SNI

SURGICAL NEUROLOGY INTERNATIONAL

SNI: Inflammation

OPEN ACCESS

For entire Editorial Board visit : http://www.surgicalneurologyint.com

Editor:
Russell Blaylock, MD
Advanced Nutritional Concepts and Theoretical Neurosciences, Flowood, MS, USA

Review Article

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

Sara Zarei, James Eggert, Laura Franqui-Dominguez, Yonatan Carl, Fernando Boria, Marina Stukova, Alessandro Avila, Cristina Rubi[1], Angel Chinea[1]

San Juan Bautista School of Medicine, Caguas, [1]Caribbean Neurological Center, Guaynabo, Puerto Rico, USA

E-mail: *Sara Zarei - sara.zarei@channing.harvard.edu; James Eggert - jeggert@sanjuanbautista.edu; Laura Franqui Dominguez - lfranqui@sanjuanbautista.edu; Yonatan Carl - yonatanc@sanjuanbautista.edu; Fernando Boria - fernandobg@sanjuanbautista.edu; Marina Stukova - marinas@sanjuanbautista.edu; Alessandro Avila - alessandroa@sanjuanbautista.edu; Cristina Rubi - cristi_rubi2010@hotmail.com; Angel Chinea - achinea@me.com
*Corresponding author

Received: 12 July 18 Accepted: 21 August 18 Published: 03 December 18

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

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/sni.sni_224_18

Quick Response Code:

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]

How to cite this article: Zarei S, Eggert J, Franqui-Dominguez L, Carl Y, Boria F, Stukova M, *et al.* Comprehensive review of neuromyelitis optica and clinical characteristics of neuromyelitis optica patients in Puerto Rico. Surg Neurol Int 2018;9:242.
http://surgicalneurologyint.com/Comprehensive-review-of-neuromyelitis-optica-and-clinical-characteristics-of-neuromyelitis-optica-patients-in-Puerto-Rico/

In 2015, the International Panel for NMO Diagnosis proposed the unifying term of neuromyelitis optica spectrum disorders (NMOSD) 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.[289] 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.[69,116] With the discovery of AQP4 antibodies, the incidence of the disease started to be studied in a more accurate way.[154,206]

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.[71,204,264] 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.[162] In the United States, there is an estimated 4000–8000 patients (1–2% of formerly diagnosed MS patients).[170]

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).[58,70] 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.[214,182,204] 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.[52] Furthermore, multiethnic 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 life 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.[214,63,70,107,162,182,208] 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.[31,65,296] Due to the

high prevalence in females, some investigators suggest the possibility of hormones influencing the development of NMO.[214] 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.[40,87,120] 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.[303] In Japan, where the incidence of NMO is 3.42/100,000, *Helicobacter pylori* neutrophil activating protein increases the neutrophil infiltration in acute lesions of NMO patients.[155,182] 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.[136] 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.[117,136]

Clostridium perfringens (*C. perfringens*) is also found to be one of the most active bacteria in NMO patients microbiota.[55] Investigators suggest that the Epsilon toxin produced by *C. perfringes* causes blood–brain barrier damage facilitating the entrance of AQP4-IgG.[305] This mechanism is described in MS patients who showed a 10 times higher immunoreactivity to Epsilon toxin of *C. perfringes* Type A compared with healthy controls.[233]

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.[189]

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 (T_{reg}) function via increased interleukin 10, as well as suppression of interferon Y, interleukin 2, and, at least in-vitro, interleukin 4.[9,41,254,287] This increase in T_{reg} 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.[90,135,182] 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.[159]

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%, $P = 0.004$).[150] 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.[249]

Other

Determinant and protective factors like breastfeeding and daycare exposure are also reported in different populations for NMO patients.[70,82]

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.[181] The specific allele HLA-DRB1*03 presents a risk for NMO in the French population.[161] In Brazilian NMO-Ig-positive patients and Afro-Caribbean populations, HLA-DRB1 * 03 is found to be more common than in healthy controls.[64,34]

In France, no association is found between NMO patients and HLA-DR-DPB1*05:01; nevertheless, a different investigation found this allele in NMO patients of African-American and Latino population.[48,96] In the Han Chinese population, DRB1 * 1602 is found to be higher in NMO patients in comparison with MS patients; DRB1*0501 correlated with higher risk of NMO.[280]

Protective factors

In Asian populations, AQP4 Ig seropositive or seronegative HLA-DRB1*0901 is protective against NMO.[302] In Southern Han Chinese population, HLA-DRB1*0901 is less common than in healthy controls (P_{uncorr} = 0.022, OR: 0.194, 95% CI: 0.043–0.876).[280] In this population, reduced risk of NMO is associated with the polymorphism in CD58 with the haplotype HATTACGG.[186] Another protective effect on the risk for NMO is found in people with single nucleotide polymorphism (SNP) in CYP7A1 in chromosomes 8q11-q12.[127]

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.[288] Matiello *et al*. 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.[167]

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.[199]

Other genes associated with neuromyelitis optica

Genes involved in regulation of the autoimmune system and regulation processes are found in NMO patients with lesions.[239] In NMO AQP-4 seropositive Chinese patients, a higher frequency of polymorphism in interleukin 17 (IL-17) gene compared to healthy controls is observed.[283] 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.[281] Programmed death-1 (PD-1) receptor gene is associated with inflammatory and autoimmune diseases such as MS, rheumatoid arthritis, and allergic asthma.[66,224] 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.[17] Han Chinese population with polymorphisms of CD58 (haplotype TAGCCCAA) have a higher risk for NMO.[156]

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.[153,278] Pisani *et al*., found that AQP-4 antibodies bind to at least two different epitopes made of three extracellular loops which changes its conformation organizing it into a supramolecular structure known as the orthogonal array of particles.[218] CNS-derived human fetal astrocytes are found to react with the sera from NMO-IgG-positive patients resulting in natural killer cell degranulation, antibody-dependent cellular cytotoxicity destruction of astrocyte, complement-dependent attraction of granulocytes, and an increased permeability of the blood–brain barrier.[278] Sera from MS patients did not react with the fetal astrocytes.[278]

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.[299] 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.[251] 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.[251] Intracerebral injection of AQP4-IgG caused astrocyte damage, inflammation, deposition of activated complement, and demyelination in CD59−/− rats.[300] CD59+/+ rats showed minimal complement deposition and loss of AQP4 under the same treatment.[300] 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.[307] Human complement with NMO-IgG injected intrathecally between the L5 and L6-produced white matter lesions in the spinal cord.[307]

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.[270,289] 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.[51,161,290] Myelitis involvement classically involves more than three spinal cord segments.[163] Urinary dysfunction is common in patients with spinal cord lesions.[298] Sensory symptoms such as numbness, dysesthesia, pain, and tonic spasms are well documented and neuropathic pruitis and sudden sensineurial 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.[193] 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 AQP-4-positive patients.[95] Atypical manifestations can include atypical transient asymptomatic elevation of creatine kinase levels. In other brainstem, diencephalic or cerebral presentations, hypersomnia 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.[91,285] Psychology changes may be associated with NMOSD.[186] Cognitive changes have been seen in NMOSD patients including impairment, depression, and suicidal ideation.[30,86,277] 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.[104,105,108]

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.[14,121,261,269,295,122,128,129,173,191,223,225,260] 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.[186] 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.[94,129,142,143] 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.[128,131] Ethnicity must also be considered as most patients with ATM convert to MS within European populations, but not in Asian populations.[79,132,268]

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.[166,289] Other diseases, like inflammatory disease due to antibody myelin oligodendrocyte glycoprotein (MOG), present with isolated neuritis and fewer relapsing courses.[133]

NMOSD is commonly associated with autoimmune disorders.[76] 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 AQP4+; therefore, most CNS involvement is due to coexisting NMOSD rather than direct CNS involvement.[130,178,310] 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, AQP4-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.[48,152,169,192,219,265] 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.[219,294] A high prevalence of thyroid abnormalities is observed in NMOSD patients, which may be due to the AQP4 shown to be present in the thyroid tissue.[157]

Neuro Behçet's disease is a subset of Behçet's disease involving the CNS and can resemble longitudinally extensive transverse myelitis (LETM) of NMOSD.[7,20,39,89,118,149] 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.[56,118,6] Behçet's is similar to NMOSD with headache, a progressive disease course and requires treatment.[5,56,123,126,301] Gluten enteropathy, or celiac disease, is also studied but causation has not been shown in NMOSD.[61] 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.[75,196]

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.[22,74,89,115,144,241] AQP4-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.[38]

Similarly, sarcoidosis is a systemic granulomatous disease that can also involve the spinal cord and optic nerve resembling phenotypes of NMOSD.[234,256] Neurosarcoidosis can present with systemic involvements of sarcoid, but without the systemic symptoms, the clinical presentation can appear to be very similar to NMOSD.[73,304]

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.[274,93,111] 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.[24,197,210,252] Other infections that can mimic NMOSD include Epstein Barr virus,[11] herpes simplex virus,[190] cytomegalovirus,[267] human t-lymphocytic virus,[279] dengue fever,[147] lyme disease,[174] tuberculosis,[100] *Mycoplasma pneumoniae*,[80] and *Streptococcus pneumoniae*.[238]

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.[129]

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.[68] 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].[290] 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.[68] The newly revised criteria included the addition of specific NMOSD-IgG serology and an emphasis on longitudinally extensive spinal cord lesions [Table 2].[292] In 2015, the International Panel recently proposed the latest up-to-date NMOSD diagnostic criteria for NMOSD diagnosis (IPND).[289] IPND has further subdivided NMOSD diagnosis based on a patient's respective laboratory IgG seropositive or seronegative status [Table 3].[289] Yet in clinical setting, both comprehensive medical history and specific patient symptom evaluations are still the crucial first steps in diagnosing NMOSD.[269] Consequently, detailed physical

Table 1: Neuromyelitis Optica Spectrum Disorders Diagnostic Criteria, Wingerchuk *et al*.[290]

Diagnosis requires all absolute criteria and one major supportive criterion or two minor supportive criteria
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/mm^3 or ≥5 neutrophils/mm^3
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

MS: Multiple sclerosis; CSF: Cerebrospinal fluid; WBC: White blood cell; MRI: Magnetic resonance imaging

Table 2: Neuromyelitis Optica Spectrum Disorders Revised Diagnostic Criteria, Wingerchuk *et al*.[292]

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

NMOSD: Neuromyelitis optica spectrum disorders; MRI: Magnetic resonance imaging; NMO: Neuromyelitis optica

and neurological examination is essential to distinguish NMO from NMOSD-mimics, including but not limited to MS, ADEM, idiopathic ATM, sarcoidosis, and other disorders.[131] 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.

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.[146] 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.[67] However, if the lesions were present, imaging scan will reveal subcortical lesions without central veins.[137] The most common sites for abnormal brain lesions are brainstem and cerebellum, followed by area postrema, thalamus, hypothalamus, corpus collosum, periependymal-third ventricle, corticospinal tract, and finally, the hemispheric white matter.[43] In addition, vomiting in NMOSD patients demonstrates association with corresponding lesions in brainstem medulla.[289] While not visible on weighted-T1 MRI, NMOSD lesion abnormalities will display cerebral T2-/FLAIR hyperintensities in 60% of the patients.[168,220]

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.[236] Also, distinguishable diagnostic NMOSD imaging sequences include bilateral optic nerve lesions with consequent extension into optic chiasm.[108] In addition, in patients presenting with acute ON, there is a presence of enhanced and diffused T2-weighted orbital MRI signal.[289]

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.[228] 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).[165] 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.[198] 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.[165,198] In NMOSD patients, acute single ON attack causes more damage to pRNFL and GCIPL layers that can be detected via OCT.[146] Currently, OCT is widely used to measure NMOSD disease progression course, as well as outcome response to NMOSD neuroprotective therapies.[269]

Neuromyelitis optica spectrum disorder spinal cord lesion MRI

The hallmark of NMOSD is acute myelitis, which is associated with acute continuous LETM lesion patterns that are detected via T2-weighted sagittal spinal MRI.[289] NMOSD lesions are usually centrally located and cover three or more vertebral segments.[49] Previous research has demonstrated that those lesions often involve swelling of a gray matter of the spinal cord with

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

cervical lesion extension to the brainstem.[146] Chronic and older NMOSD spinal cord lesions are characterized by patchy appearance with longitudinally extensive spinal cord atrophy.[146] In comparison, MS attacks tend to be less severe with MS patients displaying patchy lesions of spinal cord MRI that are rarely extend over one vertebral segment and are often located peripherally.[13,146]

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/mm^3), high neutrophil granulocyte count, and presence of eosinophils.[129] Presence of those cell types in NMOSD CSF is supportive in distinguishing NMOSD from MS.[269] As many as 30% of the patients may also present with CSF oligoclonal bands.[289] 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.[271] 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.[32] 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.[160] 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

are measured quantitatively by ELISA testing; however, NMOSD disease course and progression is independent of the titer size.[124] NMOSD patients with low titers have the same disease course and progression as patients with a high titer.[124] 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.[284] 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.[77] 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.[232] This novel finding might explain specific targeting of CNS tissues, resulting in predominantly CNS abnormalities.[232] Several recent publications document a potential role of soluble complement proteins in early oligodendrocyte injury in NMOSD patients.[266] 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.[266]

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.[253] 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.[81,158,253] 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.[59,216] As a result, the entry of AQP4 antibodies into the brain becomes facilitated and disease is exacerbated.[59,216] 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.[286] 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.[29,171,184] Current research focuses on targeting auto anti-AQP4 antibodies and their lymphoid mediated production.[134]

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.[286] These steroid hormone derivatives also carry reduced inflammatory properties, induce leukocyte apoptosis, hinder granulocyte migration, minimize capillary permeability, and reduce relapse rates.[29,134,171] 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.[171,242,289]

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.[27] However, these medications should not be used as a monotherapy due to unreliable and variable effects.[184] Dual and combination therapy with chemopharmaceuticals does show improvement in patient outcome.[171,184] Examples include methotrexate in combination with oral corticosteroids resulting in disease stabilization,[171] and prednisone and azathioprine in reduction of relapse rate.[29,53,138] The latter is also used as a first-line therapy for remission prevention. Only cyclosporine A, combined with oral corticosteroids, has induced remission in NMO patients.[138]

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.[54,212] Despite these claims, not all patients respond favorably to this medication, as several cases report relapse episodes after therapy initiation.[171,212] This can happen due to a sudden increment of the anti-AQP4 antibodies expressed by the patients after a 2-week period.[171]

Therapy against key cytokines involved in NMO pathogenesis has drawn considerable interest. IL-6 is a key factor in B-cell differentiation and antibody production.[263] Tocilizumab is a humanized anti-interleukin 6 receptor antibody that has shown to reduce neuropathic pain and fatigue within NMO patients.[15] TNF-alpha plays a critical role in neuro-inflammation linked to neurodegeneration and is regulated by the NF-kB pathway.[185] 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.[255] The NF-κB pathway has been shown to modulate chemokine, cytokine and adhesion-molecule

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.[275,185,255]

Presently, interferon beta and natalizumab are no longer used as treatment options due to exacerbating NMO relapses or symptoms.[221,209] 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.[134] 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.[221] 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.[8,102,114,148,176] 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[235] and peripheral nervous system Schwann cells,[78] 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.[44,103] 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.[28,235]

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*.[55] 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*.[305] Pro-inflammatory T-helper 17 (Th_{17}) cells from NMO patients do proliferate in response to this 10 residue peptide sequence.[273] Induced upregulation of 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 Th_{17}.[98,297] Fecal transplantation, a treatment that is rapidly gaining acceptance worldwide, is already highly effective in treating recurrent *Clostridium difficile* infections in irritable bowel syndrome.[83,202]

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.[125] 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.[195]

Mobility and ambulation

Physical therapy, in conjunction with pharmacological symptomatic management, is effective in improving measures of quality of life, functionality, and independence.[69,247] 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 t.[195,240] 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.[34] Aerobic exercise, with a gradually increasing duration, reduces fatigue and allows effective rehabilitation.[215] Minimal impact aerobic exercise programs, aimed to reduce muscle wasting, slow muscle weakness, fatigue and depression, and even raise functional ambulation and FIM scores.[35,215,240]

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.[59] The dysfunction of urinary voiding shows a significant correlation to the generalized neurodegenerative progression of the disease.[60] 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.[45,50,175] A review of antimuscarinics in the treatment of urinary urgency and incontinence determined solifenacin, oxybutynin, and propiverine to be most effective.[35] Detrusor overactivity, causing increased urinary frequency, is managed with pelvic muscle contraction exercises and localized electric muscle stimulation.[50,205,213,273] Intra-detrusor Botox® (onabotulinumtoxin A) injection is a very effective tri-annual intervention strategy to minimize incontinence, frequency, and urgency.[50,125,172,213] Treatment of urinary retention is treated with cholinergic agonists, such as bethanechol, a pure muscarinic agonist.[19,125] Newer, less lipophilic agents, such as tolterodine and trospium, are effective with less central side effects.[119] Otherwise, urinary retention is alleviated with clean intermittent self-catheterization.[119,125]

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.[33,225,309] The pain manifests from both tonic muscle spasms as well as prolonged dysthesia and paresthesia of neuropathic pain.[33,309] Current pain treatment commonly targets GABAergic agents, such as carbamazepine, baclofen and gabapentin, α_2 agonists such as tizanidine, SNRIs, tricyclics, and traditional μ opioid agonists.[125] Current research, however, is now targeting the underlying mechanisms of the neuropathic pain.[33,225,309] 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.[211,231] 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.[33,88] This intrinsic control of glutamatergic signal is lost with antibody-mediated destruction of AQ4.[88] Glutamatergic antagonists must also be mentioned, as low-dose ketamine and memantine are effective in multiple etiologies of neuropathic pain.[2,33,237]

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.[45,85,186,203] Though the rates of cognitive impairment in MS and NMO are similar, the rate of recurrent depression and suicidal ideations are higher in NMO.[45,85,186] Recent studies show that NMO patients suffer high rates of depression, similar to MS, the two greatest causal factors being pain and fatigue.[45] 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 triclyclic amitriptyline, are all used for pain management.[45,203] Stimulants such as modafinil, effective in some autoimmune neurodegenerative cases, is effective to combat fatigue.[125,246]

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.[290,292] Other risk factors such as age of onset, genetics, gender, and ethnicity affect

long-term outcomes. Additionally, other preexisting autoimmune diseases can also exacerbate the effects of NMO.[48,171,243,296] 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.[25,244] Age correlates to the degree of NMO patients' disability in cohort studies with AQP4 sero-positive patients.[292] In a recent study, patients had a hazard ratio of 1.7 for disability when compared to a subject 10 years younger.[244] 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.[99] 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.[293]

The most important factor for survival and prognosis in NMO is relapse.[99,164,222,292,294] Approximately 80% of patients with NMO have a relapse,[291] 60% relapse within the first year, and 90% relapse 3 years later.[290] 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.[291] 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.[99]

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.[222] The coexistence of an autoimmune disorder with NMO influences the long-term prognosis and is a portent for future relapse.[164] Early identification reduces relapse rates and it is correlated with a better prognosis.[164] Mortality rates are approximately 32% within the first 5 years; most of the cases are cervico-bulbar and exhibit a compromised respiratory capacity.[222]

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.[164] Although females are nine times more at risk for NMO compared to males,[62] 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.[99,244,62,293] Other factors, such as increased number of acute attacks within the first two years, show no significant results within various cohort studies.[244,292]

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	100% female		
Age range	26-63	Age average	41
Age of onset	15-59	Average age of onset	35
Antibodies to aquapotin-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 patents. 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 patents 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.[300,217] Contributing factors include higher H. pylori infection and high dietary intake of salty foods and/or *N*-nitroso compounds.[101] One study done specifically in the Puerto Rican population found a statistically significant dose response for the index of salt intake and gastric cancer.[194] Increased dietary salt intake is linked to higher prevalence of autoimmune diseases. Increased dietary salt can induce T-cell reception to IL-23 signaling, a cytokine historically linked to multiple autoimmune diseases including NMO.[140,26]

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.[201] *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.[259] 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.[229]

Smoking has been found as a most consistent nongenetic factor in different neurodegenerative diseases.[306] 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.[180]

Symptoms

Sensory symptoms, loss of motor strength in extremities, migraine 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.[3] 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 sever comorbidities compared to the younger ones. These included fibrocystic disease of breast, esophageal hiatus hernia, osteopenia, and osteoporosis. Whether these differences are as the 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.[286]

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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Abkur TM, Foran E, Kearney H, Harkin G, Byrnes V, Lynch J, *et al.* Neuromyelitis optica presenting as intractable vomiting and hyperCKaemia. J Neurol 2016;263:171-3.
2. Aiyer R, Mehta N, Gungor S, Gulati A. A systematic review of NMDA receptor antagonists for treatment of neuropathic pain in clinical practice. Clin J Pain 2018;34:450-67.
3. Ajmera MR, Boscoe A, Mauskopf J, Candrilli SD, Levy M. Evaluation of comorbidities and health care resource use among patients with highly active neuromyelitis optica. J Neurol Sci 2018;384:96-103.
4. Akaishi T, Takahashi T, Nakashima I. Chloride imbalance between serum and CSF in the acute phase of neuromyelitis optica. J Neuroimmunol 2018;315:45-9.
5. Akman-Demir G, Serdaroglu P, Tasçi B. Clinical patterns of neurological involvement in Behçet's disease: Evaluation of 200 patients. The neuro-Behçet study group. Brain 1999;122(Pt 11):2171-82.
6. Al Sawaf A, Berger JR. Longitudinally extensive transverse myelitis suspected for isolated neuro-Behçet: A diagnostic conundrum. Mult Scler Relat Disord 2015;4:395-9.
7. Al-Araji A, Kidd DP. Neuro-Behçet's disease: Epidemiology, clinical characteristics, and management. Lancet Neurol 2009;8:192-204.
8. Alharbi FM. Update in Vitamin D and multiple sclerosis. Neurosciences (Riyadh) 2015;20:329-35.
9. Allen AC, Kelly S, Basdeo SA, Kinsella K, Mulready KJ, Mills KH, *et al.* A pilot study of the immunological effects of high-dose Vitamin D in healthy volunteers. Mult Scler 2012;18:1797-800.
10. Alvarenga MP, Schimidt S, Alvarenga RP. Epidemiology of neuromyelitis optica in Latin America. Mult Scler J Exp Transl Clin 2017;3:2055217317730098.
11. Amaral DM, Parreira T, Sampaio M. Longitudinally extensive transverse myelitis and meningitis due to a rare infectious cause. BMJ Case Rep 2015;2015. pii: Bcr2015211761.
12. Amirjamshidi A, Abbassioun K, Parsa K. Hiccup and neurosurgeons: A report of 4 rare dorsal medullary compressive pathologies and review of the literature. Surg Neurol 2007;67:395-402.
13. Anadure R, Narayanan CS, Varadraj G. Recurrent longitudinally extensive myelitis and aquaporin-4 seronegativity – The expanding spectrum of neuromyelitis optica. J Clin Diagn Res 2017;11:OD05-7.
14. Apiwattanakul M, Popescu BF, Matiello M, Weinshenker BG, Lucchinetti CF, Lennon VA, *et al.* Intractable vomiting as the initial presentation of neuromyelitis optica. Ann Neurol 2010;68:757-61.
15. Araki M, Matsuoka T, Miyamoto K, Kusunoki S, Okamoto T, Murata M, *et al.* Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica: A pilot study. Neurology 2014;82:1302-6.
16. Asgari N, Lillevang ST, Skejoe HP, Falah M, Stenager E, Kyvik KO, *et al.* A population-based study of neuromyelitis optica in Caucasians. Neurology 2011;76:1589-95.
17. Asgari N, Nielsen C, Stenager E, Kyvik KO, Lillevang ST. HLA, PTPN22 and PD-1 associations as markers of autoimmunity in neuromyelitis optica. Mult Scler 2012;18:23-30.
18. Ashtari F, Safaei A, Shaygannejad V, Najafi MA, Vesal S. Neuromyelitis optica spectrum disease characteristics in Isfahan, Iran: A cross-sectional study. J Res Med Sci 2017;22:41.
19. Awad SA, Wilson JW, Fenemore J, Kiruluta HG. Dysfunction of the detrusor and urethra in multiple sclerosis: The role of drug therapy. Can J Surg 1982;25:259-62.
20. Azizlerli G, Köse AA, Sarica R, Gül A, Tutkun IT, Kulaç M, *et al.* Prevalence

of Behçet's disease in Istanbul, Turkey. Int J Dermatol 2003;42:803-6.
21. Baba T, Nakashima I, Kanbayashi T, Konno M, Takahashi T, Fujihara K, *et al.* Narcolepsy as an initial manifestation of neuromyelitis optica with anti-aquaporin-4 antibody. J Neurol 2009;256:287-8.
22. Baehring JM, Hochberg FH, Betensky RA, Longtine J, Sklar J. Immunoglobulin gene rearrangement analysis in cerebrospinal fluid of patients with lymphoproliferative processes. J Neurol Sci 2006;247:208-16.
23. Baker RW, Thompson RH, Zilkha KJ. Serum fatty acids in multiple sclerosis subject age (yr.) diagnosis. J Neurol Neurosurg Psychiat 1964;27:5.
24. Bandettini di Poggio M, Primavera A, Capello E, Bandini F, Mazzarello G, Viscoli C, *et al.* A case of secondary syphilis presenting as optic neuritis. Neurol Sci 2010;31:365-7.
25. Barbieri F, Buscaino GA. Neuromyelitis optica in the elderly. Acta Neurol (Napoli) 1989;11:247-51.
26. Barros PO, Cassano T, Hygino J, Ferreira TB, Centurião N, Kasahara TM, *et al.* Prediction of disease severity in neuromyelitis optica by the levels of interleukin (IL)-6 produced during remission phase. Clin Exp Immunol 2016;183:480-9.
27. Ben-Ari ET. Dual purpose: Some cancer therapies used to treat autoimmune diseases. J Natl Cancer Inst 2004;96:577-9.
28. Berghoff SA, Gerndt N, Winchenbach J, Stumpf SK, Hosang L, Odoardi F, *et al.* Dietary cholesterol promotes repair of demyelinated lesions in the adult brain. Nat Commun 2017;8:14241.
29. Bichuetti DB, Lobato de Oliveira EM, Oliveira DM, Amorin de Souza N, Gabbai AA. Neuromyelitis optica treatment: Analysis of 36 patients. Arch Neurol 2010;67:1131-6.
30. Blanc F, Noblet V, Jung B, Rousseau F, Renard F, Bourre B, *et al.* White matter atrophy and cognitive dysfunctions in neuromyelitis optica. PLoS One 2012;7:e33878.
31. Boström I, Stawiarz L, Landtblom AM. Sex ratio of multiple sclerosis in the national swedish MS register (SMSreg). Mult Scler 2013;19:46-52.
32. Bouzar M, Daoudi S, Hattab S, Bouzar AA, Deiva K, Wildemann B, *et al.* Neuromyelitis optica spectrum disorders with antibodies to myelin oligodendrocyte glycoprotein or aquaporin-4: Clinical and paraclinical characteristics in Algerian patients. J Neurol Sci 2017;381:240-4.
33. Bradl M, Kanamori Y, Nakashima I, Misu T, Fujihara K, Lassmann H, *et al.* Pain in neuromyelitis optica – Prevalence, pathogenesis and therapy. Nat Rev Neurol 2014;10:529-36.
34. Brum DG, Barreira AA, dos Santos AC, Kaimen-Maciel DR, Matiello M, Costa RM, *et al.* HLA-DRB association in neuromyelitis optica is different from that observed in multiple sclerosis. Mult Scler 2010;16:21-9.
35. Burks JS, Bigley GK, Hill HH. Rehabilitation challenges in multiple sclerosis. Ann Indian Acad Neurol 2009;12:296-306.
36. Buser N, Ivic S, Kessler TM, Kessels AG, Bachmann LM. Efficacy and adverse events of antimuscarinics for treating overactive bladder: Network meta-analyses. Eur Urol 2012;62:1040-60.
37. Cabrera-Gómez JA, Kurtzke JF, González-Quevedo A, Lara-Rodríguez R. An epidemiological study of neuromyelitis optica in Cuba. J Neurol 2009;256:35-44.
38. Cai G, He D, Chu L, Dai Q, Xu Z, Zhang Y, *et al.* Paraneoplastic neuromyelitis optica spectrum disorders: Three new cases and a review of the literature. Int J Neurosci 2016;126:660-8.
39. Calamia KT, Wilson FC, Icen M, Crowson CS, Gabriel SE, Kremers HM, *et al.* Epidemiology and clinical characteristics of Behçet's disease in the US: A population-based study. Arthritis Rheum 2009;61:600-4.
40. Cantorna MT, Mahon BD. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. Exp Biol Med (Maywood) 2004;229:1136-42.
41. Cantorna MT, Snyder L, Lin YD, Yang L. Vitamin D and 1,25(OH)2D regulation of T cells. Nutrients 2015;7:3011-21.
42. Cantuti-Castelvetri L, Fitzner D, Bosch-Queralt M, Weil MT, Su M, Sen P, *et al.* Defective cholesterol clearance limits remyelination in the aged central nervous system. Science 2018;359:684-8.
43. Carnero Contentti E, Daccach Marques V, Soto de Castillo I, Tkachuk V, Antunes Barreira A, Armas E, *et al.* Frequency of brain MRI abnormalities in neuromyelitis optica spectrum disorder at presentation: A cohort of Latin American patients. Mult Scler Relat Disord 2018;19:73-8.
44. Cha E, Lee KM, Park KD, Park KS, Lee KW, Kim SM, *et al.* Hydroxycholesterol levels in the serum and cerebrospinal fluid of patients with neuromyelitis optica revealed by LC-ag+CIS/MS/MS and LC-ESI/MS/MS with picolinic derivatization: Increased levels and association with disability during acute attack. PLoS One 2016;11:e0167819.
45. Chavarro VS, Mealy MA, Simpson A, Lacheta A, Pache F, Ruprecht K, *et al.* Insufficient treatment of severe depression in neuromyelitis optica spectrum disorder. Neurol Neuroimmunol Neuroinflamm 2016;3:e286.
46. Chitnis T, Ness J, Krupp L, Waubant E, Hunt T, Olsen CS, *et al.* Clinical features of neuromyelitis optica in children: US network of pediatric MS centers report. Neurology 2016;86:245-52.
47. Collongues N, de Seze J. Current and future treatment approaches for neuromyelitis optica. Ther Adv Neurol Disord 2011;4:111-21.
48. Collongues N, Marignier R, Zéphir H, Papeix C, Blanc F, Ritleng C, *et al.* Neuromyelitis optica in France: A multicenter study of 125 patients. Neurology 2010;74:736-42.
49. Combes AJE, Matthews L, Lee JS, Li DKB, Carruthers R, Traboulsee AL, *et al.* Cervical cord myelin water imaging shows degenerative changes over one year in multiple sclerosis but not neuromyelitis optica spectrum disorder. Neuroimage Clin 2017;16:17-22.
50. Corcos J. A urological challenge: Voiding dysfunction in multiple sclerosis. Can Urol Assoc J 2013;7:S181-2.
51. Cornelio DB, Braga RP, Rosa MW, Ayub AC. Devic's neuromyelitis optica and pregnancy: Distinction from multiple sclerosis is essential. Arch Gynecol Obstet 2009;280:475-7.
52. Cossburn M, Tackley G, Baker K, Ingram G, Burtonwood M, Malik G, *et al.* The prevalence of neuromyelitis optica in South East wales. Eur J Neurol 2012;19:655-9.
53. Costanzi C, Matiello M, Lucchinetti CF, Weinshenker BG, Pittock SJ, Mandrekar J, *et al.* Azathioprine: Tolerability, efficacy, and predictors of benefit in neuromyelitis optica. Neurology 2011;77:659-66.
54. Cree BA, Lamb S, Morgan K, Chen A, Waubant E, Genain C, *et al.* An open label study of the effects of rituximab in neuromyelitis optica. Neurology 2005;64:1270-2.
55. Cree BA, Spencer CM, Varrin-Doyer M, Baranzini SE, Zamvil SS. Gut microbiome analysis in neuromyelitis optica reveals overabundance of *Clostridium perfringens*. Ann Neurol 2016;80:443-7.
56. Criteria for diagnosis of Behçet's disease. International study group for Behçet's disease. Lancet 1990;335:1078-80.
57. Cruz-Herranz A, Sagan SA, Sobel RA, Green AJ, Zamvil SS. T cells targeting neuromyelitis optica autoantigen aquaporin-4 cause paralysis and visual system injury. J Nat Sci 2017;3. pii: e358.
58. Daoudi S, Bouzar M. Neuromyelitis optica spectrum disorders in Algeria: A preliminary study in the region of Tizi Ouzou. Mult Scler Relat Disord 2016;6:37-40.
59. de Bie J, Lim CK, Guillemin GJ. Progesterone alters kynurenine pathway activation in IFN-γ-activated macrophages – Relevance for neuroinflammatory diseases. Int J Tryptophan Res 2016;9:89-93.
60. de Carvalho FL, Gomes CM, Apostolos-Pereira SL, Bessa J Jr., Pinheiro M, Marchiori PE, *et al.* Voiding dysfunction in patients with neuromyelitis optica spectrum disorders. Neurourol Urodyn 2016;35:39-43.
61. de Oliveira P, de Carvalho DR, Brandi IV, Pratesi R. Serological prevalence of celiac disease in Brazilian population of multiple sclerosis, neuromyelitis optica and myelitis. Mult Scler Relat Disord 2016;9:125-8.
62. de Seze J, Lebrun C, Stojkovic T, Ferriby D, Chatel M, Vermersch P, *et al.* Is Devic's neuromyelitis optica a separate disease? A comparative study with multiple sclerosis. Mult Scler 2003;9:521-5.
63. Derle E, Güneş HN, Konuşkan B, Tuncer-Kurne A. Neuromyelitis optica in children: A review of the literature. Turk J Pediatr 2014;56:573-80.
64. Deschamps R, Paturel L, Jeannin S, Chausson N, Olindo S, Béra O, *et al.* Different HLA class II (DRB1 and DQB1) alleles determine either susceptibility or resistance to NMO and multiple sclerosis among the French Afro-Caribbean population. Mult Scler 2011;17:24-31.
65. Dilokthornsakul P, Valuck RJ, Nair KV, Corboy JR, Allen RR, Campbell JD, *et al.* Multiple sclerosis prevalence in the united states commercially insured population. Neurology 2016;86:1014-21.
66. Dmitrieva-Zdorova EV, Gabaeva MV, Seregin YA, Bodoev NV, Voronko OE. PDCD1 PD-1.3 polymorphism and allergic bronchial asthma in Russian and buryat patients. J Asthma 2017;54:46-52.
67. Downer JJ, Leite MI, Carter R, Palace J, Küker W, Quaghebeur G, *et al.*

Diagnosis of neuromyelitis optica (NMO) spectrum disorders: Is MRI obsolete? Neuroradiology 2012;54:279-85.
68. Drori T, Chapman J. Diagnosis and classification of neuromyelitis optica (Devic's syndrome). Autoimmun Rev 2014;13:531-3.
69. Eaneff S, Wang V, Hanger M, Levy M, Mealy MA, Brandt AU, *et al.* Patient perspectives on neuromyelitis optica spectrum disorders: Data from the patientsLikeMe online community. Mult Scler Relat Disord 2017;17:116-22.
70. Eskandarieh S, Nedjat S, Abdollahpour I, Moghadasi AN, Azimi AR, Sahraian MA, *et al.* Comparing epidemiology and baseline characteristic of multiple sclerosis and neuromyelitis optica: A case-control study. Mult Scler Relat Disord 2017;12:39-43.
71. Etemadifar M, Nasr Z, Khalili B, Taherioun M, Vosoughi R. Epidemiology of neuromyelitis optica in the world: A systematic review and meta-analysis. Mult Scler Int 2015;2015:174720.
72. Felix CM, Levin MH, Verkman AS. Complement-independent retinal pathology produced by intravitreal injection of neuromyelitis optica immunoglobulin G. J Neuroinflammation 2016;13:275.
73. Flanagan EP, Kaufmann TJ, Krecke KN, Aksamit AJ, Pittock SJ, Keegan BM, *et al.* Discriminating long myelitis of neuromyelitis optica from sarcoidosis. Ann Neurol 2016;79:437-47.
74. Flanagan EP, O'Neill BP, Porter AB, Lanzino G, Haberman TM, Keegan BM, *et al.* Primary intramedullary spinal cord lymphoma. Neurology 2011;77:784-91.
75. Fragoso YD, Adoni T, Bichuetti DB, Brooks JB, Ferreira ML, Oliveira EM, *et al.* Neuromyelitis optica and pregnancy. J Neurol 2013;260:2614-9.
76. Freitas E, Guimarães J. Neuromyelitis optica spectrum disorders associated with other autoimmune diseases. Rheumatol Int 2015;35:243-53.
77. Frigeri A, Gropper MA, Umenishi F, Kawashima M, Brown D, Verkman AS, *et al.* Localization of MIWC and GLIP water channel homologs in neuromuscular, epithelial and glandular tissues. J Cell Sci 1995;108(Pt 9):2993-3002.
78. Fu Q, Goodrum JF, Hayes C, Hostettler JD, Toews AD, Morell P, *et al.* Control of cholesterol biosynthesis in Schwann cells. J Neurochem 1998;71:549-55.
79. Gajofatto A, Monaco S, Fiorini M, Zanusso G, Vedovello M, Rossi F, *et al.* Assessment of outcome predictors in first-episode acute myelitis: A retrospective study of 53 cases. Arch Neurol 2010;67:724-30.
80. Gebhardt A, Buehler R, Wiest R, Tewald F, Sellner J, Humpert S, *et al.* Mycoplasma pneumonia as a cause of neuromyelitis optica? J Neurol 2008;255:1268-9.
81. Gouin JP, Hantsoo L, Kiecolt-Glaser JK. Immune dysregulation and chronic stress among older adults: A review. Neuroimmunomodulation 2008;15:251-9.
82. Graves J, Grandhe S, Weinfurtner K, Krupp L, Belman A, Chitnis T, *et al.* Protective environmental factors for neuromyelitis optica. Neurology 2014;83:1923-9.
83. Halkjær SI, Boolsen AW, Günther S, Christensen AH, Petersen AM. Can fecal microbiota transplantation cure irritable bowel syndrome? World J Gastroenterol 2017;23:4112-20.
84. Hall LM, Kimlin MG, Aronov PA, Hammock BD, Slusser JR, Woodhouse LR, *et al.* Vitamin D intake needed to maintain target serum 25-hydroxyvitamin D concentrations in participants with low sun exposure and dark skin pigmentation is substantially higher than current recommendations. J Nutr 2010;140:542-50.
85. He D, Chen X, Zhao D, Zhou H. Cognitive function, depression, fatigue, and activities of daily living in patients with neuromyelitis optica after acute relapse. Int J Neurosci 2011;121:677-83.
86. He D, Wu Q, Chen X, Zhao D, Gong Q, Zhou H, *et al.* Cognitive impairment and whole brain diffusion in patients with neuromyelitis optica after acute relapse. Brain Cogn 2011;77:80-8.
87. Hemminki K, Li X, Sundquist J, Sundquist K. The epidemiology of graves' disease: Evidence of a genetic and an environmental contribution. J Autoimmun 2010;34:J307-13.
88. Hinson SR, Roemer SF, Lucchinetti CF, Fryer JP, Kryzer TJ, Chamberlain JL, *et al.* Aquaporin-4-binding autoantibodies in patients with neuromyelitis optica impair glutamate transport by down-regulating EAAT2. J Exp Med 2008;205:2473-81.
89. Hoang-Xuan K, Bessell E, Bromberg J, Hottinger AF, Preusser M, Rudà R, *et al.* Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: Guidelines from the European association for neuro-oncology. Lancet Oncol 2015;16:e322-32.
90. Houzen H, Niino M, Hirotani M, Fukazawa T, Kikuchi S, Tanaka K, *et al.* Increased prevalence, incidence, and female predominance of multiple sclerosis in Northern Japan. J Neurol Sci 2012;323:117-22.
91. Hsu CL, Yeh JH, Lau CI. Persistent hyperthermia in a patient with aquaporin-4-antibody-positive neuromyelitis optica spectrum disorder. J Clin Neurol 2016;12:515-6.
92. Huppke P, Blüthner M, Bauer O, Stark W, Reinhardt K, Huppke B, *et al.* Neuromyelitis optica and NMO-IgG in European pediatric patients. Neurology 2010;75:1740-4.
93. Hurst RW, Kenyon LC, Lavi E, Raps EC, Marcotte P. Spinal dural arteriovenous fistula: The pathology of venous hypertensive myelopathy. Neurology 1995;45:1309-13.
94. Hyun JW, Jeong IH, Joung A, Kim SH, Kim HJ. Evaluation of the 2015 diagnostic criteria for neuromyelitis optica spectrum disorder. Neurology 2016;86:1772-9.
95. Iorio R, Lucchinetti CF, Lennon VA, Farrugia G, Pasricha PJ, Weinshenker BG, *et al.* Intractable nausea and vomiting from autoantibodies against a brain water channel. Clin Gastroenterol Hepatol 2013;11:240-5.
96. Isobe N, Oksenberg JR. Genetic studies of multiple sclerosis and neuromyelitis optica: Current status in European, African American and Asian populations. Clin Exp Neuroimmunol 2014;5:61-8.
97. Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, *et al.* Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell 2009;139:485-98.
98. Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, *et al.* The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+T helper cells. Cell 2006;126:1121-33.
99. Jacob A, Matiello M, Wingerchuk DM, Lucchinetti CF, Pittock SJ, Weinshenker BG, *et al.* Neuromyelitis optica: Changing concepts. J Neuroimmunol 2007;187:126-38.
100. Jain RS, Kumar S, Tejwani S. A rare association of tuberculous longitudinally extensive transverse myelitis (LETM) with brain tuberculoma. Springerplus 2015;4:476.
101. Jakszyn P, Gonzalez CA. Nitrosamine and related food intake and gastric and oesophageal cancer risk: A systematic review of the epidemiological evidence. World J Gastroenterol 2006;12:4296-303.
102. James E, Dobson R, Kuhle J, Baker D, Giovannoni G, Ramagopalan SV, *et al.* The effect of Vitamin D-related interventions on multiple sclerosis relapses: A meta-analysis. Mult Scler 2013;19:1571-9.
103. Janowski BA, Willy PJ, Devi TR, Falck JR, Mangelsdorf DJ. An oxysterol signalling pathway mediated by the nuclear receptor LXR alpha. Nature 1996;383:728-31.
104. Jarius S, Jacobi C, de Seze J, Zephir H, Paul F, Franciotta D, *et al.* Frequency and syndrome specificity of antibodies to aquaporin-4 in neurological patients with rheumatic disorders. Mult Scler 2011;17:1067-73.
105. Jarius S, Paul F, Franciotta D, de Seze J, Münch C, Salvetti M, *et al.* Neuromyelitis optica spectrum disorders in patients with myasthenia gravis: Ten new aquaporin-4 antibody positive cases and a review of the literature. Mult Scler 2012;18:1135-43.
106. Jarius S, Paul F, Franciotta D, Ruprecht K, Ringelstein M, Bergamaschi R, *et al.* Cerebrospinal fluid findings in aquaporin-4 antibody positive neuromyelitis optica: Results from 211 lumbar punctures. J Neurol Sci 2011;306:82-90.
107. Jarius S, Ruprecht K, Kleiter I, Borisow N, Asgari N, Pitarokoili K, *et al.* MOG-igG in NMO and related disorders: A multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. J Neuroinflammation 2016;13:280.
108. Jarius S, Ruprecht K, Wildemann B, Kuempfel T, Ringelstein M, Geis C, *et al.* Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A multicentre study of 175 patients. J Neuroinflammation 2012;9:14.
109. Jarius S, Wildemann B, Paul F. Neuromyelitis optica: Clinical features, immunopathogenesis and treatment. Clin Exp Immunol 2014;176:149-64.
110. Jarius S, Wildemann B. The history of neuromyelitis optica. J Neuroinflammation 2013;10:8.
111. Jellema K, Canta LR, Tijssen CC, van Rooij WJ, Koudstaal PJ, van Gijn J, *et al.* Spinal dural arteriovenous fistulas: Clinical features in 80 patients. J Neurol Neurosurg Psychiatry 2003;74:1438-40.

112. Jin X, Pei S, Liu Y, Li X. Clinical analysis of neuromyelitis optica presenting as intractable nausea, vomiting and hiccups. Int J Neurosci 2017;127:854-8.
113. Jitprapaikulsan J, Siritho S, Prayoonwiwat N. Vitamin D level status in thai neuromyelitis optica patients. J Neuroimmunol 2016;295-296:75-8.
114. Jitprapaikulsan SS. Vitamin D and neuromyelitis optica spectrum disorders. Austin J Mult Scler Neuroimmunol 2016;3:1-3.
115. Johnson BA, Fram EK, Johnson PC, Jacobowitz R. The variable MR appearance of primary lymphoma of the central nervous system: Comparison with histopathologic features. AJNR Am J Neuroradiol 1997;18:563-72.
116. Juryńczyk M, Craner M, Palace J. Overlapping CNS inflammatory diseases: Differentiating features of NMO and MS. J Neurol Neurosurg Psychiatry 2015;86:20-5.
117. Kagawa Y. Impact of westernization on the nutrition of Japanese: Changes in physique, cancer, longevity and centenarians. Prev Med 1978;7:205-17.
118. Kalra S, Silman A, Akman-Demir G, Bohlega S, Borhani-Haghighi A, Constantinescu CS, *et al.* Diagnosis and management of neuro-Behçet's disease: International consensus recommendations. J Neurol 2014;261:1662-76.
119. Kalsi V, Fowler CJ. Therapy insight: Bladder dysfunction associated with multiple sclerosis. Nat Clin Pract Urol 2005;2:492-501.
120. Kampman MT, Steffensen LH. The role of Vitamin D in multiple sclerosis. J Photochem Photobiol B 2010;101:137-41.
121. Kanamori Y, Nakashima I, Takai Y, Nishiyama S, Kuroda H, Takahashi T, *et al.* Pain in neuromyelitis optica and its effect on quality of life: A cross-sectional study. Neurology 2011;77:652-8.
122. Kanbayashi T, Shimohata T, Nakashima I, Yaguchi H, Yabe I, Nishizawa M, *et al.* Symptomatic narcolepsy in patients with neuromyelitis optica and multiple sclerosis: New neurochemical and immunological implications. Arch Neurol 2009;66:1563-6.
123. Kanoto M, Hosoya T, Toyoguchi Y, Oda A. Brain stem and cerebellar atrophy in chronic progressive neuro-Behçet's disease. Eur J Radiol 2013;82:146-50.
124. Kessler RA, Mealy MA, Jimenez-Arango JA, Quan C, Paul F, López R, *et al.* Anti-aquaporin-4 titer is not predictive of disease course in neuromyelitis optica spectrum disorder: A multicenter cohort study. Mult Scler Relat Disord 2017;17:198-201.
125. Kessler RA, Mealy MA, Levy M. Treatment of neuromyelitis optica spectrum disorder: Acute, preventive, and symptomatic. Curr Treat Options Neurol 2016;18:2.
126. Kikuchi H, Takayama M, Hirohata S. Quantitative analysis of brainstem atrophy on magnetic resonance imaging in chronic progressive neuro-Behçet's disease. J Neurol Sci 2014;337:80-5.
127. Kim HJ, Park HY, Kim E, Lee KS, Kim KK, Choi BO, *et al.* Common CYP7A1 promoter polymorphism associated with risk of neuromyelitis optica. Neurobiol Dis 2010;37:349-55.
128. Kim SM, Go MJ, Sung JJ, Park KS, Lee KW. Painful tonic spasm in neuromyelitis optica: Incidence, diagnostic utility, and clinical characteristics. Arch Neurol 2012;69:1026-31.
129. Kim SM, Kim SJ, Lee HJ, Kuroda H, Palace J, Fujihara K, *et al.* Differential diagnosis of neuromyelitis optica spectrum disorders. Ther Adv Neurol Disord 2017;10:265-89.
130. Kim SM, Waters P, Vincent A, Kim SY, Kim HJ, Hong YH, *et al.* Sjogren's syndrome myelopathy: Spinal cord involvement in Sjogren's syndrome might be a manifestation of neuromyelitis optica. Mult Scler 2009;15:1062-8.
131. Kim SM, Waters P, Woodhall M, Kim JY, Kim JE, Yang JW, *et al.* Utility of aquaporin-4 antibody assay in patients with neuromyelitis optica spectrum disorders. Mult Scler 2013;19:1060-7.
132. Kim SM, Waters P, Woodhall M, Yang JW, Yang H, Kim JE, *et al.* Characterization of the spectrum of Korean inflammatory demyelinating diseases according to the diagnostic criteria and AQP4-ab status. BMC Neurol 2014;14:93.
133. Kim SM, Woodhall MR, Kim JS, Kim SJ, Park KS, Vincent A, *et al.* Antibodies to MOG in adults with inflammatory demyelinating disease of the CNS. Neurol Neuroimmunol Neuroinflamm 2015;2:e163.
134. Kimbrough DJ, Fujihara K, Jacob A, Lana-Peixoto MA, Leite MI, Levy M, *et al.* Treatment of neuromyelitis optica: Review and recommendations. Mult Scler Relat Disord 2012;1:180-7.
135. Kinoshita M, Obata K, Tanaka M. Latitude has more significant impact on prevalence of multiple sclerosis than ultraviolet level or Sunshine duration in Japanese population. Neurol Sci 2015;36:1147-51.
136. Kira J. Genetic and environmental factors underlying the rapid changes in epidemiological and clinical features of multiple sclerosis and neuromyelitis optica in Japanese. Clin Exp Neuroimmunol 2013;4:261-73.
137. Kister I, Herbert J, Zhou Y, Ge Y. Ultrahigh-field MR (7T) imaging of brain lesions in neuromyelitis optica. Mult Scler Int 2013;2013:398259.
138. Kitley J, Elsone L, George J, Waters P, Woodhall M, Vincent A, *et al.* Methotrexate is an alternative to azathioprine in neuromyelitis optica spectrum disorders with aquaporin-4 antibodies. J Neurol Neurosurg Psychiatry 2013;84:918-21.
139. Kitley J, Waters P, Woodhall M, Leite MI, Murchison A, George J, *et al.* Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte glycoprotein antibodies: A comparative study. JAMA Neurol 2014;71:276-83.
140. Kleinewietfeld M, Manzel A, Titze J, Kvakan H, Yosef N, Linker RA, *et al.* Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. Nature 2013;496:518-22.
141. Kleiter I, Hellwig K, Berthele A, Kümpfel T, Linker RA, Hartung HP, *et al.* Failure of natalizumab to prevent relapses in neuromyelitis optica. Arch Neurol 2012;69:239-45.
142. Koelman DL, Chahin S, Mar SS, Venkatesan A, Hoganson GM, Yeshokumar AK, *et al.* Acute disseminated encephalomyelitis in 228 patients: A retrospective, multicenter US study. Neurology 2016;86:2085-93.
143. Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, *et al.* International pediatric multiple sclerosis study group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: Revisions to the 2007 definitions. Mult Scler 2013;19:1261-7.
144. Kumar N, Keegan BM, Rodriguez FJ, Hammack JE, Kantarci OH. Intravascular lymphoma presenting as a longitudinally-extensive myelitis: Diagnostic challenges and etiologic clues. J Neurol Sci 2011;303:146-9.
145. Kume K, Deguchi K, Ikeda K, Takata T, Kokudo Y, Kamada M, *et al*. Neuromyelitis optica spectrum disorder presenting with repeated hypersomnia due to involvement of the hypothalamus and hypothalamus-amygdala linkage. Mult Scler 2015;21:960-2.
146. Lalan S, Khan M, Schlakman B, Penman A, Gatlin J, Herndon R, *et al.* Differentiation of neuromyelitis optica from multiple sclerosis on spinal magnetic resonance imaging. Int J MS Care 2012;14:209-14.
147. Larik A, Chiong Y, Lee LC, Ng YS. Longitudinally extensive transverse myelitis associated with dengue fever. BMJ Case Rep 2012;2012. pii: bcr1220115378.
148. Laursen JH, Søndergaard HB, Sørensen PS, Sellebjerg F, Oturai AB. Vitamin D supplementation reduces relapse rate in relapsing-remitting multiple sclerosis patients treated with natalizumab. Mult Scler Relat Disord 2016;10:169-73.
149. Lee HS, Kim do Y, Shin HY, Choi YC, Kim SM. Spinal cord involvement in Behçet's disease. Mult Scler 2016;22:960-3.
150. Lee JD. Multiple Sclerosis in Asian Populations: The Genetic and Environmental Determinants of Variable Susceptibility and Clinical Profile; 2014. Available from: https://www.open.library.ubc.ca/clRcle/collections/ubctheses/24/items/1.0165922. [Last accessed on 2018 Apr 09].
151. Lee YK, Menezes JS, Umesaki Y, Mazmanian SK. Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. Proc Natl Acad Sci U S A 2011;108 Suppl 1:4615-22.
152. Leite MI, Coutinho E, Lana-Peixoto M, Apostolos S, Waters P, Sato D, *et al.* Myasthenia gravis and neuromyelitis optica spectrum disorder: A multicenter study of 16 patients. Neurology 2012;78:1601-7.
153. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med 2005;202:473-7.
154. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, *et al.* A serum autoantibody marker of neuromyelitis optica: Distinction from multiple sclerosis. Lancet 2004;364:2106-12.
155. Li W, Minohara M, Piao H, Matsushita T, Masaki K, Matsuoka T, *et al.* Association of anti-*Helicobacter pylori* neutrophil-activating protein antibody response with anti-aquaporin-4 autoimmunity in Japanese patients with multiple sclerosis and neuromyelitis optica. Mult Scler 2009;15:1411-21.
156. Liu J, Shi Z, Lian Z, Chen H, Zhang Q, Feng H, *et al.* Association of CD58 gene polymorphisms with NMO spectrum disorders in a Han Chinese

population. J Neuroimmunol 2017;309:23-30.
157. Long Y, Zheng Y, Chen M, Zhang B, Gao C, Shan F, *et al.* Serum thyroid-stimulating hormone and anti-thyroglobulin antibody are independently associated with lesions in spinal cord in central nervous system demyelinating diseases. PLoS One 2014;9:e100672.
158. Lovera J, Reza T. Stress in multiple sclerosis: Review of new developments and future directions. Curr Neurol Neurosci Rep 2013;13:398.
159. Lucas RM, Ponsonby AL, Dear K, Valery PC, Pender MP, Taylor BV, *et al.* Sun exposure and Vitamin D are independent risk factors for CNS demyelination. Neurology 2011;76:540-8.
160. Luppe S, Robertson NP. MOG-IgG in neuromyelitis optica. J Neurol 2014;261:640-2.
161. Marignier R, De Sèze J, Vukusic S, Durand-Dubief F, Zéphir H, Vermersch P, *et al.* NMO-igG and devic's neuromyelitis optica: A French experience. Mult Scler 2008;14:440-5.
162. Martínez-Lapiscina EH, Fraga-Pumar E, Pastor X, Gómez M, Conesa A, Lozano-Rubí R, *et al.* Is the incidence of optic neuritis rising? Evidence from an epidemiological study in barcelona (Spain), 2008-2012. J Neurol 2014;261:759-67.
163. Masters-Israilov A, Robbins MS. Headache in neuromyelitis optica. Curr Pain Headache Rep 2017;21:20.
164. Masuda H, Mori M, Uzawa A, Muto M, Uchida T, Kuwabara S, *et al.* Serum antinuclear antibody may be associated with less severe disease activity in neuromyelitis optica. Eur J Neurol 2016;23:276-81.
165. Mateo J, Esteban O, Martínez M, Grzybowski A, Ascaso FJ. The contribution of optical coherence tomography in neuromyelitis optica spectrum disorders. Front Neurol 2017;8:493.
166. Matiello M, Lennon VA, Jacob A, Pittock SJ, Lucchinetti CF, Wingerchuk DM, *et al.* NMO-IgG predicts the outcome of recurrent optic neuritis. Neurology 2008;70:2197-200.
167. Matiello M, Schaefer-Klein JL, Hebrink DD, Kingsbury DJ, Atkinson EJ, Weinshenker BG, *et al.* Genetic analysis of aquaporin-4 in neuromyelitis optica. Neurology 2011;77:1149-55.
168. Matthews L, Marasco R, Jenkinson M, Küker W, Luppe S, Leite MI, *et al.* Distinction of seropositive NMO spectrum disorder and MS brain lesion distribution. Neurology 2013;80:1330-7.
169. McKeon A, Lennon VA, Jacob A, Matiello M, Lucchinetti CF, Kale N, *et al.* Coexistence of myasthenia gravis and serological markers of neurological autoimmunity in neuromyelitis optica. Muscle Nerve 2009;39:87-90.
170. Mealy MA, Wingerchuk DM, Greenberg BM, Levy M. Epidemiology of neuromyelitis optica in the United States: A multicenter analysis. Arch Neurol 2012;69:1176-80.
171. Mealy MA, Wingerchuk DM, Palace J, Greenberg BM, Levy M. Comparison of relapse and treatment failure rates among patients with neuromyelitis optica: Multicenter study of treatment efficacy. JAMA Neurol 2014;71:324-30.
172. Mehnert U, Birzele J, Reuter K, Schurch B. The effect of botulinum toxin type a on overactive bladder symptoms in patients with multiple sclerosis: A pilot study. J Urol 2010;184:1011-6.
173. Merle H, Olindo S, Bonnan M, Donnio A, Richer R, Smadja D, *et al.* Natural history of the visual impairment of relapsing neuromyelitis optica. Ophthalmology 2007;114:810-5.
174. Meurs L, Labeye D, Declercq I, Piéret F, Gille M. Acute transverse myelitis as a main manifestation of early stage II neuroborreliosis in two patients. Eur Neurol 2004;52:186-8.
175. Michel MC, Barendrecht MM. Physiological and pathological regulation of the autonomic control of urinary bladder contractility. Pharmacol Ther 2008;117:297-312.
176. Miclea A, Miclea M, Pistor M, Hoepner A, Chan A, Hoepner R, *et al.* Vitamin D supplementation differentially affects seasonal multiple sclerosis disease activity. Brain Behav 2017;7:e00761.
177. Milo R, Kahana E. Multiple sclerosis: Geoepidemiology, genetics and the environment. Autoimmun Rev 2010;9:A387-94.
178. Min JH, Kim HJ, Kim BJ, Lee KW, Sunwoo IN, Kim SM, *et al.* Brain abnormalities in Sjogren syndrome with recurrent CNS manifestations: Association with neuromyelitis optica. Mult Scler 2009;15:1069-76.
179. Min JH, Waters P, Vincent A, Cho HJ, Joo BE, Woo SY, *et al.* Low levels of Vitamin D in neuromyelitis optica spectrum disorder: Association with disease disability. PLoS One 2014;9:e107274.
180. Miranda MT, Suárez E, Abbas M, Chinea A, Tosado R, Mejías IA, *et al.* HLA class I & II alleles in multiple sclerosis patients from Puerto Rico. Bol Asoc Med P R 2013;105:18-23.
181. Mirsattari SM, Johnston JB, McKenna R, Del Bigio MR, Orr P, Ross RT, *et al.* Aboriginals with multiple sclerosis: HLA types and predominance of neuromyelitis optica. Neurology 2001;56:317-23.
182. Miyamoto K, Fujihara K, Kira JI, Kuriyama N, Matsui M, Tamakoshi A, *et al.* The prevalence and characteristics of neuromyelitis optica in Japan: A nationwide epidemiological study. J Neurol Sci 2017;381:787.
183. Miyara M, Gorochov G, Ehrenstein M, Musset L, Sakaguchi S, Amoura Z, *et al.* Human foxP3+ regulatory T cells in systemic autoimmune diseases. Autoimmun Rev 2011;10:744-55.
184. Mok CC, To CH, Mak A, Poon WL. Immunoablative cyclophosphamide for refractory lupus-related neuromyelitis optica. J Rheumatol 2008;35:172-4.
185. Montgomery SL, Bowers WJ. Tumor necrosis factor-alpha and the roles it plays in homeostatic and degenerative processes within the central nervous system. J Neuroimmune Pharmacol 2012;7:42-59.
186. Moore P, Methley A, Pollard C, Mutch K, Hamid S, Elsone L, *et al.* Cognitive and psychiatric comorbidities in neuromyelitis optica. J Neurol Sci 2016;360:4-9.
187. Morrow MJ, Wingerchuk D. Neuromyelitis optica. J Neuroophthalmol 2012;32:154-66.
188. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 2006;296:2832-8.
189. Muto M, Mori M, Sato Y, Uzawa A, Masuda S, Kuwabara S, *et al.* Seasonality of multiple sclerosis and neuromyelitis optica exacerbations in Japan. Mult Scler 2013;19:378-9.
190. Nakajima H, Furutama D, Kimura F, Shinoda K, Ohsawa N, Nakagawa T, *et al.* Herpes simplex virus myelitis: Clinical manifestations and diagnosis by the polymerase chain reaction method. Eur Neurol 1998;39:163-7.
191. Nakajima H, Hosokawa T, Sugino M, Kimura F, Sugasawa J, Hanafusa T, *et al.* Visual field defects of optic neuritis in neuromyelitis optica compared with multiple sclerosis. BMC Neurol 2010;10:45.
192. Nakamura H, Usa T, Motomura M, Ichikawa T, Nakao K, Kawasaki E, *et al.* Prevalence of interrelated autoantibodies in thyroid diseases and autoimmune disorders. J Endocrinol Invest 2008;31:861-5.
193. Nakano H, Tanaka M, Kinoshita M, Tahara M, Matsui M, Tanaka K, *et al.* Epileptic seizures in Japanese patients with multiple sclerosis and neuromyelitis optica. Epilepsy Res 2013;104:175-80.
194. Nazario CM, Szklo M, Diamond E, Román-Franco A, Climent C, Suarez E, *et al.* Salt and gastric cancer: A case-control study in Puerto Rico. Int J Epidemiol 1993;22:790-7.
195. Nechemia Y, Moreh E, Weingarden H, Bloch A, Givon U, Vaknin-Dembinsky A, *et al.* Effectiveness of multi-disciplinary rehabilitation for patients with neuromyelitis optica. J Spinal Cord Med 2016;39:311-6.
196. Nour MM, Nakashima I, Coutinho E, Woodhall M, Sousa F, Revis J, *et al.* Pregnancy outcomes in aquaporin-4-positive neuromyelitis optica spectrum disorder. Neurology 2016;86:79-87.
197. O'Connell K, Marnane M, McGuigan C. Bilateral ocular perineuritis as the presenting feature of acute syphilis infection. J Neurol 2012;259:191-2.
198. Oertel FC, Zimmermann H, Paul F, Brandt AU. Optical coherence tomography in neuromyelitis optica spectrum disorders: Potential advantages for individualized monitoring of progression and therapy. EPMA J 2018;9:21-33.
199. Ogasawara M, Meguro A, Sakai T, Mizuki N, Takahashi T, Fujihara K, *et al.* Genetic analysis of the aquaporin-4 gene for anti-AQP4 antibody-positive neuromyelitis optica in a Japanese population. Jpn J Ophthalmol 2016;60:198-205.
200. Ortiz AP, Soto-Salgado M, Calo WA, Tortolero-Luna G, Pérez CM, Romero CJ, *et al.* Incidence and mortality rates of selected infection-related cancers in Puerto Rico and in the United States. Infect Agent Cancer 2010;5:10.
201. Pait AS, Whitall DR, Jeffrey CF, Caldow C, Mason AL, Lauenstein GG, *et al.* Chemical contamination in Southwest Puerto Rico: An assessment of organic contaminants in nearshore sediments. Mar Pollut Bull 2008;56:580-7.
202. Pamer EG. Fecal microbiota transplantation: Effectiveness, complexities, and lingering concerns. Mucosal Immunol 2014;7:210-4.
203. Pan J, Zhao P, Cai H, Su L, Wood K, Shi FD, *et al.* Hypoxemia, sleep disturbances, and depression correlated with fatigue in neuromyelitis optica

spectrum disorder. CNS Neurosci Ther 2015;21:599-606.
204. Pandit L, Kundapur R. Prevalence and patterns of demyelinating central nervous system disorders in urban Mangalore, South India. Mult Scler 2014;20:1651-3.
205. Pandit L, Mustafa S, Kunder R, Shetty R, Misri Z, Pai S, *et al.* Optimizing the management of neuromyelitis optica and spectrum disorders in resource poor settings: Experience from the mangalore demyelinating disease registry. Ann Indian Acad Neurol 2013;16:572-6.
206. Papadopoulos MC, Verkman AS. Aquaporin 4 and neuromyelitis optica. Lancet Neurol 2012;11:535-44.
207. Papadopoulos MC, Verkman AS. Aquaporin water channels in the nervous system. Nat Rev Neurosci 2013;14:265-77.
208. Papais-Alvarenga RM, Miranda-Santos CM, Puccioni-Sohler M, de Almeida AM, Oliveira S, Basilio De Oliveira CA, *et al.* Optic neuromyelitis syndrome in Brazilian patients. J Neurol Neurosurg Psychiatry 2002;73:429-35.
209. Papeix C, Vidal JS, de Seze J, Pierrot-Deseilligny C, Tourbah A, Stankoff B, *et al.* Immunosuppressive therapy is more effective than interferon in neuromyelitis optica. Mult Scler 2007;13:256-9.
210. Parker SE, Pula JH. Neurosyphilis presenting as asymptomatic optic perineuritis. Case Rep Ophthalmol Med 2012;2012:621872.
211. Pellkofer HL, Havla J, Hauer D, Schelling G, Azad SC, Kuempfel T, *et al.* The major brain endocannabinoid 2-AG controls neuropathic pain and mechanical hyperalgesia in patients with neuromyelitis optica. PLoS One 2013;8:e71500.
212. Pellkofer HL, Krumbholz M, Berthele A, Hemmer B, Gerdes LA, Havla J, *et al.* Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab. Neurology 2011;76:1310-5.
213. Pereira CM, Castiglione M, Kasawara KT. Effects of physiotherapy treatment for urinary incontinence in patient with multiple sclerosis. J Phys Ther Sci 2017;29:1259-63.
214. Pereira WL, Reiche EM, Kallaur AP, Kaimen-Maciel DR. Epidemiological, clinical, and immunological characteristics of neuromyelitis optica: A review. J Neurol Sci 2015;355:7-17.
215. Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW, *et al.* Impact of aerobic training on fitness and quality of life in multiple sclerosis. Ann Neurol 1996;39:432-41.
216. Petković F, Castellano B. The role of interleukin-6 in central nervous system demyelination. Neural Regen Res 2016;11:1922-3.
217. Pinheiro PS, Sherman RL, Trapido EJ, Fleming LE, Huang Y, Gomez-Marin O, *et al.* Cancer incidence in first generation U.S. Hispanics: Cubans, Mexicans, Puerto Ricans, and New Latinos. Cancer Epidemiol Biomarkers Prev 2009;18:2162-9.
218. Pisani F, Mastrototaro M, Rossi A, Nicchia GP, Tortorella C, Ruggieri M, *et al.* Identification of two major conformational aquaporin-4 epitopes for neuromyelitis optica autoantibody binding. J Biol Chem 2011;286:9216-24.
219. Pittock SJ, Lennon VA, de Seze J, Vermersch P, Homburger HA, Wingerchuk DM, *et al.* Neuromyelitis optica and non organ-specific autoimmunity. Arch Neurol 2008;65:78-83.
220. Pittock SJ, Lennon VA, Krecke K, Wingerchuk DM, Lucchinetti CF, Weinshenker BG, *et al.* Brain abnormalities in neuromyelitis optica. Arch Neurol 2006;63:390-6.
221. Pittock SJ, Lennon VA, McKeon A, Mandrekar J, Weinshenker BG, Lucchinetti CF, *et al.* Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: An open-label pilot study. Lancet Neurol 2013;12:554-62.
222. Pittock SJ, Weinshenker BG, Lucchinetti CF, Wingerchuk DM, Corboy JR, Lennon VA, *et al.* Neuromyelitis optica brain lesions localized at sites of high aquaporin 4 expression. Arch Neurol 2006;63:964-8.
223. Popescu BF, Lennon VA, Parisi JE, Howe CL, Weigand SD, Cabrera-Gómez JA, *et al.* Neuromyelitis optica unique area postrema lesions: Nausea, vomiting, and pathogenic implications. Neurology 2011;76:1229-37.
224. Prokunina L, Padyukov L, Bennet A, de Faire U, Wiman B, Prince J, *et al.* Association of the PD-1.3A allele of the PDCD1 gene in patients with rheumatoid arthritis negative for rheumatoid factor and the shared epitope. Arthritis Rheum 2004;50:1770-3.
225. Qian P, Lancia S, Alvarez E, Klawiter EC, Cross AH, Naismith RT, *et al.* Association of neuromyelitis optica with severe and intractable pain. Arch Neurol 2012;69:1482-7.
226. Rafael H, Omental transplantation against nmo and MS: A method to Decrease or Prevent Relapses. Neurol Clin Therapeut J 2018;2:102.
227. Rafael H. Omental transplantation for neuromyelitis optica. J Neurol Stroke 2017;6:00194.
228. Ramanathan S, Prelog K, Barnes EH, Tantsis EM, Reddel SW, Henderson AP, *et al.* Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis. Mult Scler 2016;22:470-82.
229. Ramírez-Vick M, Hernández-Dávila L, Rodríguez-Rivera N, López-Valentín M, Haddock L, Rodríguez-Martínez R, *et al.* Prevalence of Vitamin D insufficiency and deficiency among young physicians at university district hospital in San Juan, Puerto Rico. *P* R Health Sci J 2015;34:83-8.
230. Rodríguez-Quiroga SA, Abaroa L, Arakaki T, Garretto NS, Villa AM. Commentary on neuromyelitis optica associated with painful paroxysmal dystonia: Case report and literature review. Acta Neurol Belg 2015;115:523-4.
231. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005;65:812-9.
232. Rosito S, Nicchia GP, Palazzo C, Lia A, Buccoliero C, Pisani F, *et al.* Supramolecular aggregation of aquaporin-4 is different in muscle and brain: Correlation with tissue susceptibility in neuromyelitis optica. J Cell Mol Med 2018;22:1236-46.
233. Rumah KR, Linden J, Fischetti VA, Vartanian T. Isolation of clostridium perfringens type B in an individual at first clinical presentation of multiple sclerosis provides clues for environmental triggers of the disease. PLoS One 2013;8:e76359.
234. Rybicki BA, Major M, Popovich J Jr., Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: A 5-year study in a health maintenance organization. Am J Epidemiol 1997;145:234-41.
235. Saher G, Brügger B, Lappe-Siefke C, Möbius W, Tozawa R, Wehr MC, *et al.* High cholesterol level is essential for myelin membrane growth. Nat Neurosci 2005;8:468-75.
236. Sahraian MA, Moghadasi AN, Azimi AR, Asgari N, H Akhoundi F, Abolfazli R, *et al.* Diagnosis and management of neuromyelitis optica spectrum disorder (NMOSD) in Iran: A consensus guideline and recommendations. Mult Scler Relat Disord 2017;18:144-51.
237. Sang CN. NMDA-receptor antagonists in neuropathic pain: Experimental methods to clinical trials. J Pain Symptom Manage 2000;19:S21-5.
238. Sato DK, Callegaro D, Lana-Peixoto MA, Nakashima I, Fujihara K. Seronegative neuromyelitis optica spectrum – The challenges on disease definition and pathogenesis. Arq Neuropsiquiatr 2014;72:445-50.
239. Satoh J, Obayashi S, Misawa T, Tabunoki H, Yamamura T, Arima K, *et al.* Neuromyelitis optica/Devic's disease: Gene expression profiling of brain lesions. Neuropathology 2008;28:561-76.
240. Schreiber AL, Fried GW, Formal CS, DeSouza BX. Rehabilitation of neuromyelitis optica (Devic syndrome): Three case reports. Am J Phys Med Rehabil 2008;87:144-8.
241. Scott BJ, Douglas VC, Tihan T, Rubenstein JL, Josephson SA. A systematic approach to the diagnosis of suspected central nervous system lymphoma. JAMA Neurol 2013;70:311-9.
242. Sellner J, Boggild M, Clanet M, Hintzen RQ, Illes Z, Montalban X, *et al.* EFNS guidelines on diagnosis and management of neuromyelitis optica. Eur J Neurol 2010;17:1019-32.
243. Seok JM, Cho HJ, Ahn SW, Cho EB, Park MS, Joo IS, *et al.* Clinical characteristics of late-onset neuromyelitis optica spectrum disorder: A multicenter retrospective study in Korea. Mult Scler 2017;23:1748-56.
244. Sepúlveda M, Armangué T, Sola-Valls N, Arrambide G, Meca-Lallana JE, Oreja-Guevara C, *et al.* Neuromyelitis optica spectrum disorders. Neurol Neuroimmunol Neuroinflammation 2016;3:e225.
245. Shan Y, Tan S, Zhang L, Huang J, Sun X, Wang Y, *et al.* Serum 25-hydroxyvitamin D3 is associated with disease status in patients with neuromyelitis optica spectrum disorders in South China. J Neuroimmunol 2016;299:118-23.
246. Sheng P, Hou L, Wang X, Wang X, Huang C, Yu M, *et al.* Efficacy of modafinil on fatigue and excessive daytime sleepiness associated with neurological disorders: A systematic review and meta-analysis. PLoS One 2013;8:e81802.
247. Sherman E, Han MH. Acute and chronic management of neuromyelitis optica spectrum disorder. Curr Treat Options Neurol 2015;17:48.

248. Shevach EM. Regulatory T cells in autoimmmunity*. Annu Rev Immunol 2000;18:423-49.
249. Simon KC, Schmidt H, Loud S, Ascherio A. Risk factors for multiple sclerosis, neuromyelitis optica and transverse myelitis. Mult Scler 2015;21:703-9.
250. Singh B, Schwartz JA, Sandrock C, Bellemore SM, Nikoopour E. Modulation of autoimmune diseases by interleukin (IL)-17 producing regulatory T helper (Th17) cells. Indian J Med Res 2013;138:591-4.
251. Singhrao SK, Neal JW, Rushmere NK, Morgan BP, Gasque P. Spontaneous classical pathway activation and deficiency of membrane regulators render human neurons susceptible to complement lysis. Am J Pathol 2000;157:905-18.
252. Smith GT, Goldmeier D, Migdal C. Neurosyphilis with optic neuritis: An update. Postgrad Med J 2006;82:36-9.
253. Smith SM, Vale WW. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin Neurosci 2006;8:383-95.
254. Spach KM, Nashold FE, Dittel BN, Hayes CE. IL-10 signaling is essential for 1,25-dihydroxyvitamin D3-mediated inhibition of experimental autoimmune encephalomyelitis. J Immunol 2006;177:6030-7.
255. Spooren A, Kooijman R, Lintermans B, Van Craenenbroeck K, Vermeulen L, Haegeman G, *et al.* Cooperation of NFkappaB and CREB to induce synergistic IL-6 expression in astrocytes. Cell Signal 2010;22:871-81.
256. Stern BJ, Krumholz A, Johns C, Scott P, Nissim J. Sarcoidosis and its neurological manifestations. Arch Neurol 1985;42:909-17.
257. Stiebel-Kalish H, Lotan I, Brody J, Chodick G, Bialer O, Marignier R, *et al.* Retinal nerve fiber layer may be better preserved in MOG-IgG versus AQP4-IgG optic neuritis: A Cohort study. PLoS One 2017;12:e0170847.
258. Storoni M, Petzold A, Plant GT. The use of serum glial fibrillary acidic protein measurements in the diagnosis of neuromyelitis optica spectrum optic neuritis. PLoS One 2011;6:e23489.
259. Suárez-Martínez EB, Pérez CM, Cruz SK, Khorsandi S, Chardón C, Ferder L, *et al.* Importance of Vitamin D and Vitamin D levels status in Puerto Ricans. J Health Care Poor Underserved 2013;24:38-47.
260. Suzuki K, Nakamura T, Hashimoto K, Miyamoto M, Komagamine T, Nagashima T, *et al*. Hypothermia, hypotension, hypersomnia, and obesity associated with hypothalamic lesions in a patient positive for the anti-aquaporin 4 antibody: A case report and literature review. Arch Neurol 2012;69:1355-9.
261. Takahashi T, Miyazawa I, Misu T, Takano R, Nakashima I, Fujihara K, *et al.* Intractable hiccup and nausea in neuromyelitis optica with anti-aquaporin-4 antibody: A herald of acute exacerbations. J Neurol Neurosurg Psychiatry 2008;79:1075-8.
262. Tanaka M, Tanaka K. Sudden hearing loss as the initial symptom in Japanese patients with multiple sclerosis and seropositive neuromyelitis optica spectrum disorders. J Neuroimmunol 2016;298:16-8.
263. Tanaka T, Kishimoto T. Targeting interleukin-6: All the way to treat autoimmune and inflammatory diseases. Int J Biol Sci 2012;8:1227-36.
264. Tenembaum S, Chitnis T, Nakashima I, Collongues N, McKeon A, Levy M, *et al.* Neuromyelitis optica spectrum disorders in children and adolescents. Neurology 2016;87:S59-66.
265. Thorlacius S, Aarli JA, Riise T, Matre R, Johnsen HJ. Associated disorders in myasthenia gravis: Autoimmune diseases and their relation to thymectomy. Acta Neurol Scand 1989;80:290-5.
266. Tradtrantip L, Yao X, Su T, Smith AJ, Verkman AS. Bystander mechanism for complement-initiated early oligodendrocyte injury in neuromyelitis optica. Acta Neuropathol 2017;134:35-44.
267. Tran C, Du Pasquier RA, Cavassini M, Guex-Crosier Y, Meuli R, Ciuffreda D, *et al.* Neuromyelitis optica following CMV primo-infection. J Intern Med 2007;261:500-3.
268. Transverse Myelitis Consortium Working Group. Proposed diagnostic criteria and nosology of acute transverse myelitis. Neurology 2002;59:499-505.
269. Trebst C, Jarius S, Berthele A, Paul F, Schippling S, Wildemann B, *et al.* Update on the diagnosis and treatment of neuromyelitis optica: Recommendations of the neuromyelitis optica study group (NEMOS). J Neurol 2014;261:1-6.
270. Uribe-San Martin R, Ciampi E, Galilea A, Sandoval P, Miranda H, Mellado P, *et al.* Neuromyelitis optica spectrum disorders: Profile of a cohort according to the 2015 diagnostic criteria. Rev Neurol 2017;65:193-202.
271. Uzawa A, Mori M, Arai K, Sato Y, Hayakawa S, Masuda S, *et al.* Cytokine and chemokine profiles in neuromyelitis optica: Significance of interleukin-6. Mult Scler 2010;16:1443-52.
272. Vahtera T, Haaranen M, Viramo-Koskela AL, Ruutiainen J. Pelvic floor rehabilitation is effective in patients with multiple sclerosis. Clin Rehabil 1997;11:211-9.
273. Vaknin-Dembinsky A, Brill L, Kassis I, Petrou P, Ovadia H, Ben-Hur T, *et al.* T-cell responses to distinct AQP4 peptides in patients with neuromyelitis optica (NMO). Mult Scler Relat Disord 2016;6:28-36.
274. Van Dijk JM, TerBrugge KG, Willinsky RA, Farb RI, Wallace MC. Multidisciplinary management of spinal dural arteriovenous fistulas: Clinical presentation and long-term follow-up in 49 patients. Stroke 2002;33:1578-83.
275. van Loo G, De Lorenzi R, Schmidt H, Huth M, Mildner A, Schmidt-Supprian M, *et al.* Inhibition of transcription factor NF-kappaB in the central nervous system ameliorates autoimmune encephalomyelitis in mice. Nat Immunol 2006;7:954-61.
276. van Pelt ED, Wong YY, Ketelslegers IA, Hamann D, Hintzen RQ. Neuromyelitis optica spectrum disorders: Comparison of clinical and magnetic resonance imaging characteristics of AQP4-IgG versus MOG-IgG seropositive cases in the Netherlands. Eur J Neurol 2016;23:580-7.
277. Vanotti S, Cores EV, Eizaguirre B, Melamud L, Rey R, Villa A, *et al.* Cognitive performance of neuromyelitis optica patients: Comparison with multiple sclerosis. Arq Neuropsiquiatr 2013;71:357-61.
278. Vincent T, Saikali P, Cayrol R, Roth AD, Bar-Or A, Prat A, *et al.* Functional consequences of neuromyelitis optica-IgG astrocyte interactions on blood-brain barrier permeability and granulocyte recruitment. J Immunol 2008;181:5730-7.
279. von Glehn F, Jarius S, Penalva de Oliveira AC, Brandão CO, Farias AS, Damasceno A, *et al.* Aquaporin-4 antibodies are not related to HTLV-1 associated myelopathy. PLoS One 2012;7:e39372.
280. Wang H, Dai Y, Qiu W, Zhong X, Wu A, Wang Y, *et al.* HLA-DPB1 0501 is associated with susceptibility to anti-aquaporin-4 antibodies positive neuromyelitis optica in Southern Han Chinese. J Neuroimmunol 2011;233:181-4.
281. Wang H, Wang K, Wang C, Xu F, Qiu W, Hu X, *et al.* Increased plasma interleukin-32 expression in patients with neuromyelitis optica. J Clin Immunol 2013;33:666-70.
282. Wang H, Wang K, Zhong X, Dai Y, Qiu W, Wu A, *et al.* Notable increased cerebrospinal fluid levels of soluble interleukin-6 receptors in neuromyelitis optica. Neuroimmunomodulation 2012;19:304-8.
283. Wang H, Zhong X, Wang K, Qiu W, Li J, Dai Y, *et al.* Interleukin 17 gene polymorphism is associated with anti-aquaporin 4 antibody-positive neuromyelitis optica in the Southern Han Chinese – A case control study. J Neurol Sci 2012;314:26-8.
284. Wang J, Tian Y, Shao Y, Feng H, Qin L, Xu W, *et al.* Comparison of spontaneous brain activity revealed by regional homogeneity in AQP4-IgG neuromyelitis optica-optic neuritis versus MOG-IgG optic neuritis patients: A resting-state functional MRI study. Neuropsychiatr Dis Treat 2017;13:2669-79.
285. Watanabe M, Furusho K, Takahashi T, Tamaoka A. Galactorrhea in a patient with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder: A case report and review of the literature. Neurologist 2015;20:101-3.
286. Watanabe S, Misu T, Miyazawa I, Nakashima I, Shiga Y, Fujihara K, *et al.* Low-dose corticosteroids reduce relapses in neuromyelitis optica: A retrospective analysis. Mult Scler 2007;13:968-74.
287. Weaver CT, Elson CO, Fouser LA, Kolls JK. The Th17 pathway and inflammatory diseases of the intestines, lungs, and skin. Annu Rev Pathol 2013;8:477-512.
288. Wei Q, Yanyu C, Rui L, Caixia L, Youming L, Jianhua H, *et al.* Human aquaporin 4 gene polymorphisms in Chinese patients with neuromyelitis optica. J Neuroimmunol 2014;274:192-6.
289. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, *et al.* International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177-89.
290. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999;53:1107-14.
291. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet Neurol 2007;6:805-15.
292. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG.

Revised diagnostic criteria for neuromyelitis optica. Neurology 2006;66:1485-9.
293. Wingerchuk DM, Weinshenker BG. Neuromyelitis optica: Clinical predictors of a relapsing course and survival. Neurology 2003;60:848-53.
294. Wingerchuk DM, Weinshenker BG. The emerging relationship between neuromyelitis optica and systemic rheumatologic autoimmune disease. Mult Scler 2012;18:5-10.
295. Wingerchuk DM. Neuromyelitis optica: Current concepts. Front Biosci 2004;9:834-40.
296. Wingerchuk DM. Neuromyelitis optica: Effect of gender. J Neurol Sci 2009;286:18-23.
297. Wu C, Yosef N, Thalhamer T, Zhu C, Xiao S, Kishi Y, *et al.* Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. Nature 2013;496:513-7.
298. Yamamoto T, Mori M, Uzawa A, Uchiyama T, Sakakibara R, Yanagisawa M, *et al.* Urinary symptoms and neurological disabilities are differentially correlated between multiple sclerosis and neuromyelitis optica. Clin Exp Neuroimmunol 2016;7:52-8.
299. Yao X, Verkman AS. Complement regulator CD59 prevents peripheral organ injury in rats made seropositive for neuromyelitis optica immunoglobulin G. Acta Neuropathol Commun 2017;5:57.
300. Yao X, Verkman AS. Marked central nervous system pathology in CD59 knockout rats following passive transfer of neuromyelitis optica immunoglobulin G. Acta Neuropathol Commun 2017;5:15.
301. Yesilot N, Mutlu M, Gungor O, Baykal B, Serdaroglu P, Akman-Demir G, *et al.* Clinical characteristics and course of spinal cord involvement in Behçet's disease. Eur J Neurol 2007;14:729-37.
302. Yoshimura S, Isobe N, Matsushita T, Yonekawa T, Masaki K, Sato S, *et al.* Distinct genetic and infectious profiles in Japanese neuromyelitis optica patients according to anti-aquaporin 4 antibody status. J Neurol Neurosurg Psychiatry 2013;84:29-34.
303. Zaidi SF. *Helicobacter pylori* associated asian enigma: Does diet deserve distinction? World J Gastrointest Oncol 2016;8:341-50.
304. Zajicek JP, Scolding NJ, Foster O, Rovaris M, Evanson J, Moseley IF, *et al.* Central nervous system sarcoidosis – Diagnosis and management. QJM 1999;92:103-17.
305. Zamvil SS, Spencer CM, Baranzini SE, Cree BA. The gut microbiome in neuromyelitis optica. Neurotherapeutics 2018;15:92-101.
306. Zarei S, Carr K, Reiley L, Diaz K, Guerra O, Altamirano PF, *et al.* A comprehensive review of amyotrophic lateral sclerosis. Surg Neurol Int 2015;6:171.
307. Zhang H, Verkman AS. Longitudinally extensive NMO spinal cord pathology produced by passive transfer of NMO-IgG in mice lacking complement inhibitor CD59. J Autoimmun 2014;53:67-77.
308. Zhao S, Mutch K, Elsone L, Miller J, Jacob A. An unusual case of 'itchy paralysis': Neuromyelitis optica presenting with severe neuropathic itch. Pract Neurol 2015;15:149-51.
309. Zhao S, Mutch K, Elsone L, Nurmikko T, Jacob A. Neuropathic pain in neuromyelitis optica affects activities of daily living and quality of life. Mult Scler 2014;20:1658-61.
310. Zhong YH, Zhong ZG, Zhou Z, Ma ZY, Qiu MY, Peng FH, *et al.* Comparisons of presentations and outcomes of neuromyelitis optica patients with and without Sjögren's syndrome. Neurol Sci 2017;38:271-7.