desmielinizantes y autoinmunes | 2020 | Spanish | Article | https://pubmed.ncbi.nlm.nih.gov/32622510/ |
| | | Neuromielitis óptica | 2019 | Spanish | Article | https://pubmed.ncbi.nlm.nih.gov/31603846/ |
| | | Espectro de la neuromielitis óptica: trastornos psiquiátricos y riesgo de suicidio | 2020 | Spanish | Article | https://pubmed.ncbi.nlm.nih.gov/32900527/ |
| | | Experiencia con tocilizumab en pacientes con espectro de la neuromielitis óptica | 2019 | Spanish | Article | https://pubmed.ncbi.nlm.nih.gov/30928236/ |
| | | Espectro de neuromielitis óptica: ¿seropositivo para la Anticuaporina es una entidad diferente de los pacientes que son seronegativos? Una perspectiva de Colombia | 2020 | Spanish | Article | https://pubmed.ncbi.nlm.nih.gov/33162220/ |
| | | Uso del análisis de la capa de células ganglionares para el diagnóstico en la neuromielitis óptica anti-glucoproteína de la mielina del oligodendrocito | 2019 | Spanish | Article | https://pubmed.ncbi.nlm.nih.gov/31980323/ |
| | | Espectro de neuromielitis óptica: descripción de una cohorte según los criterios diagnósticos de 2015 | 2017 | Spanish | Article | https://pubmed.ncbi.nlm.nih.gov/28849860/ |
| | | Update on neuromyelitis optica spectrum disorder | 2020 | English | Article | https://pubmed.ncbi.nlm.nih.gov/33009077/ |
| | | Neuromyelitis optica | 2020 | English | Article | https://pubmed.ncbi.nlm.nih.gov/33093467/ |
| 3 | UpToDate | Neuromyelitis optica spectrum disorders | 2021 | English | Article | https://www.uptodate.com/contents/neuromyelitis-optica-spectrum-disorders |
| | | Optic neuritis: Pathophysiology, clinical features, and diagnosis | 2018 | English | Article | https://www.uptodate.com/contents/optic-neuritis-pathophysiology-clinical-features-and-diagnosis?search=neuromielitis%20optica&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2 |
| | | Optic neuritis: Prognosis and treatment | 2018 | English | Article | https://www.uptodate.com/contents/optic-neuritis-prognosis-and-treatment?search=neuromielitis%20optica&source=search_result&selectedTitle=15~150&usage_type=default&display_rank=15 |
| 4 | Chrocane Library | High-Frequency Impulse Therapy for Neuropathic Pain in NMOSD | 2020 | English | Clinical Essay | https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02197196/full?highlightAbstract=neuromyel%7Cdevic%27s%7Cneuromyelitis%7Coptic%7Coptica%7Cdevic |
| | | The effect of ginseng on fatigue in neuromyelitis optica spectrum disorder | 2020 | English | Clinical Essay | https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02187979/full?highlightAbstract=neuromyel%7Cdevic%27s%7Cneuromyelitis%7Coptic%7Coptica%7Cdevic |
| | | Rituximab for neuromyelitis optica relapses: RIN-1 Study | 2017 | English | Article | https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01451258/full?highlightAbstract=neuromyel%7Cdevic%27s%7Cneuromyelitis%7Coptic%7Coptica%7Cdevic |
| 5 | Scopus | Neuromyelitis optica is an HLA associated disease different from Multiple Sclerosis: a systematic review with meta-analysis | 2021 | English | Article | https://www-scopus-com.vpn.ucacue.edu.ec/record/display.uri?eid=2-s2.0-85098947279&origin=resultslist&sort=plf-f&src=s&sid=ff946bfc109a1e3637fc235e0e3dfac3&sot=b&sdt=b&sl=35&s=TITLE-ABS-KEY%28Neuromyelitis+optica%29&relpos=0&citeCnt=0&searchTerm= |
| | | Recent advances in optic nerve magnetic resonance imaging and post-processing | 2021 | English | Article | https://www-scopus-com.vpn.ucacue.edu.ec/record/display.uri?eid=2-s2.0-85103062406&origin=resultslist&sort=plf-f&src=s&nlo=&nlr=&nls=&sid=82145af67840f1662f5e78206c0c3045&sot=b&sdt=cl&cluster=scosubjabbr%2c%22MEDI%22%2ct&sl=35&s=TITLE-ABS-KEY%28Neuromyelitis+optica%29&relpos=7&citeCnt=0&searchTerm= |
| | | Efficacy of Rituximab in the treatment of neuromyelitis optica spectrum disorders: An updated systematic review and meta-analysis | 2021 | English | Article | https://www-scopus-com.vpn.ucacue.edu.ec/record/display.uri?eid=2-s2.0-85101412874&origin=resultslist&sort=plf-f&src=s&nlo=&nlr=&nls=&sid=82145af67840f1662f5e78206c0c3045&sot=b&sdt=cl&cluster=scosubjabbr%2c%22MEDI%22%2ct&sl=35&s=TITLE-ABS-KEY%28Neuromyelitis+optica%29&relpos=11&citeCnt=0&searchTerm= |
| | | Effectiveness of treatments in Neuromyelitis optica to modify the course of disease in adult patients. A systematic review of the literature. | 2021 | English | Article | https://www-scopus-com.vpn.ucacue.edu.ec/record/display.uri?eid=2-s2.0-85102105180&origin=resultslist&sort=plf-f&src=s&nlo=&nlr=&nls=&sid=82145af67840f1662f5e78206c0c3045&sot=b&sdt=cl&cluster=scosubjabbr%2c%22MEDI%22%2ct&sl=35&s=TITLE-ABS-KEY%28Neuromyelitis+optica%29&relpos=14&citeCnt=0&searchTerm= |
| | | Recent advances in the treatment of neuromyelitis optica spectrum disorders | 2021 | English | Article | https://www-scopus-com.vpn.ucacue.edu.ec/record/display.uri?eid=2-s2.0-85103607513&origin=resultslist&sort=plf-f&src=s&nlo=&nlr=&nls=&sid=82145af67840f1662f5e78206c0c3045&sot=b&sdt=cl&cluster=scosubjabbr%2c%22MEDI%22%2ct&sl=35&s=TITLE-ABS-KEY%28Neuromyelitis+optica%29&relpos=19&citeCnt=0&searchTerm= |
| | | Autologous hematopoietic stem cell transplantation in a pediatric patient with aquaporin-4 neuromyelitis optica spectrum disorder | 2021 | English | Article | https://www-scopus-com.vpn.ucacue.edu.ec/record/display.uri?eid=2-s2.0-85101772953&origin=resultslist&sort=plf-f&src=s&nlo=&nlr=&nls=&sid=82145af67840f1662f5e78206c0c3045&sot=b&sdt=cl&cluster=scosubjabbr%2c%22MEDI%22%2ct&sl=35&s=TITLE-ABS-KEY%28Neuromyelitis+optica%29&relpos=17&citeCnt=0&searchTerm= |
| | | New Therapeutic Landscape in Neuromyelitis Optica | 2021 | English | Article | https://www-scopus-com.vpn.ucacue.edu.ec/record/display.uri?eid=2-s2.0-85103538078&origin=resultslist&sort=plf-f&src=s&nlo=&nlr=&nls=&sid=de9e4c3c58318cb6426815660b63d870&sot=b&sdt=cl&cluster=scosubjabbr%2c%22MEDI%22%2ct%2bscoaffilctry%2c%22United+States%22%2ct&sl=35&s=TITLE-ABS-KEY%28Neuromyelitis+optica%29&relpos=4&citeCnt=0&searchTerm= |
| Total Number of Articles | | | | | | 27 |

Graph 1. Article selection flow chart

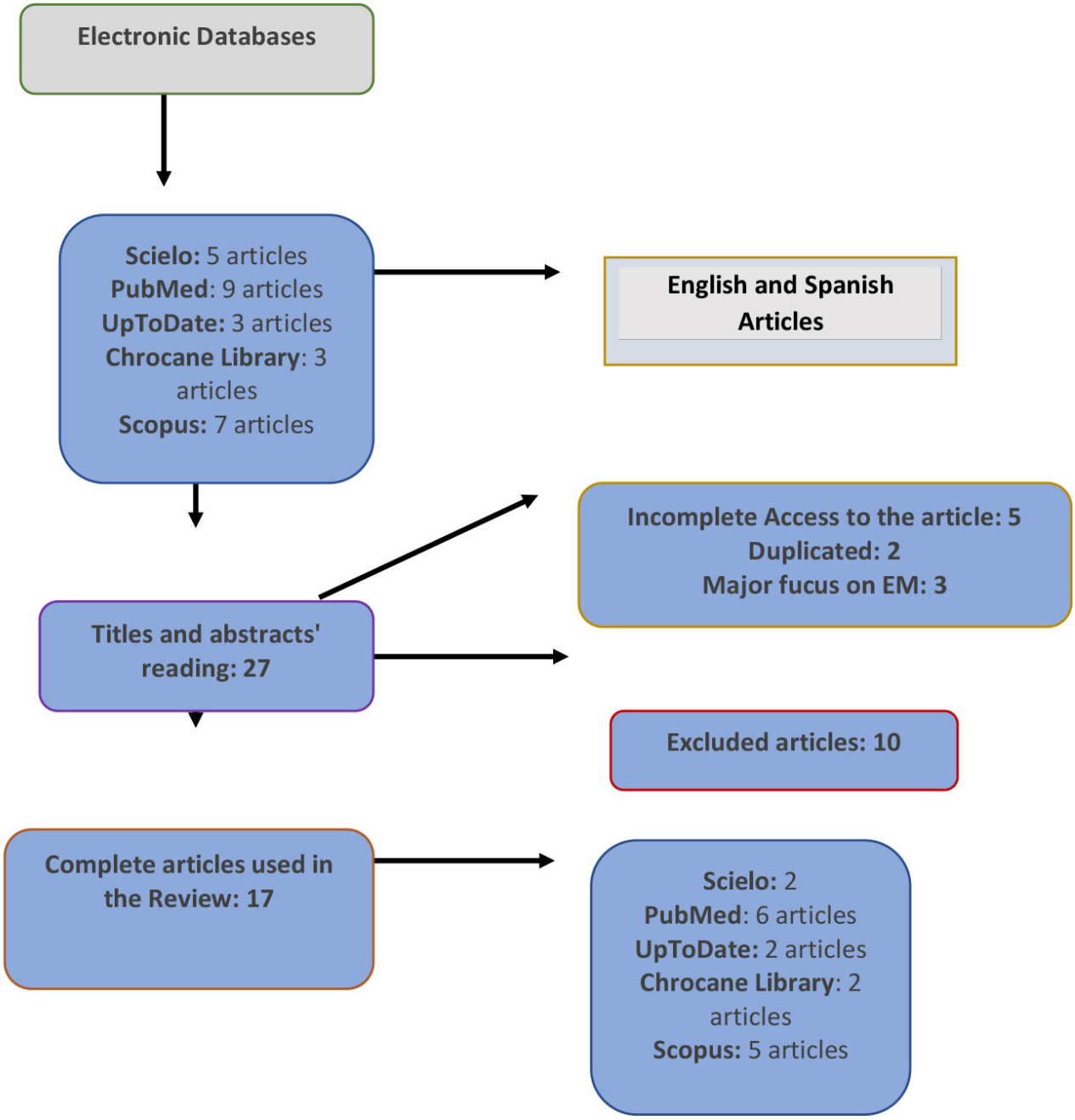

**Table 2. Articles' description, containing their corresponding database, publishing year, author, journal, and language.**

| N□ | Database | Publishing date: | Authors | Year | Language | Title | Objectives |
|---|---|---|---|---|---|---|---|
| 1 | Scielo | Rev. Soc. Esp. Dolor vol.23 | L. A. Templos Esteban, P. Salgado Villalobos, N. Galán López, N. E. Rangel Domínguez y M. M. Salado Ávila | 2016 | Spanish | Manejo del dolor en un caso de neuromielitis óptica (enfermedad de Devic) | The purpose is to present a clinical update on the neuromyelitis Optica's state of the art, progression, diagnosis, and treatment; with a specific focus on pain treatment, as well as a clinical case presentation and its multidisciplinary approach. |
| 2 | Scielo | Rev chil neuro-psiquiat 2016; 54 (3) | Claudio Meza P., Alejandro Henríquez C., Andrés Jara Q. y Pilar Canales F | 2016 | Spanish | Aspectos clínicos en el espectro de neuromielitis óptica: revisión de la literatura | This article aims to present a subject update, emphasizing the most relevant NMOSD features, like its epidemiology, clinical manifestations, diagnosis, treatment, and prognosis. |
| 3 | PubMed | Neurología. 2019 | E Carreón Guarnizo et al. | 2019 | Spanish | Experiencia con tocilizumab en pacientes con espectro de la neuromielitis óptica | The objective of the study is to evaluate the efficacy and safety provided by tocilizumab treatment administered to patients with ENMO who have not previously responded to other DMARDs. |
| 4 | PubMed | Archivos de la sociedad española de oftalmología. Vol. 95. Núm. 3 | A Cerveró , M J Sedano-Tous , J Madera , A López-de-Eguileta , A Casado | 2019 | Spanish | Uso del análisis de la capa de células ganglionares para el diagnóstico en la neuromielitis óptica anti-glucoproteína de la mielina del oligodendrocito | A 26-year-old patient presented recurrent episodes of optic neuritis and suspected diagnosis of neuromyelitis optica. In the first event, the patient presented severe visual acuity impairment in the left eye. The optical coherence tomography showed ganglion cell layer damage in both eyes, evidencing a possible nerve lesion that reached the optic chiasm. |
| 5 | PubMed | Rev Neurol 2017 Sep 1;65(5):193-202. | R. Uribe-San Martín, et al. | 2017 | Spanish | Espectro de neuromielitis óptica: descripción de una cohorte según los criterios diagnósticos de 2015 | The objective is to describe the clinical-radiological and prognostic characteristics of patients diagnosed with NMO according to the 2015 criteria. |
| 6 | PubMed | Archivos de la Sociedad Española de Oftalmología Vol 95 | A. García Ortega , F.J. Montañez Campos, S. Muñoz, B. Sánchez-Dalmau | 2020 | Spanish | Neuritis ópticas desmielinizantes y autoinmunes | In the last decade, the knowledge of demyelinating and autoimmune optic neuropathies has undergone a revolution, after discovering the Anti-Aquaporin 4 (AQP4) antibodies. |
| 7 | PubMed | Curr Opin Ophthalmol. 020 Nov;31(6):462-468. doi: 10.1097/ICU.0000000000000703. | Kathryn B Holroyd, Giovanna S Manzano, Michael Levy | 2020 | English | Update on neuromyelitis optica spectrum disorder | Neuromyelitis optica spectrum disorder is an autoimmune disease that causes optic neuritis and transverse myelitis. Attacks can cause severe neurological damage leading to blindness and paralysis. Understanding of the immunopathogenesis of this disease has led to major breakthroughs in diagnosis and treatment. In the past 18 months, three successful phase 3 clinical trials have been published using targeted approaches to preventing relapses. |
| 8 | PubMed | Nat Rev Dis Primers. 2020 Oct 22;6(1):85. doi: 10.1038/s41572-020-0214-9. | Sven Jarius, Friedemann Paul, Brian G Weinshenker, Michael Levy, Ho Jin Kim, Brigitte Wildemann | 2020 | English | Neuromyelitis optica | Neuromyelitis optica (NMO; also known as Devic syndrome) is a clinical syndrome characterized by attacks of acute optic neuritis and transverse myelitis. In most patients, NMO is caused by pathogenetic serum IgG autoantibodies to aquaporin 4 (AQP4), the most abundant water-channel protein in the central nervous system. In a subset of patients negative for AQP4-IgG, pathogenetic serum IgG antibodies to myelin oligodendrocyte glycoprotein, an antigen in the outer myelin sheath of central nervous system neurons, are present |
| 9 | UpToDate | UpToDate | Benjamín Osborne Laura J Balcer, MD | 2018 | English | Optic neuritis: Pathophysiology, clinical features, and diagnosis | The epidemiology, pathophysiology, clinical features, and diagnosis of demyelinating optic neuritis will be covered here. |
| 10 | UpToDate | UpToDate | Benjamín Osborne, Laura J Balcer, MD | 2018 | English | Optic neuritis: Prognosis and treatment | The prognosis and treatment of demyelinating optic neuritis will be reviewed on this topic. |
| 11 | Chrocane | Journal of the neurological sciences | Tahara M, Oeda T, Sawada H | 2017 | English | Rituximab for neuromyelitis optica relapses: RIN-1 Study | To evaluate prognostic factors for first relapse in Thai patients with NMOSD. |
| 12 | Chrocane | Cochrane Central Register of Controlled Trials | Michael Levy, Harvard Medical School | 2020 | English | High Frequency Impulse Therapy for Neuropathic Pain in NMOSD | Subjects will be randomized to either the intervention or the control group, fitted and trained to use an ENSO device to self-administer treatment for at least one hour each day. The subjects will not know to which arm they are randomized. |
| 13 | Scopus | International Journal of Neuroscience | Masoud Etemadifar, et al. | 2021 | English | Ginseng in the treatment of fatigue in multiple sclerosis: a randomized, placebo-controlled, double-blind pilot study | The purpose of this study was to evaluate the efficacy and safety of ginseng in the treatment of fatigue and the quality of life of MS patients |
| 14 | Scopus | Multiple Sclerosis and Related Disorders Volume 50 Principio del formulario Final del formulario | Wang, Y. Chang, H., Zhang, X. Yin, L. | 2021 | English | Efficacy of Rituximab in the treatment of neuromyelitis optica spectrum disorders: An updated systematic review and meta-analysis | The present review aimed to conduct an updated systematic review and meta-analysis of the efficacy of RTX in the treatment of NMOSD and analyze the main factors affecting the efficacy of RTX. |
| 15 | Scopus | Multiple Sclerosis and Related Disorders Volume 50 | Mario Velasco. Luis Alfonso Zarco. Mariana Agudelo. Isabel Torres. Elkin García. Oscar Muñoz | 2021 | English | Effectiveness of treatments in Neuromyelitis optica to modify the course of disease in adult patients. A systematic review of the literature. | To make treatment recommendations and management guidelines, it is imperative to define an appropriate standard of care. |
| 16 | Scopus | rheumatology Volume 33, Principio del formulario Final del formulario | Andrew R Romeo | 2021 | English | Recent advances in the treatment of neuromyelitis optica spectrum disorders | This review examines recently published randomized placebo-controlled trials for the treatment of neuromyelitis optica spectrum disorders (NMOSD). |
| 17 | Scopus | Current Treatment Options in Neurology Volume 23 | Madina Tugizova MD, Luka Vlahovic MD, MSCR, Anna Tomczak MS, Nora Sandrine Wetzel & May Htwe Han MD | 2021 | English | New Therapeutic Landscape in Neuromyelitis Optica | This review discusses the current treatment trends and emerging therapeutic landscape for patients with neuromyelitis optica spectrum disorder (NMOSD). |

## Discussion

In 1999, the Mayo Clinic first proposed diagnostic criteria for Devic's neuromyelitis optica based on the clinical and image aspects. The anti-AQP4 antibodies, also called Anti-Aquaporin, were discovered in 2004. The discovery triggered the previously proposed diagnostic criteria update. As a result, in 2006, the discoverers of anti-AQP4 validated the new diagnostic criteria with 99% sensitivity and 90% specificity of[3]

On this basis, diagnostic criteria are stated in NMOSD and seropositive for AQP4-IgG and seronegative for AQP4-IgG. These criteria are described in Tables **3** and **4**, respectively. The following essential clinical features should accompany them: 1. optic neuritis, 2. acute myelitis, 3. Postrem area syndrome which symptoms include unexplained nausea and vomiting, 4. acute brainstem syndrome, 5. symptomatic narcolepsy or acute diencephalic syndrome with diencephalic damages, characteristic of NMOSD, in MRI, and 6. symptomatic cerebral syndrome with characteristic brain damages in the NMOSD MRI[4].

These essential criteria can be classified as absolute and supportive or supplementary. Among the first ones are optic neuritis and acute myelitis. Among the second criteria is the brain MRI without requirements for multiple sclerosis, spinal MRI with lesion located through three or more segments of the spinal cord and seropositivity for anti-aquaporin antibodies[5]

| Table 3. Diagnostic criteria in NMOSD seropositive for AQP4-IgG |
|---|
| Diagnostic criteria in NMOSD seropositive for AQP4-IgG |
| At least one essential clinical characteristic |
| Positive test for AQPA-IgG using the most efficient detection method possible |
| Eliminate differential or alternative diagnoses. |

| Table 4. Diagnostic criteria in NMOSD seronegative for AQP4-IgG |
|---|
| Diagnostic criteria in NMOSD seronegative for AQP4-IgG |
| At least two essential clinical characteristics because of 1 or more clinical seizures presenting:<br>a) One essential feature must be optic neuritis, acute myelitis with postrem area MTEL or Sx.<br>b) In-place Dissemination<br>c) Must comply with the additional MR requirements |
| A negative test for AQPA-IgG using the most efficient detection method possible |
| Eliminate differential or alternative diagnoses. |

The AQP4-IgG test has some limitations, unfortunately, it is not available in all regions and has a high false-negative rate, therefore, the International Panel for the diagnosis of NMOSD provided diagnostic criteria for this disorder in those cases of suspected AQP4-IgG with negative or inconclusive results in their serological analysis. Criteria A, B, and C must be met for a definitive diagnosis[2]

**Criteria A:**

- Negative or inconclusive results in serological tests for AQP4-IgG [2]

**Criterion B:**

Two or more of the following conditions which one of them must be acute onset optic neuritis, myelitis, or area postrema syndrome

1. Clinical manifestations of optic neuritis including an MRI scan showing an optic nerve lesion greater than or equal to one-half the length of the distance between the orbit and the optic chiasm, i.e., an extensive optic nerve lesion; or
   - A lesion at the level of the optic nerve that affects the optic chiasm, or
   - Absence of brain lesions or inconclusive lesions in the white matter.
2. Clinical manifestations of acute myelitis with nuclear magnetic resonance images showing a lesion of great longitudinal extension continuously in three or more complete segments of the vertebra with the intramedullary lesion, or three or more continuous segments of delimited spinal atrophy with or without T2 signal in cases in which acute myelitis is present as a medical history of the patient.
3. Clinical manifestations of acute onset postrema area syndrome plus nuclear magnetic resonance imaging showing dorsal medullary lesion, which in most cases is usually bilateral but can also present unilaterally.
4. Clinical manifestations of acute encephalitis at the level of the brainstem plus a nuclear magnetic resonance imaging showing lesion around the ependymal covering of the fourth ventricle.
5. Clinical manifestations of acute inflammation of the diencephalon, symptomatic narcolepsy, accompanied by lesion around the ependyma covering the third ventricle or lesion affecting the hypothalamus or thalamus.
6. Acute inflammation of the telencephalon plus an MRI scan showing lesion around the ependyma overlying the lateral ventricles, or
   - Deep or subcortical lesion in the white matter areas, or
   - Lesion with large longitudinal extension, i.e., greater than or equal to half its length, diffuse, heterogeneous, or with the presence of edema at the level of the corpus callosum, or
   - Lesion of great longitudinal extension of the corpus callosum involving the internal capsule and cerebral peduncles [2]

**Criterion C:**

Rule out other diagnoses [2]

a. Spread of lesions in space and not in time is a prerequisite [2]

Concerning image tests, MRI is the best test to identify NMOSD lesions. The use of MRI lies in the identification and assignment of characteristics to the lesions in cases of NMOSD and allows us to perform differential diagnoses between NMOSD and multiple sclerosis. Hyperintense lesions will be seen in severe cases in t2-Flair, and in T1 hypointense sequences that become more intense when interacting with gadolinium. The most common alteration on MRI is extensive longitudinal myelitis, which is present in 75% of cases, followed by the fourth ventricle peri-ependymal brainstem lesions, deep and subcortical lesions converge in the substantia alba, diencephalon damage, and extensive gadolinium-absorbing brain lesions around the ependyma. The less frequently occurring lesions include lesions of the dorsal bulb postrema area, the optic nerves and callosum corpus, and corticospinal tract damages[6]. Lesions located in the dorsal medulla, postrema, and cerebral area are more common in children and present AQP4 expression predominance[7].

Some evidence in anti-MOG seropositive NMOSD cases showed thickening and hyper-intensity in the optic nerve, which affects the optic chiasm in the brain MRI. When there is initial damage in the right eye's ganglion cell layer in the first episodes of optic neuritis, without an MRI at that time, it could be considered a compromise sign of the optic nerve optic chiasm. This situation leads to the suspicion of seropositive anti-MOG NMOSD, which enables the preventive treatment previously medullary and visual field involvement[8].

Lumbar puncture is another diagnostic test. Although it is not essential, it must be applied in atypical NMOSD cases, in which the lesion is bilateral, the patient is under 15 years old, or infection is suspected[9].

More proteins and pleocytosis with predominant polymorphonuclear cells can be found when examining cerebrospinal fluid. In a small percentage of patients, oligoclonal bands may be found, which usually disappear over time. In addition, an astrocytic protein GFAP's percentage increase has been found in patients presenting more relapses. The GFAP presence is widely associated with disability development[6].

Currently, there is no one established therapeutic manual for good pain relief or disease treatment protocols. In most cases, the therapy protocol used in general neuropathic pain is used, but it does not cover the patients' needs. According to Templos Esteban et al., carbamazepine had provided better pain-relieving results, especially when combined with neuromodulators and potent opioids. They reduce the patients' anxiety, pain, and depression[3].

A new alternative for NMOSD patients is transcutaneous electrical nerve stimulation therapy (TENS). The treatment consists of stimulating the patient to reduce pain in a non-invasive manner with transcutaneous electrical stimulation applied to ascending or sensory tissues and reorganizing maladaptive signage pathways. Patients report pain relief after ten consecutive days of receiving this therapy[10].

To treat the typical disease fatigue, a new therapy has been proposed apart from the commonly used drugs (amantadine and modafinil, among others), which includes using ginseng, as the neuroprotection produced by its antioxidant effects, also regulates neurotransmitters such as GABA, dopamine, serotonin, and noradrenaline. However, more studies are necessary to corroborate its safety and efficacy[11].

Regarding severe episodes' therapy, Meza et al. propose using corticosteroids, specifically, methylprednisolone dosed at 1 gram daily for five days, or 30 mg/kg/day for 5 days, with a maximum dose of 1000 mg; following with oral prednisone at 1mg/kg per day, which will be gradually reduced over a year. This medicine will help reduce inflammation; leukocyte apoptosis, suppress PMFN migration and prevent decreased capillary permeability[4,6].

According to Osborne and Balce, intravenous methylprednisolone accelerates vision recovery. This drug also decreased the risk of NMOD developing into multiple sclerosis over two years. However, no differences were found in the rates of multiple sclerosis development after five years in studied patients' groups[9].

If corticosteroid therapy will not work, plasmapheresis is recommended as a second option, as it rapidly elevates anti-AQP4 antibodies that, when combined with immune suppressants, may decrease rebound effects[4].

In case the aforementioned therapies result not to be effective, intravenous immunoglobulin can be used, especially if the treatments are contraindicated; another option is to use intravenous cyclophosphamide[7].

As for the remission phase, the treatment consists of combining prednisone and azathioprine; the doses for the second one is of 50 mg/day and, according to the patient's tolerance; increasing it by 2 to 3 mg/kg/day, as this drug acts slowly (between three to seven months). Prednisone 1mg/kg/day is also applied, and its dose goes will decrease for a year. When the disease remission is achieved, immunosuppressive treatment should be initiated as the only drug and at lower doses than the effective ones[4].

The efficacy of mycophenolate mofetil is based on bone marrow suppression. Two to three grams per day are administered in divided doses. The effect must be monitored by absolute lymphocyte count and, in case the drug has the expected effect, the count should be less than 1500/$\mu$L[6].

Rituximab is a specific chimerical monoclonal antibody directed against CD20+ B cells. This drug reduces the number of serum lymphocytes. This effect lasts for weeks, reducing the number of relapses and improving the patient's neurological condition. The dose to be administered is 375 mg/m$^2$ for 28 days and thereafter, it is repeated every six months. This drug is usually used especially when there is no favorable response of the patient to azathioprine plus corticosteroids. The recurrence risk when using Rituximab is minimal compared to other drugs[3,5,11]. It has been shown that Rituximab can both, ameliorate the degree of disability in NMOSD patients and reduce the ARR (Annual Relapse Rate)[13]. According to Carreón et al., another drug recommended for treating NMOD is tocili-

zumab, an immunosuppressant that acts as a recombinant humanized IgG1 monoclonal anti-interleukin-6 receptor antibody. Tocilizumab reduces the yearly (ARR) relapse rate and improves the EDDS (Expanded Disability Status Scale) patients' score; especially when the patient does not adequately tolerate Rituximab. The dose would be 8mg/kg intravenously at 28-day intervals[14].

Other monoclonal antibodies such as Satralizumab and Eculizumab showed efficacy in preventing relapses during treatment. Despite not being better than Rituximab, these drugs showed superiority over drugs like azathioprine and mycophenolate, as these last-mentioned medicines showed less favorable risk-benefit ratios. They are considered optional when the patients do not have access to monoclonal antibodies[15].

Satralizumab is a specific humanized monoclonal antibody that targets interleukin-6 (IL-6), an inflammation-promoting cytokine that is closely related to the inflammatory process's characteristic of NMOSD, as its levels are usually elevated in serum and CSF tests. Eculizumab is also a drug considered a monoclonal antibody, but it acts at the level of the complement system, specifically on the C5 protein, preventing it from cleaving into C5a and C5b, which are proteins that promote inflammation. The PREVENT trial demonstrated high efficacy in adult patients with NMOSD who received Eculizumab or placebo[16]

Eculizumab inhibits complement C5-terminal protein cleavage, and Satralizumab inhibits interleukin-6 receptors. Inebilizumab is another monoclonal antibody that could be effective as NMOSD therapy. This antibody eliminates the immune B-lymphocyte lineage cells, which are often used when the neuromyelitis optical results to be seropositive for AQP-4. However, the risk-benefit of Eculizumabs should be considered. It may cause meningococcal infection and Inebilizumab, triggering infection and hypogammaglobulinemia[16,18].



## Conclusions

Neuromyelitis optica is a chronic disease in which inflammation causes the central nervous system demyelination and affects the spinal cord and the optic chiasm. The Gold Standard for diagnosing this pathology is magnetic resonance imaging, which must meet specific imaging parameters to ensure this diagnosis and differentiate it from other pathologies such as multiple sclerosis. The diagnosis is also supported by the criteria established by the Mayo Clinic and the antibody tests determined for the two subtypes of this disease: 4 IgG y anti-MOG IgG. This disease has no cure; however, treatment consists of pain control, acute episodes, and relapses prevention. Nowadays, strong analgesics such as opioids are indicated for pain treatment. Corticosteroids, preferably methylprednisolone as well as an immunosuppressant, are used for relapses. According to several studies, Rituximab is the most effective drug to prevent relapse. Nevertheless, numerous studies have been conducted concerning the efficacy of other immunosuppressive drugs such as Tocilizumab, Satralizumab, Inebilizumab, and Eculizumab for treating Devic's neuromyelitis optica. So far, no research has been highly conclusive, and in most studies, Rituximab remains superior to the drugs previously mentioned.

**Acknowledgments**

Dr. Ebingen Villavicencio Caparo. Editor-EDUNICA, Catholic University of Cuenca

Dra. Tania Bustamante, Institute of Languages Catholic University of Cuenca

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