Review Article

Comprehensive review of neuromyelitis optica and clinical characteristics of neuromyelitis optica patients in Puerto Rico

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Abstract

Neuromyelitis optica (NMO) is an immune-mediated inflammatory disorder of the central nervous system. It is characterized by concurrent inflammation and demyelination of the optic nerve (optic neuritis [ON]) and the spinal cord (myelitis). Multiple studies show variations in prevalence, clinical, and demographic features of NMO among different populations. In addition, ethnicity and race are known as important factors on disease phenotype and clinical outcomes. There are little data on information about NMO patients in underserved groups, including Puerto Rico (PR). In this research, we will provide a comprehensive overview of all aspects of NMO, including epidemiology, environmental risk factors, genetic factors, molecular mechanism, symptoms, comorbidities and clinical differentiation, diagnosis, treatment, its management, and prognosis. We will also evaluate the demographic features and clinical phenotype of NMO patients in PR. This will provide a better understanding of NMO and establish a basis of knowledge that can be used to improve care. Furthermore, this type of population-based study can distinguish the clinical features variation among NMO patients and will provide insight into the potential mechanisms that cause these variations.

Key Words: AQP4 antibodies, multiple sclerosis, myelitis, neuromyelitis optica, optic neuritis

INTRODUCTION

In 1894, Eugène Devic and his student Fernand Gault created the term neuromyelitis optica (NMO) in a published review of early cases of patients that presented with bilateral optic neuritis (ON) and myelitis accompanied by debilitating disability after series of attacks.[109,110] For years, NMO was considered a special form of multiple sclerosis (MS).[47]
In 2015, the International Panel for NMO Diagnosis proposed the unifying term of neuromyelitis optica spectrum disorders (NOMSD) for patients presenting selective demyelination of the spinal cord and the optic nerve. Specific criteria were established to facilitate earlier and more accurate diagnoses in AQP4 antibodies seropositive or seronegative patients presenting with ON, transverse myelitis, or area postrema clinical syndrome associated with a medullary MRI lesion.[20] Historically, NMO and MS are seen as overlapping central nervous system (CNS) inflammatory diseases. NMO was considered a variant of MS and the diagnosis of patients with NMO was delayed for many years due to the absence of specific criteria to recognize and distinguish the disease from MS.[10,11] With the discovery of AQP4 antibodies, the incidence of the disease started to be studied in a more accurate way.[12,20] In the following sections, we will provide a comprehensive review of NMO that covers its epidemiology, environmental risk factors, genetic factors, molecular mechanism, symptoms, comorbidities and clinical differentiation, diagnosis, treatment, its management, and prognosis.

In addition, we also provide information specific to NMO patients in Puerto Rico (PR).

A recent study on Latin Americans with NMO (including patients from Caribbean islands) found the prevalence of NMO in this population ranged from 0.37/100,000 to 4.2/100,000 with African, Brazilian young women having the highest frequency.[10] However, there is no prior study on NMO patients specifically from PR.

We will evaluate contributing factors and clinical phenotype of NMO patients in PR. This type of population-based study can help the treating physicians with understanding the prognosis of NMO among this specific population. Furthermore, it will enhance their knowledge on the variability of the disease that is based on environmental factors and ethnicity. We believe that this research can delineate the clinical features variation among NMO patients and will provide insight into the potential mechanisms behind these variations.

**Epidemiology of Neuromyelitis Optica**

The evolution in the knowledge of NMO and the changes in the selection criteria have influenced the incidence and prevalence rates reported in many countries, with prevalence ranging from 0.05 to 4.4/100,000 worldwide.[11,20,24] The highest incidence and prevalence reported is from a study performed from 2008 to 2012 in Barcelona, Spain with incidence of 5.35/100,000 and prevalence of 7.87/100,000; both values are outliers in the data found in literature.[10] In the United States, there is an estimated 4000–8000 patients (1–2% of formerly diagnosed MS patients).[17]

In some countries, the studies for diagnosing NMO are scarce and only an average age of onset for the disease is reported, such as in Algeria with a mean of 29.4 years old (range 16–44 years) or Iran with a mean of 36.6 years old (mode of 30).[18,70] A study in Spain reported a mean onset of 36 years, one study in Brazil reported a mean onset of 32.8 years (range 14–55), and in a study of six patients from Germany, there was a range of onset from 5 to 14 years.[92,162,208] These data represent a lower average age of onset than the numbers reported in different countries 5–10 years ago (41.1–45 years old), possibly attributed to improvement in technology and diagnostic studies.[172] There is also reportedly an increase in NMO risk among patients older than 48 years.[70] For many years, NMO has been associated with Indian, black, and Asian populations: the Japanese population, for example, has one of the highest documented prevalence of NMO in the world at 3.4/100,000.[21,4,12,204] On the other hand, in studies performed in South East Wales, NMO is as frequent in populations of Northern European as in populations that are non-Caucasian.[32] Furthermore, multietnic studies performed in Cuba found that prevalence rates do not differ between ethnic groups; black patients were older and experienced more relapses of NMO and worse motor deficiencies during their lifetime which could lead to a longer period presenting symptoms and higher probability of being diagnosed in comparison with whites.[37] Recent studies in Southern Denmark also proposed that NMO prevalence in Caucasian population is higher than previously reported; results showed that all patients with complete criteria for NMO were Caucasian except for one. The prevalence was found to be 4.4/100,000 in this population.[16]

Studies in Latin America show patterns of higher relative frequency of NMO in relation with MS in populations with a higher presence of non-white descendants. In Buenos Aires, Argentina, the lowest relative frequency is reported at 2.1% in a population of high European descent. Paraguay, composed of 30% of mestizos population, reports a frequency of 8.7%. Caracas, Venezuela, reports the highest relative frequency of NMO at 11.8% with the highest non-white presence 79.15%.[10] Female preponderance is reported in NMO patients, in both pediatrics and adults.[63] In many regions of the world, there is a pattern of female predominance: east Brazil 5:1, Iran 5:9:1, 2.8:1 in Germany, 7:1 in Pediatric patients treated at Mayo Clinic, Spain 2.4:1, Southern Denmark 2.8:1, and in Japan 6:4:1.[21,4,6,7,9,10,162,18,208] The disease predilection for females in NMO is stronger than in MS, in which gender ratio varies from 1.1:1 to 3.4:1 in Europe and 3:1:1 in United States.[31,61,296] Due to the
high prevalence in females, some investigators suggest the possibility of hormones influencing the development of NMO. Pregnant females with NMO have an increased odds ratio of miscarriage which have been associated with an imbalance in Th1 and Th2 cytokines. [75,196]

ENVIRONMENTAL RISK FACTORS IN NEUROMYELITIS OPTICA

The association between environmental factors with the incidence of autoimmune diseases is well studied over many years. In this section, we review the most important environmental factors that promote the development of NMO.

Gastrointestinal

Many studies look for the association between diet and gastrointestinal infections with prevalent diseases in the Asian population. In Japan, where the incidence of NMO is 5.42/100,000, Helicobacter pylori neutrophil activating protein increases the neutrophil infiltration in acute lesions of NMO patients. [153,152] Furthermore, a significantly higher number of patients positive to anti-H. pylori and anti-Chlamydia pneumoniae IgG are found among anti-AQP4 Ab-positive NMO patients in comparison with control patients, suggesting the association of H. pylori infection in NMO pathogenesis. [156] A higher prevalence of MS as compared to NMO is found in the northern latitudes of Japan. [135] In this area, westernization, changes in diet, and improvements in sanitation are more common. These processes may have played a contributive factor in decreasing the rate of infection of H. pylori and reduced the risk for NMO in the North during the past century. [117,156]

Clostridium perfringens (C. perfringens) is also found to be one of the most active bacteria in NMO patients microbiota. [51] Investigators suggest that the Epsilon toxin produced by C. perfringens causes blood-brain barrier damage facilitating the entrance of AQP4-IgG. [301] This mechanism is described in MS patients who showed a 10 times higher immunoreactivity to Epsilon toxin of C. perfringens Type A compared with healthy controls. [219]

Studies regarding the change in climate and seasonal viral infections in Japan showed an association with relapses in MS patients but not in NMO patients. [199]

Vitamin D

Though the importance of active vitamin D, or 1,25-dihydroxycholecalciferol, in immune system function is well known, it’s role in the pathogenesis of autoimmune-mediated demyelinating neuropathies is only now just starting to be understood. Vitamin D acts to increase regulatory T cell (Treg) function via increased interleukin 10, as well as suppression of interferon Y, interleukin 2, and, at least in vitro, interleukin 4. [9,41,254,257] This increase in Treg dampens T-helper activation and is generally accepted as a means to control the immune system and avoid pathological self-reactivity. [183,248,250] Vitamin D dysregulation is posited as part of the pathophysiology of NMO. [114]

Vitamin D synthesis is dependent on ultraviolet (UV) light and is needed for adequate immunologic responses. [40,84] Decreased sun exposure, a demonstrated risk for MS, is not proven as a risk for NMO. [177] However, an increase in sun exposure could be a potential risk factor for NMO. The number of cases of NMO reported in 2011 in southern Japan is significantly higher in comparison with the North, which could be related to higher UV indices and annual sunshine duration. [90,135,152] On the contrary, in Korean NMO patients, levels of vitamin D were found to be significantly lower than controls and deficiency of vitamin D was found in patients having an NMO attack. [179] Also, studies performed in Thai NMO patients showed no association of vitamin D insufficiency with disease process and disease disability. [113]

Additional studies show a correlation between both NMO and MS and vitamin D deficiency, though neither study found correlation between either prevalence nor degree of vitamin D deficiency and annualized relapse rates of NMO. [114,179] One study did find an inverse relation between levels of vitamin D and the severity of NMO symptoms, while yet another study identified higher prevalence of reduced vitamin D levels in acute relapse of NMO versus stable remission. [179,245]

Other investigators report independent roles for the amount of vitamin D in the body and history of sun exposure on demyelinating disorders and this is an area in need of further study. [199]

Smoking

One study reports that smoking is more frequent in MS than NMO for two case cohorts, Canadian (37.5% vs. 10.5%, P = 0.039) and Chinese (14.5% vs. 0%, P = 0.004). [136] History of smoking is also reportedly inversely correlated to NMO in another study in which 72% of whites, 19% African-American, and 8% of Asian with NMO answer no to smoking history compared to the control group. [299]

Other

Determinant and protective factors like breastfeeding and daycare exposure are also reported in different populations for NMO patients. [70,32]

GENETIC RISK FACTORS IN NEUROMYELITIS OPTICA

Genetic predisposition of NMO to different alleles of Class I and II human leukocyte antigen (HLA) has been
studied since NMO was considered a variant of MS. Studies performed before 2001 on natives of Canada with demyelinated lesions in optic nerve and cervical spinal cord showed association of these lesions with HLA alleles DRB1 and DQB1. The specific allele HLA-DRB1*03 presents a risk for NMO in the French population. In Brazilian NMO-Ig-positive patients and Afro-Caribbean populations, HLA-DRB1*03 is found to be more common than in healthy controls.

In France, no association is found between NMO patients and HLA-DR-DRB1*05:01; nevertheless, a different investigation found this allele in NMO patients of African-American and Latino population. In the Han Chinese population, DRB1*1602 is found to be higher in NMO patients in comparison with MS patients; DRB1*05:01 correlated with higher risk of NMO.

Protective factors
In Asian populations, AQP4 Ig seropositive or seronegative HLA-DRB1*0901 is protective against NMO. In Southern Han Chinese population, HLA-DRB1*0901 is less common than in healthy controls (P = 0.022, OR: 0.194, 95% CI: 0.043–0.876). In this population, reduced risk of NMO is associated with the polymorphism in CD58 with the haplotype HATTACGG. Another protective effect on the risk for NMO is found in people with single nucleotide polymorphism (SNP) in CYP7A1 in chromosomes 8q11-q12.

Genes associated with AQP4
Studies in Chinese patients found the 3' UTR region of AQP4 gene to be susceptible in several sites to SNP that may represent a risk for NMO. In a study of AQP4 SNP reported two missense allelic mutations at Arg 19 that result in array formation changes of the AQP4 protein and are specific for NMO. In AQP4-Ig-positive Japanese patients, the allele frequency of T rs2075575 is higher than in controls (50% vs. 25.7%; P = 0.0036) and represents higher risk for AQP4-Ig NMO.

Other genes associated with neuromyelitis optica
Genes involved in regulation of the autoimmune system and regulation processes are found in NMO patients with lesions. In NMO AQP-4 seropositive Chinese patients, a higher frequency of polymorphism in interleukin 17 (IL-17) gene compared to healthy controls is observed. Upregulation of inflammatory cytokines like IL-17, IL-6, and IL-32 is seen in patients with increased levels of these cytokines in plasma which could describe the process of NMO immune-mediated chronic inflammatory disease. Programmed death-1 (PD-1) receptor gene is associated with inflammatory and autoimmune diseases such as MS, rheumatoid arthritis, and allergic asthma. The polymorphisms in allele PD-1 PD-1.3 G/A is found in a higher frequency in NMO patients (P < 0.026) compared to the healthy controls and is found in familial cases of NMO and MS. Han Chinese population with polymorphisms of CD58 (haplotype TAGCCCAA) have a higher risk for NMO.

MOLECULAR MECHANISM OF NEUROMYELITIS OPTICA

Antibody mediated damage
The major pathological mechanism of injury in seropositive NMO involves the autoantibodies aquaporin-4 (AQP4-IgG) binding to aquaporin-4 water channels in the astrocytes of brain, spinal cord, and optic nerve, followed by inflammation, disruption of blood–brain barrier, and complement-dependent cytotoxicity. Studies in Chinese patients found the 3' UTR region of AQP4 gene to be susceptible in several sites to SNP that may represent a risk for NMO.

Role of complement
The MAC-inhibitory protein, CD59 is responsible for protection from membrane attack complex (MAC) formation in AQP4-expressing tissues in the periphery of seropositive NMO patients. CD59 and CD55, complement-regulating proteins also known as decay accelerating factor, are produced in limited quantities in the brain, providing limited ability to regulate complement. While peripheral injury is not usually seen due to sufficient production of CD59, activated complement, inflammation, and injury were seen in skeletal muscle and kidney of CD59−/− rats. Intracerebral injection of AQP4-IgG caused astrocyte damage, inflammation, deposition of activated complement, and demyelination in CD59−/− rats. CD59+/+ rats showed minimal complement deposition and loss of AQP4 under the same treatment. NMO-IgG-dependent complement-dependent cytotoxicity is also seen in astrocyte cultures and ex vivo spinal cord slice cultures in both CD59−/− mice and in CD59+/+ mice after inhibition by a CD59 neutralizing antibody. Human complement with NMO-IgG injected intrathecally between the L5 and L6-produced white matter lesions in the spinal cord.
T-cell-mediated damage

T cells may also play an important role. T cells from mice lacking AQP4 channels recognize AQP4 epitopes, unlike the T cells of wild-type mice. \[^{57}\]\, TH17 cells specific for myelin-oligodendrocyte glycoprotein damage retinal ganglion cells and axons within the spinal cords of wild type. \[^{57}\]\ This not only demonstrates a role for T cells in the mechanism of NMO (though the exact mechanism is not fully elucidated) but also suggests thymic negative selection plays an important role in removing autoreactive T cells, further evidenced by a higher frequency of reactive T cells in NMO patients. \[^{57}\]\

Other mechanisms

Autoantibodies against myelin–oligodendrocyte glycoprotein, a membrane protein expressed on the oligodendrocyte cell surface and the outermost surface of myelin sheaths, are found in AQP4-IgG-seronegative patients who meet the diagnostic criteria for NMO. \[^{139}\]\ In addition to complement-related pathology, passive transfer of AQP4-IgG also caused deposition on retinal Müller cells and decreased AQP4 expression, and increased glial fibrillary acidic protein (GFAP) and is associated with retinal abnormalities including thinning of the retinal nerve fiber layer. \[^{72}\]\ The loss of AQP4 took place even in the presence of prior complement inactivation, as opposed to the complement-dependent injury typically seen in the brain, spinal cord, and optic nerve. \[^{72}\]\

**SYMPTOMS OF NEUROMYELITIS OPTICA**

The international criteria for the diagnosis of NMOSD include core clinical characteristics related to the optic nerve, spinal cord, area postrema, brainstem, diencephalic, or cerebral presentations. \[^{270,279}\]\ Optic nerve involvement can be unilateral or bilateral \[^{163}\]\ and is a painful condition worsened by movement with decreased visual acuity in the affected eye and is the most common initial symptom. \[^{18,187}\]\ Half of patients lose functional vision within 5 years of onset. \[^{5,163,290}\]\ Myelitis involvement classically involves more than three spinal cord segments. \[^{163}\]\ Urinary dysfunction is common in patients with spinal cord lesions. \[^{290}\]\ Sensory symptoms such as numbness, dysesthesia, pain, and tonic spasms are well documented and neuropathic pruritis and sudden sensorineural hearing loss are also reported. \[^{230,262,290,308}\]\ Headache of several etiologies is reported and is another possible first-presenting symptom. \[^{163}\]\ NMOSD patients are also at an increased risk of seizures. \[^{99}\]\ Involvement of the area postrema of the medulla, along with related nucleus solitaries, ventrolateral respiratory center, and nucleus ambiguous symptoms, can cause symptoms that include intractable nausea, vomiting, and hiccups. \[^{1,12,112}\]\ Intractable vomiting is the initial presenting symptom in up to 12% of AQP4-positive patients. \[^{95}\]\ Atypical manifestations can include atypical transient asymptomatic elevation of creatine kinase levels. In other brainstem, diencephalic or cerebral presentations, hypersonnia and narcolepsy can be an initial symptom, presenting in both the hypothalamus and the temporal lobe. \[^{21,145}\]\ Hypothalamic involvement can also include hyperthermia and galactorrhea. \[^{9,125}\]\ Psychology changes may be associated with NMOSD. \[^{136}\]\ Cognitive changes have been seen in NMOSD patients including impairment, depression, and suicidal ideation. \[^{10,6,277}\]\ It was found that this criteria also apply well to the pediatric population. \[^{46}\]\

**CLINICAL DIFFERENTIATION AND COMORBIDITIES OF NEUROMYELITIS OPTICA**

Neurological pathologies present from several etiologies and the clinician must be able to identify subtle differences between the presentations by taking a detailed medical history. \[^{269}\]\ The diagnosis of NMOSD from an alternative or concomitant autoimmune or neurologic disorder is identified through disease indicators such as AQP4 but the clinical presentation is significant in the differential. \[^{104,105,106}\]\

The predominant symptom in NMOSD is ON. As NMO and NMOSD are recent classifications apart from MS, the presentations between NMOSD and MS are similar. ON as a visual defect other than cecocentral scotoma and severe vision loss in the chronic stage occurs more frequently in NMOSD than in MS, as do the brainstem symptoms such as hiccup and nausea, myelitis with neuropathic pain, complete paraplegia, and tonic spasms. \[^{14,121,261,269,299,122,126,129,173,191,223,225,260}\]\ Although the prevalence and profile of cognitive impairment and depression is equal in NMOSD and MS, NMOSD has significantly higher rates of recurrent depression and suicidal ideation. \[^{136}\]\ Acute disseminated encephalomyelitis (ADEM) is another demyelinating disorder of the CNS that presents with ON. Clinically, NMOSD presents with a higher female predominance, focused neurologic symptoms at onset, higher recurrence rate and is less common to pediatric populations and lacks the characteristic onset encephalopathy of ADEM. \[^{94,129,142,141}\]\ Idiopathic causes of both acute transverse myelitis (ATM) and ON must also be considered. Idiopathic ATM presents as an inflammatory spinal cord disorder without evidence of other etiologies, such as the characteristic paroxysmal spasms, female predominance, or recurrent course seen in NMOSD. \[^{129,131}\]\ Ethnicity must also be considered as most patients with ATM convert to MS within European populations, but not in Asian populations. \[^{79,312,269}\]\

Idiopathic ON can be considered if the clinical presentation of relapsing disease course, bilateral simultaneous nerve involvement, and poor visual
outcomes of NMOSD are absent. Other diseases, like inflammatory disease due to antibody myelin oligodendrocyte glycoprotein (MOG), present with isolated neuritis and fewer relapsing courses. NMOSD is commonly associated with autoimmune disorders. Sjogren’s syndrome is the most common accompanying autoimmune disorder. Sjogren’s myelitis has longitudinal spinal cord involvement that can be diagnosed as NMO or is AQ4++; therefore, most CNS involvement is due to coexisting NMOSD rather than direct CNS involvement. In multiple studies, these types of comorbidities amongst NMO patients are discussed as an indication that NMO could be a complication of multisystem rheumatologic disease. Furthermore, the coexistence of these autoimmune comorbidities also suggested that NMO is an indication of a genetic propensity toward humoral autoimmunity.

In the limited research into the concurrent cases of myasthenia gravis (MG) and NMOSD, AQ4-NMOSD is recognized to be associated with other autoimmune manifestations in 25–50% of cases, suggesting that patients with NMOSD and MG have a predisposition to autoimmune disorders. Systemic lupus erythematosus can present with several neurological symptoms including headache, seizure, and hemiparesis but only a few have ON or myelitis pointing to susceptibility to multiple autoimmune disorders. A high prevalence of thyroid abnormalities is observed in NMOSD patients, which may be due to the AQ4 shown to be present in the thyroid tissue.

Neuro Behçet’s disease is a subset of Behçet’s disease involving the CNS and can resemble longitudinally extensive transverse myelitis (LETM) of NMOSD. The diagnosis of Behçet’s normally includes ulcers, but the neuropathic symptoms can appear before the systemic symptoms and are not included in the recent diagnostic criteria. Behçet’s is similar to NMOSD with headache, a progressive disease course and requires treatment. Gluten enteropathy, or celiac disease, is also studied but causation has not been shown in NMOSD. Pregnancy induces changes in the immune system and may also have an effect on NMOSD. NMOSD may increase the risk of miscarriage, but larger databases are needed to study this population outcomes and treatment.

Invasive etiologies may also be considered; NMOSD can be misdiagnosed for primary CNS lymphoma; diagnostic studies are important to differentiate the two. CNS lymphoma should be considered in patients with LETM if they continue to worsen despite treatment. AQ4-NMOSD can also present as a paraneoplastic syndrome, in which NMOSD symptoms present after the diagnosis of a tumor, especially in those over the age of 50, with the most frequent being carcinoma.

Similarly, sarcoidosis is a systemic granulomatous disease that can also involve the spinal cord and optic nerve resembling phenotypes of NMOSD. Neurosarcoidosis can present with systemic involvements of sarcoïd, but without the systemic symptoms, the clinical presentation can appear to be very similar to NMOSD. Another process that can be considered in the differential is a spinal dural arteriovenous fistula. A spinal dural arteriovenous fistula is a vascular malformation in spinal cord that can present as subacute and progressive myelopathy; symptoms appear after exercise or prolonged rest. Radiology or catheter angiography is required for diagnosis.

An additional cause of neurological disorders is infection. Syphilis is a sexually transmitted infection that can cause ON that can mimic NMOSD. Other infections that can mimic NMOSD include Epstein Barr virus, herpes simplex virus, cytomegalovirus, human t-lymphocytic virus, dengue fever, lyme disease, tuberculosis, Mycoplasma pneumoniae, and Streptococcus pneumoniae.

Finally, Leber hereditary optic neuropathy is the most common hereditary ON affecting males in the second or third decade of life due to mutations in the mitochondria and can be considered in the differential.

**DIAGNOSIS OF NEUROMYELITIS OPTICA**

With improved sensitivity and specificity of immunoassay techniques, as well as a deeper understanding of the pathogenesis of the disease, NMOSD diagnosis criteria have appreciably evolved over the past two decades. In 1999, the Wingerchuk group proposed its original diagnostic criteria, which was limited to CNS involvement of brain, optic nerves, and spinal cord [Table 1]. Since the original criteria had challenges in diagnosing patients presenting with symptoms involving other areas, the NMOSD diagnostic criteria were again revised by the same group in 2006. The newly revised criteria included the addition of specific NMOSD-IgG serology and an emphasis on longitudinally extensive spinal cord lesions [Table 2]. In 2015, the International Panel recently proposed the latest up-to-date NMOSD diagnostic criteria for NMOSD diagnosis (IPND). IPND has further subdivided NMOSD diagnosis based on a patient’s respective laboratory IgG seropositive or seronegative status [Table 3]. Yet in clinical setting, both comprehensive medical history and specific patient symptom evaluations are still the crucial first steps in diagnosing NMOSD. Consequently, detailed physical
While not visible on NMOSD lesions are usually centrally located. Previous studies have identified abnormalities in optic coherence tomography (OCT) in NMOSD patients. OCT is widely used to measure retinal nerve fiber layer (RNFL) thickness and ganglion cell complex (GCC) thickness, which are sensitive markers for optic nerve damage and are used to monitor disease activity. OCT can reveal NMOSD-specific intraretinal pathologies, such as thinning of the GCC and RNFL, which can be detected via high-resolution 3D images of retinal structures that reveal damage to the RNFL and GCC via retinal examination in NMOSD patients.

In patients presenting with ON, T1-weighted gadolinium coronal images or an increase in T2-weighted MRI signal of optic nerve and optic chiasm are seen unilaterally or bilaterally, after 2 weeks of onset, and may be associated with severe vision loss. Also, distinguishable diagnostic NMOSD imaging sequences include bilateral optic nerve lesions with consequent extension into optic chiasm. In addition, in patients presenting with acute ON, there is a presence of enhanced and diffused T2-weighted orbital MRI signal.

**Neuromyelitis optica spectrum disorder optical coherence tomography**

ON is one of the primary clinical manifestations detected in 55% of NMOSD patients and leads to progressive changes in vision, reduction in high or low contrast visual acuity, and potential complete vision loss within several weeks from disease onset. Affected structures include optic nerve and optic chiasm, with the retina being one of the most affected regions due to thinning of peripapillary retinal nerve fiber layer (pRNFL) and retinal ganglion cell-inner plexiform layer (GCIPL). For several years, a great effort has been dedicated to understanding the role of optic coherence tomography (OCT) as a minimally invasive imaging technique to diagnose NMOSD. In addition, OCT is employed to assess neurodegenerative damage to pRNFL and GCIPL via retinal examination in NMOSD patients. OCT employs low-coherent light to produce backscattered and reflected cross-sectional high-resolution 3D images of retinal structures that reveal NMOSD-specific intraretinal pathologies, but most importantly, OCT can provide differential diagnosis between MS and NMOSD. In NMOSD patients, acute single ON attack causes more damage to pRNFL and GCIPL layers that can be detected via OCT. Currently, OCT is widely used to measure NMOSD disease progression course, as well as outcome response to NMOSD neuroprotective therapies.

**Neuromyelitis optica spectrum disorder brain and optic nerve MRI**

Paraclinical imaging of brain-associated MRI lesions is widely employed for NMOSD supportive diagnosis but most importantly as a tool for differentiating NMOSD from MS. Early asymptomatic NMOSD onset usually does not display any MRI scan lesions and almost always will be performed before the specific NMO-IgG biomarker serology. However, if the lesions were present, imaging scan will reveal subcortical lesions without central veins. The most common sites for abnormal brain lesions are brainstem and cerebellum, followed by area postrema, thalamus, hypothalamus, and neurological examination is essential to distinguish NMO from NMOSD-mimics, including but not limited to MS, ADEM, idiopathic ATM, sarcoidosis, and other disorders. Since NMOSD is characterized by worse prognosis in comparison with MS, accurate and early diagnosis can be critical for preventing flares and relapse of monophasic NMOSD.

**Table 1: Neuromyelitis Optica Spectrum Disorders**

**Diagnosis requirements**

- **Absolute criteria**
  - Optic neuritis
  - Acute myelitis
    - No evidence of clinical disease outside of the optic nerve or spinal cord
- **Major supportive criteria**
  - Brain MRI at disease onset does not fulfill MS imaging criteria
  - Spinal cord MRI shows a lesion extending over ≥3 vertebral segments
  - CSF is significant for ≥50 WBC/mm³ or ≥5 neutrophils/mm³
- **Minor supportive criteria**
  - Bilateral optic neuritis
  - Severe optic neuritis with visual acuity worse than 20/200 in at least one eye
  - Severe, fixed, attack-related weakness in one or more limbs

**Table 2: Neuromyelitis Optica Spectrum Disorders Revised Diagnostic Criteria, Wingerchuk et al.**

**Definite NMOSD**
- **Optic neuritis**
- **Acute myelitis**
- At least two of three supportive criteria
  - Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments
  - Brain MRI not meeting diagnostic criteria for multiple sclerosis
  - NMO-IgG seropositive status

**NMO:*** Neuromyelitis optica spectrum disorders; MRI: Magnetic resonance imaging; NMO: Neuromyelitis optica.
Both IL-6 and IL-6R can also
appear in recent years documenting presence of higher levels of interleukin-6 (IL-6) and interleukin-6 receptor (IL-6R) in NMOSD patients when comparing them with MS patients.[276] Both IL-6 and IL-6R can also serve as additional biomarkers facilitating differentiation of NMOSD from other demyelinating diseases such as ADEM, idiopathic ATM, idiopathic ON, neuro-Behçet disease, and Leber heriditary optic neuropathy among others.[129,282]

Neuromyelitis optica spectrum disorder serum AQP4-AB IGG

Beyond certain characteristic clinical manifestations and specific neuroimaging findings, the presence of antibodies against water channel aquaporin-4 (AQP4), which is expressed in the astrocyte cell plasma membrane, is central for NMOSD diagnosis.[12] Eighty percent of the NMOSD patients test positive for AQP4-IgG.[124] AQP4 is also associated with peripheral tissues; however, in CNS, it is responsible for maintenance of cerebral water balance, blood–brain barrier development, and integrity.[207] AQP4-IgG positive antibody is produced by plasmablasts in peripheral circulation and is more frequently present in NMOSD patients presenting with MRI findings of ON and transverse myelitis.[276] In cases where patients may test negative for AQP4-IgG, a physician can also order a MOG-IgG serum antibody titer that binds to specific CNS tissues.[160] Patients who test positive for MOG-IgG are also at high risk of developing NMOSD.[166] In comparison with AQP4-IgG, a MOG-IgG serum antibody targets retinal nerve fibers of the patients.[257] MOG-IgG-positive patients also present with longitudinally extensive ON lesions. Both antibodies

| Table 3: International Panel for Neuromyelitis Optica Diagnosis Neuromyelitis Optica Spectrum Disorders Diagnostic Criteria for adult patients, Wingerchuk et al.[289] |
|-----------------|----------------------------------------|
| Diagnostic criteria for NMOSD with AQP4-IgG |
| At least 1 core clinical characteristic |
| Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended) |
| Exclusion of alternative diagnoses |
| Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status |
| At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements |
| At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome |
| Dissemination in space |
| (2 or more different core clinical characteristics) |
| Fulfillment of additional MRI requirements, as applicable |
| Negative tests for AQP4-IgG using best available detection method, or testing unavailable |
| Exclusion of alternative diagnoses |
| Core clinical characteristics |
| Optic neuritis |
| Acute myelitis |
| Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting |
| Acute brainstem syndrome |
| Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions |
| Symptomatic cerebral syndrome with NMOSD-typical brain lesions |
| Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status |
| Acute optic neuritis: requires brain MRI showing |
| Normal findings or only nonspecific white matter lesions, OR |
| Optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over 1/2 optic nerve length or involving optic chiasm |
| Acute myelitis: requires associated intramedullary MRI lesion extending over 3 contiguous segments (LETM) OR contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis |
| Area postrema syndrome: requires associated dorsal medulla/area postrema lesions |
| Acute brainstem syndrome: requires associated periependymal brainstem lesions |

LETM: Longitudinally extensive transverse myelitis; NMOSD: Neuromyelitis optica spectrum disorders; MRI: Magnetic resonance imaging; OR: Odds ratio

Neuromyelitis optica spectrum disorder cerebrospinal fluid analysis

Examination of cerebrospinal fluid (CSF) can be performed in patients with acute NMOSD attacks since many NMOSD CSF distinctive cell types and biomarkers disappear once patients go into remission.[106] Suggestive NMOSD CSF diagnosis findings include moderate or severe pleocytosis (up to 1000/mm³), high neutrophil granulocyte count, and presence of eosinophils.[129] Presence of those cell types in NMOSD CSF is supportive in distinguishing NMOSD from MS.[260] As many as 30% of the patients may also present with CSF oligoclonal bands.[290] Presence of higher levels of GFAP indicative of astrocytic damage is also usually detected in CSF of NMOSD patients.[258] GFAP, cytoskeleton intermediate filament, indicative of astrocyte damage currently serves as a novel biomarker useful in differentiating NMOSD from MS, especially during NMOSD ON acute episodes.[258] Recent publications also indicate higher levels of electrolytes, such as chloride, in CSF of NMOSD patients, present during acute phase of ON; however, the chloride levels have reported to be much lower during the phase of acute myelitis.[4] Several publications have appeared in recent years documenting presence of higher levels of interleukin-6 (IL-6) and interleukin-6 receptor (IL-6R) in NMOSD patients when comparing them with MS patients.[276] Both IL-6 and IL-6R can also serve as additional biomarkers facilitating differentiation of NMOSD from other demyelinating diseases such as ADEM, idiopathic ATM, idiopathic ON, neuro-Behçet disease, and Leber heriditary optic neuropathy among others.[129,282]
are measured quantitatively by ELISA testing; however, NMOSD disease course and progression is independent of the titer size. NMOSD patients with low titers have the same disease course and progression as patients with a high titer. Recent studies have also shown that patients who test positive for both AQP4-IgG and MOG-IgG biomarkers may suffer from visual, motor, and cognitive impairment due to inability of their neurons to function and relay information in a synchronized manner. Although AQP4-Ab IgG antibody is also expressed in peripheral tissues, such as kidney stomach and skeletal muscle, in NMOSD patients, those other organs are not affected by AQP4-Ab IgG antibody. A recent study shows that this occurs because the AQP4-Ab IgG receptor epitopes hold different supramolecular assemblies that account for low affinity of AQP4-IgG for its’ receptors in those tissues. This novel finding might explain specific targeting of CNS tissues, resulting in predominantly CNS abnormalities. Several recent publications document a potential role of soluble complement proteins in early oligodendrocyte injury in NMOSD patients. The complement cascade is activated following AQP4-IgG binding to astrocyte’s AQP4 epitope receptor, resulting in subsequent deposition of the complement MAC on the same or neighboring oligodendrocytes. The use of intravenous corticosteroids and/or plasmapheresis is two preventative measures to control sudden outbreaks for NMO patients. According to present literature, low-dose corticosteroid use is effective and reduces relapse rates in patients within a 1-year period. These steroid hormone derivatives also carry reduced inflammatory properties, induce leukocyte apoptosis, hinder granulocyte migration, minimize capillary permeability, and reduce relapse rates. For patients with acute crisis, plasmapheresis can be considered an alternative therapy. Combination therapy with immunosuppressors and plasmapheresis exhibits decreased anti-AQP4 antibody serum levels.

There are various options for treatment during remission on the market; however, selecting an appropriate treatment plan can be complicated. For this reason, choosing a first-line therapy is the focus of recent studies. Chemo-pharmaceuticals such as mycophenolate, cyclophosphamide, and methotrexate show certain therapeutic effects for plasma cell dyscrasia and immunosuppression. However, these medications should not be used as a monotherapy due to unreliable and variable effects. Dual and combination therapy with chemo-pharmaceuticals does show improvement in patient outcome. Examples include methotrexate in combination with oral corticosteroids resulting in disease stabilization and prednisone and azathioprine in reduction of relapse rate. The latter is also used as a first-line therapy for remission prevention. Only cyclosporine A, combined with oral corticosteroids, has induced remission in NMOSD patients.

An alternative therapy is rituximab, a selective monoclonal antibody that reduces serum CD20+ B lymphocytes, with effects lasting weeks due to its long half-life which include observed benefits such as reduced relapse rates and maintained or improved patients’ neurological health. Despite these claims, not all patients respond favorably to this medication, as several cases report relapse episodes after therapy initiation. This can happen due to a sudden increment of the anti-AQP4 antibodies expressed by the patients after a 2-week period.

Treatments against key cytokines involved in NMO pathogenesis has drawn considerable interest. IL-6 is a key factor in B-cell differentiation and antibody production. Tocilizumab is a humanized anti-interleukin 6 receptor antibody that has shown to reduce neuropathic pain and fatigue within NMOSD patients. TNF-alpha plays a critical role in neuro-inflammation linked to neurodegeneration and is regulated by the NF-kB pathway. Simultaneous stimulation of beta-adrenergic and TNF-alpha receptors has led to variable expression of certain NF-kB genes and stimulation of genes associated with IL-6. The NF-kB pathway has been shown to modulate chemokine, cytokine and adhesion-molecule

TREATMENT OF NEUROMYELITIS OPTICA

Identifying an effective therapy for NMO is founded upon a basic understanding of the biological mechanisms that lead to the disease. Recent studies postulate that relapse in NMO disease has an association with chronic stress and hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis. Consequently, during chronic stress or HPA axis overactivity, there is an overproduction of corticosteroids which causes the desensitization of glucocorticoid receptors in granular and lymphoid cells. Elevated levels of catecholamines increase the release of cytokines MMP-9, IFN-gamma, TNF-alpha, and IL-6, which are in turn responsible for blood–brain barrier damage and AQP4 antibody production. As a result, the entry of AQP4 antibodies into the brain becomes facilitated and disease is exacerbated. The main therapies for NMO target specific steps in this disease process; it entails maintaining the disease in remission and preventing sudden outbreaks of symptoms. Classic corticosteroid and immunosuppressant clinical studies have contributed to the understanding of NMO and lead to the development of novel therapy options. Treatment specifically focuses on diminishing inflammatory and/or autoimmune mechanisms that are characteristic of the disease. Monotherapy yields variable results and multiple compound therapy potentiates the effectiveness of the treatment. Current research focuses on targeting auto anti-AQP4 antibodies and their lymphoid mediated production.
expression, CNS inflammatory cell migration, and along with TNF-alpha, could prove to be a future target for site-directed therapies.\[^{275}\] Further research is needed into NF-kB function as a signaling mediator and as a possible facilitator of crosstalk between multiple signaling cascades in order to ensure effective therapy.\[^{275,183,251}\]

Presently, interferon beta and natalizumab are no longer used as treatment options due to exacerbating NMO relapses or symptoms.\[^{221,200}\] In recent years, new therapies are surfacing for NMO patients and a few have promising results, while others must be investigated further. Aquaporumab, a monoclonal NMO-derived antibody of high affinity to AQP4, is a prospective first-line treatment for relapses or acute and severe attacks.\[^{114}\] Eculizumab, a humanized monoclonal antibody, neutralizes the C5 in the complement cascade and appears to reduce attack frequency and stabilize the neurological health in patients.\[^{224}\] Finally, surgical intervention is the most novel and drastic approach for treating NMO. Recent studies have indicated that vascular hypoxia could play a role in NMO exacerbation.\[^{227}\] Omental transplantation could decrease stress, and future relapses, by revascularizing the hippocampus, temporal lobes, and the surrounding structures. This would normalize the activity of the HPA axis and reduce its effects on the immune system of the NMO patient.\[^{226}\]

### DIETARY SUPPLEMENTATION IN NEUROMYELITIS OPTICA

Diet and nutrition, as either a management paradigm or as possible factor in NMO pathogenesis, has been minimally investigated. Current, cutting edge research, though, is starting to break the surface in three important areas: Vitamin D and its’ regulatory role in the immune system; cholesterol and cholesterol metabolites as inflammatory regulators; and finally, aberrations to the gut microbiome as inducers of pro-inflammatory T-helper cells.

### Vitamin D

To date, there are no studies as to any palliative or curative efficacy of a vitamin D treatment in patients with NMO. MS research, though, has touched on the question and recent investigations into the effect of high-dose vitamin D therapies in reducing relapse rates are divided, some showing a promising reduction in relapse rates, while others are inconclusive.\[^{8,102,114,149,170}\]

As of 2016, there are six active large-scale studies into high-dose vitamin D treatment in reducing MS symptom severity and rate of relapse, with results pending.\[^{8}\] A single prospective case control study to date into a putative neuroprotective role for vitamin D against demyelination diseases showed the risk for MS significantly decreased with increasing levels of 25-hydroxyvitamin D in blood.\[^{188}\]

### Cholesterol

For its role as a precursor in myelination of neurons by both CNS oligodendrocytes and peripheral nervous system Schwann cells, cholesterol synthesis and homeostasis in glial cells are considered a valid area of interest in demyelinating pathophysiology.\[^{23,28,42}\] Recent studies hone in on specific hydroxycholesterol metabolites, such as 25 and 27 hydroxycholesterol, known control points in microglia inflammatory regulation.\[^{44,108}\] Studies do show that there is a correlation between distinct genetic variants in 25 hydroxycholesterol metabolism and NMO, as well as increased levels of both 25 and 27 hydroxycholesterols, both in NMO patients, and as markers of severity of acute relapse.\[^{44}\] Though such research does not imply that dietary cholesterol nor even systemic cholesterol homeostasis may have either protective or causative role in NMO pathology, it must be noted that dietary cholesterol has now begun to be a topic of research in MS.\[^{26,231}\]

### Gut microflora

One of the most interesting recent discoveries as to the actual pathogenesis of NMO may lie in the ubiquitous commensal flora of the human gut. Recent gut microbiome analyses of NMO patients show a marked overabundance \(C.\ perfringens\).\[^{151}\] The AQP-4 epitope that CD4+ T cells target in NMO is defined as a 10 residue sequence that shares 90% homology to a specific ATP Binding Cassette Transporter of \(C.\ perfringens\). Pro-inflammatory T-helper 17 (\(\text{Th}_{17}\)) cells from NMO patients do proliferate in response to this 10 residue peptide sequence.\[^{223}\] Induced upregulation of \(\text{Th}_{17}\) with ileal colonization of segmented filamentous bacteria increases susceptibility to autoimmune encephalomyelitis (EAE), an experimental model of MS.\[^{97,98,151}\] A logical sequitur to these findings is dietary modification or fecal transplantation to reduce pro-inflammatory effects of \(C.\ perfringens\) or as a treatment to avoid acute relapse. Dietary modifications could be avoidance of salt and long-chain fatty acids, both shown to be inducers of pro-inflammatory \(\text{Th}_{17}\) cells.\[^{98,297}\] Fecal transplantation, a treatment that is rapidly gaining acceptance worldwide, is already highly effective in treating recurrent \(\text{Clostridium difficile}\) infections in irritable bowel syndrome.\[^{183,202}\]

### SYMPTOM MANAGEMENT OF NEUROMYELITIS OPTICA

NMO is a challenging neurodegenerative disease whose long-term management strategy is confounded by the high prevalence of pain, urinary incontinence, loss of mobility, fatigue, and depression.\[^{60,45,69,225,247}\] Long-term management strategies in NMO are aimed at...
rehabilitation and recovery of any loss of mobility for the patient, as well as improvement in the patient’s quality of life via symptomatic treatment. The current physical rehabilitation strategies, as well as pharmacological therapies, employed for NMO patients are similar to those used for MS, as both diseases show varying rates and degrees of impairment to bladder and bowel function, limb weakness and impairment to movement, pain, and depression. 

**Mobility and ambulation**

Physical therapy, in conjunction with pharmacological symptomatic management, is effective in improving measures of quality of life, functionality, and independence. Cases studies highlighting functional blindness and advanced loss of ambulation do show increased functional independence measures (FIM) scores, but case studies show that such patients remain paraplegic and with no restoration of sigh. A basic challenge in rehabilitation therapy in both NMO and MS is fatigue, a common result of the pharmacological treatments, pain, sleep dysfunction, as well as the underlying nerve conduction disturbance. Aerobic exercise, with a gradually increasing duration, reduces fatigue and allows effective rehabilitation. Minimal impact aerobic exercise programs, aimed to reduce muscle wasting, slow muscle weakness, fatigue and depression, and even raise functional ambulation and FIM scores.

**Urinary function**

A recent study focusing on urinary dysfunction in NMO patients found detrusor-sphincter dyssynergia and detrusor overactivity, either alone or together, in more than half of the patients assessed. The dysfunction of urinary voiding shows a significant correlation to the generalized neurodegenerative progression of the disease. Similar to MS, NMO patients often suffer incontinence with or without urinary retention, dependent upon the location of the lesion. Cervical lesions damage both sympathetic and parasympathetic outflow tracts, while a parasympathetic loss predominates with lumbar damage. A review of antimuscarinics in the treatment of urinary urgency and incontinence determined solifenacin, oxybutynin, and propiverine to be most effective. Detrusor overactivity, causing increased urinary frequency, is managed with pelvic muscle contraction exercises and localized electric muscle stimulation. Intra-detrusor Botox® (onabotulinumtoxin A) injection is a very effective tri-annual intervention strategy to minimize incontinence, frequency, and urgency. Treatment of urinary retention is treated with cholinergic agonists, such as bethanechol, a pure muscarinic agonist. Newer, less lipophilic agents, such as tolterodine and trospium, are effective with less central side effects. Otherwise, urinary retention is alleviated with clean intermittent self-catheterization.

**Pain**

With a prevalence of up to 86%, more than twice as common in occurrence compared to MS, and up to three times more severe, pain is a great challenge for management of NMO patients. The pain manifests from both tonic muscle spasms as well as prolonged dysthesia and paresthesia of neuropathic pain. Current pain treatment commonly targets GABAergic agents, such as carbamazepine, baclofen and gabapentin, α2 agonists such as tizanidine, SNRIs, tricyclics, and traditional μ opioid agonists. Current research, however, is now targeting the underlying mechanisms of the neuropathic pain. For example, the cannabinoids are an interesting new drug target, given the role of local astrocyte-produced 2-arachidonoylglycerol (2-AG), a cannabinoid, in decreasing glutamatergic signaling and augmenting GABAergic signaling. Co-expressed molecules in Aquaporin 4 (AQP4) membrane micro-domains include excitatory amino acid transporter 2, which limits synaptic glutamatergic signaling by removing synaptic glutamate. This intrinsic control of glutamatergic signal is lost with antibody-mediated destruction of AQP4. Glutamatergic antagonists must also be mentioned, as low-dose ketamine and memantine are effective in multiple etiologies of neuropathic pain.

**Depression**

A recent study showed a direct positive correlation between the severity of depression in NMO and the degree of neuropathic pain reported by patients. Though the rates of cognitive impairment in MS and NMO are similar, the rate of recurrent depression and suicidal ideations are higher in NMO. Recent studies show that NMO patients suffer high rates of depression, similar to MS, the two greatest causal factors being pain and fatigue. Current NMO depression management is similar to that of MS: SNRIs, such as duloxetine and venlafaxine; SSRIs, such as citalopram and sertraline; atypical antidepressants, including mirtazapine and the tricyclic amitriptyline, are all used for pain management. Stimulants such as modafinil, effective in some autoimmune neurodegenerative cases, is effective to combat fatigue.

**SURVIVAL AND PROGNOSIS OF NEUROMYELITIS OPTICA**

The prognosis of NMO can be challenging. The disease has either a monophasic or relapsing nature. NMO relapse can serve as the main indicator for survival and prognosis. Other risk factors such as age of onset, genetics, gender, and ethnicity affect survival and prognosis.
long-term outcomes. Additionally, other preexisting autoimmune diseases can also exacerbate the effects of NMO. The factors that lead to a worse clinical outcome can be multifaceted.

The age of onset of NMO can severely affect the patient’s prognosis. The average age of onset for NMO is 39 years, but the disease can manifest in children and adults as well. Age correlates to the degree of NMO patients’ disability in cohort studies with AQP4 sero-positive patients. In a recent study, patients had a hazard ratio of 1.7 for disability when compared to a subject 10 years younger. Another study found that the onset of NMO in patients below the age of 30 serves as a protective factor while the onset in patients above the age of 50 has higher chances of developing clinically significant symptoms. On the other hand, monophasic NMO does present earlier, with average age of 27 years. Monophasic presents with constant relapses, a torpid progression, and aggressive behavior, with neurological disability and a poor prognosis.

The most important factor for survival and prognosis in NMO is relapse. Approximately 80% of patients with NMO have a relapse. 60% relapse within the first year, and 90% relapse 3 years later. Patients who experience worsening clinical prognosis tend to exhibit more than two relapses within the first 2 years of onset and a severe initial episode. The prognosis of patients with relapses is not favorable, most attacks are moderate or severe, remissions are not constant, and neurological incapacities accumulate with time.

Over 60% of patients will develop severe vision loss within the first two years of onset and a severe ambulatory disability within the first 5 years of the disease. The coexistence of an autoimmune disorder with NMO influences the long-term prognosis and is a portent for future relapse. Early identification reduces relapse rates and it is correlated with a better prognosis. Mortality rates are approximately 32% within the first 5 years; most of the cases are cervico-bulbar and exhibit a compromised respiratory capacity.

Gender can affect the severity of NMO prognosis. Males have a higher age of onset (48.7 vs. 41 years, P = 0.037), and though they show a higher incidence rate of isolated myelitis, males present with a milder degree of ON upon onset and are more likely to not suffer ON attacks. Although females are nine times more at risk for NMO compared to males, the severity of disease among women is comparably less. Females have a lower age of onset for NMO, giving a better prognosis overall and survival. Other factors, such as increased number of acute attacks within the first two years, show no significant results within various cohort studies.

CHARACTERISTICS OF PATIENTS IN PUERTO RICO WITH NEUROMYELITIS OPTICA

**Introduction**

Despite recent advancements in understanding and diagnosing NMO, there has never been an epidemiological study of NMO patients from PR specifically.

**Table 4: Characteristics of patients in Puerto Rico with neuromyelitis optica**

| Demographic information | Gender | Age range 26-63 | Age average 41 | Age of onset 15-59 | Average age of onset 35 | Antibodies to aquaporin-4 90% | Unable to work 90% Using walking aid 66% | Prior diagnosis with MS 22% |
|-------------------------|--------|----------------|----------------|-------------------|------------------------|---------------------------|----------------------------|--------------------------|
| **Environmental factors** |        |                |                |                   |                        |                           |                            |                          |
| Higher incident of Helicobacter pylori infection |        |                |                |                   |                        |                           |                            |                          |
| High exposure to active Clostridium perfringens |        |                |                |                   |                        |                           |                            |                          |
| Higher dietary intake of salty foods |        |                |                |                   |                        |                           |                            |                          |
| Vitamin D deficiency |        |                |                |                   |                        |                           |                            |                          |
| Smoking |        |                |                |                   |                        |                           |                            |                          |
| **Genetic factors** |        |                |                |                   |                        |                           |                            |                          |
| HLA-DRB1*03 |        |                |                |                   |                        |                           |                            |                          |
| **Most common initial symptoms (11-56%)** |        |                |                |                   |                        |                           |                            |                          |
| Sensory symptoms |        |                |                |                   |                        |                           |                            |                          |
| Migraine headache |        |                |                |                   |                        |                           |                            |                          |
| Decreased vision acuity |        |                |                |                   |                        |                           |                            |                          |
| Seizure |        |                |                |                   |                        |                           |                            |                          |
| Vomiting |        |                |                |                   |                        |                           |                            |                          |
| psychiatric problems |        |                |                |                   |                        |                           |                            |                          |
| **Comorbidities (11-33%)** |        |                |                |                   |                        |                           |                            |                          |
| Thyroid disorders |        |                |                |                   |                        |                           |                            |                          |
| Gastritis |        |                |                |                   |                        |                           |                            |                          |
| Allergy |        |                |                |                   |                        |                           |                            |                          |
| Asthma |        |                |                |                   |                        |                           |                            |                          |
| Seizure |        |                |                |                   |                        |                           |                            |                          |
| Anemia |        |                |                |                   |                        |                           |                            |                          |
| Hyperlipidemia |        |                |                |                   |                        |                           |                            |                          |
| Arthritis |        |                |                |                   |                        |                           |                            |                          |
| Osteopenia |        |                |                |                   |                        |                           |                            |                          |
| Bronchitis |        |                |                |                   |                        |                           |                            |                          |
| Scoliosis |        |                |                |                   |                        |                           |                            |                          |
| Immune thrombocytopenic purpura |        |                |                |                   |                        |                           |                            |                          |
| Rheumatoid arthritis |        |                |                |                   |                        |                           |                            |                          |

HLA: Human leukocyte antigen
For this study, we obtained the records of all NMO patients who visited Caribbean Neurological Center in PR. Table 4 provides a summary of the characteristic of these patients. There are nine NMO patients at the Neurological Center, all females aged from 26 to 63 years with average age of 41. The average age of disease onset was 35 years. For diagnosis, 90%, or eight out of nine patients, developed antibodies to aquaporin-4 (NMO-IgG or AQP4-Ab) which is a highly sensitive and specific NMO serum marker. Of the nine patients with NMO, 90% of patients reported that they are not able to work due to their medical limitations and 11% claimed to be totally disabled. Sixty-six percent of patients were using walking aid since they were no longer able to keep their balance when walking.

Environmental factors

Gastritis is one of the unique comorbidities found in Puerto Rican NMO patients. Multiple studies have found higher incidence and prevalence of stomach cancer in PR compared to non-Hispanic Whites populations in the United States. Contributing factors include higher H. pylori infection and high dietary intake of salty foods and/or N-nitroso compounds. One study done specifically in the Puerto Rican population found a statistically significant dose response for the index of salt intake and gastric cancer. Increased dietary salt intake is linked to higher prevalence of autoimmune diseases. Increased dietary salt can induce T-cell receptor to IL-23 signaling, a cytokine historically linked to multiple autoimmune diseases including NMO.

Whether NMO patients in PR have active C. perfringens bacteria or not is not captured in our data. However, in a study done by Pait et al., chemical and biological contaminants in the marine sediments of southwest of PR were recorded and analyzed. According to their result, the southwest region of PR, specifically Guanica Bay, has over 1700 colony forming units of C. perfringes per gram of sediment sample. C. perfringes usually exists in fecal pollution sources and its presence in water implies contamination of water by sewage or similar wastes, which could in turn be a risk factor for the development of NMO.

Despite conflicting evidence between populations, vitamin D deficiency could also be a risk factor for NMO illness. The population of PR is vitamin D deficient, with only 31.5% of the studied population having sufficient vitamin D levels. There are studies that analyzed the prevalence of vitamin D deficiency with influencing factors such as obesity among Puerto Ricans and concluded that individuals with a higher adiposity had a lower vitamin D status.

Smoking has been found as a most consistent nongenetic factor in different neurodegenerative diseases. Among our NMO patients in PR, only one patient out of nine had a smoking history. Her average number of relapse in 1 year was higher compared to other patients. In addition, at age 31, she had right eye blindness, severe chronic fibromyalgia, and neuropathic pain. Whether smoking contributed to the state of her NMO progression remains uncertain but we can conclude she presented with the most exacerbations in the study.

Genetic factors

HLA-DRB1*03 was also the most prevalent allele found in MS patients from PR. Among contributing factors, contributing factors include smoking, age of disease onset, and genetic factors such as obesity among Puerto Ricans and smoking, a smoking history. Her average number of relapse in 1 year was higher compared to other patients. In addition, at age 31, she had right eye blindness, severe chronic fibromyalgia, and neuropathic pain. Whether smoking contributed to the state of her NMO progression remains uncertain but we can conclude she presented with the most exacerbations in the study.

Symptoms

Sensory symptoms, loss of motor strength in extremities, migrane headache, decreased vision acuity, seizure, vomiting, and psychiatric problems are among the most common initial symptoms in NMO patients from PR. Two of the nine patients were previously diagnosed with progressive-relapsing multiple sclerosis before being diagnosed with NMO due to similarities of symptoms between the two disorders.

Comorbidities

Thyroid abnormalities were the most frequent comorbidities among NMO patients in PR. Two of the common autoimmune disorders among Puerto Rican NMO patients were immune thrombocytopenic purpura and rheumatoid arthritis.

In a study conducted by Ajmera et al., they found comorbidities among NMO patients in United States that were reported in ≥2% of patients. In comparison to their study, Puerto Rican NMO patients presented with some unique comorbidities that were not listed in the aforementioned study. These include allergy, asthma, seizure, gastritis, anemia, hyperlipidemia, arthritis, osteopenia, bronchitis, and scoliosis. The differences among comorbidities can be related to multiple factors such as ethnicity, environmental factors, and diet habits due to cultural differences.

Future studies measuring these factors in a broader range of NMO participants will be required to validate and to expand upon these results.

Survival and prognosis

The average onset age for Puerto Rican NMO patients was 35 ranging from 15 to 59 years old. The patient with older age of onset had more severe comorbidities compared to the younger ones. These included fibrocystic disease of breast, esophageal hiatus hernia, osteopenia, and osteoporosis. Whether these differences are as a result of late age of NMO onset or normal aging comorbidities needs to be further investigated.

More than half of Puerto Rican NMO patients had at least one relapse in 1-year period, which again is the most important factor for survival and prognosis. Long-term studies can chart these outcomes and capture prognostic data for future generations.
DISCUSSION

Even though according to the information we obtained that all the NMO patients from Caribbean Neurological Center were female, such a small prevalence of NMO and the lack of male patients suggest that a systemic collection and publication of NMO patients data and epidemiology could benefit the process of investigation, treatment innovation, and improvement of NMO within this population and worldwide.

CONCLUSION

Improving knowledge of NMO pathogenesis is critical in developing diagnostic methods for earlier detection and planning new effective treatments. Thus, an extensive understanding in a range of information regarding NMO epidemiology, environmental and genetic factors, molecular mechanism, symptoms, clinical differentiation, treatment, dietary supplementation, management, and survival and prognosis is essential. As of now, there is no treatment that completely cures the NMO and patients can face debilitating disabilities throughout the course of their disease. Multiple compound therapy including corticosteroid, immunosuppressant, monoclonal antibody, and plasmapheresis reduces the relapse rates and also decreases anti-AQP4 antibody serum levels in some cases.[236]

Although the underlying mechanism of NMO has already been elucidated, implicating predominantly the existence of (AQP4-IgG) antibodies in NMO patients, changes in ethnicity and environmental factors also show their pivotal role in variations of NMO clinical features and prognosis.

One of the main limitations of this study was our small sample size of NMO patients. This prevented us from performing any statistical analysis or hypothesis testing to establish comprehensive results. After reviewing all these patients’ information, our findings suggest a unique set of comorbidities among NMO patients in PR that were different compared to the NMO patients in United States. They also had higher female-to-male ratio with a wide range of age of onset from 15 to 59 years.

These differences could be associated with environmental and/or genetic factors that we discussed earlier in our study. They include higher incidents of gastritis, presence of HLA-DRB1 * 03 allele, higher exposure to C. perfringens, vitamin D deficiency, and higher daily intake of salt in diet. Some of these factors may be eliminated by reducing the exposures to the infectious agents and improvements in access to preventive and treatment care. Further research studies are certainly warranted to confirm the prevalence and epidemiology of NMO in PR and to understand the observed differences.

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Conflicts of interest
There are no conflicts of interest.

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