**Trabajo original**

https://doi.org/10.22379/24224022265

Acta Neurológica Colombiana

# Clinical, Paraclinical and Imaging Characterization of a Population of Colombian Patients with Neuromyelitis Optica Spectrum Disorder at the Hospital Universitario San Ignacio, Bogotá, Colombia

## Caracterización clínica, paraclínica e imaginológica de una población de pacientes Colombianos con espectro de Neuromielitis óptica del Hospital Universitario San Ignacio

**Cindy Andrea Díaz Becerra (1), Luis Alfonso Zarco Montero (2), Pieralessandro Lasalvia (3)**

**SUMMARY**

**Introduction:** Neuromyelitis Optica (NMO) is an inflammatory syndrome of the central nervous system, different from multiple sclerosis, that is associated with aquaporin-4 IgG antibodies (AQP4-IgG). The new nomenclature defines a unified term of Neuromyelitis Optica Spectrum Disorder (NMOSD), seropositive or seronegative according to the AQP4-IgG positivity.

**Objectives:** Demographic, clinical, imaging and cerebrospinal fluid (CSF) cytochemistry characterization of patients diagnosed with NMOSD at the Hospital Universitario San Ignacio (HUSI), Bogotá, Colombia, during 2006-2017.

**Methods:** A descriptive observational longitudinal study of patients diagnosed with NMO according to the International consensus diagnostic criteria for neuromyelitis optica spectrum disorders 2015 evaluated in HUSI during 2006-2017. An analysis of quantitative variables was performed with mean, standard deviation, median and interquartile range (IQR), and of qualitative variables with absolute numbers and percentages. A Wilcoxon sign-rank sum test was performed for paired data to evaluate the correlation between visual acuity (VA) and EDSS disability scale at admission and discharge after treatment.

**Results:** Data was collected for 37 patients. The mean age was 42 years-old. The form of presentation was optic neuritis (ON) in 81.1% of the cases. In patients who presented as ON, it was typical in 21.6%, atypical in 43.2% and bilateral in 18.9% of them. An average of 4.6 plasmapheresis (PPH) were performed; at discharge 45.9% presented a visual acuity (VA) lower than 20/800. The mean Expanded Disability Status Scale (EDSS) on admission was 2.8 (SD 1,4) and 2.2 (SD: 1,4). at discharge.

**Conclusion:** Colombian NMOSD patients have shown an increasingly frequent phenotype variability Including a higher proportion of patients with bilateral optic neuritis, smaller number of patients with oligoclonal bands pattern II and with typical lesions of multiple sclerosis (MS) in MRI with seropositive NMO and a greater number of cases debuting with partial segment partial myelitis.

KEYWORDS: Aquaporin 4, Demyelinating Autoimmune Diseases, CNS. Devic Disease. Myelitis, Transverse. NMO Spectrum Disorder . Neuromyelitis Optica (MeSH) .

**RESUMEN**

**Introducción:** La Neuromielitis óptica (NMO) es un síndrome inflamatorio del sistema nervioso central diferente a la esclerosis múltiple que se asocia con anticuerpos IgG acuaporina-4 (AQP4-IgG). La nueva nomenclatura define el termino unificado de trastornos del espectro de Neuromielitis óptica (NMOSD), seropositiva o negativa de acuerdo a la positividad de AQP4-IgG.

(1) Neurological Resident. Department of Neurology, Hospital Universitario San Ignacio, Universidad Javeriana, Bogotá, Colombia.

(2) Neuroimmunologist, Director of the Neurology Service, Hospital Universitario San Ignacio, Universidad Javeriana, Bogotá, Colombia.

(3) Clinical Epidemiology Doctoral Student, School of Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia.

Recibido 7/5/19. Aceptado: 21/11/19.

Correspondencia: Cyndi Andrea Díaz, candru_diaz@hotmail.com

**Objetivos:** Caracterización demográfica, clínica, imaginológica y del citoquímico de líquido cefalorraquídeo (LCR) en los pacientes con diagnóstico de NMOSD en el Hospital Universitario San Ignacio (HUSI), Bogotá, Colombia del año 2006-2017.

**Métodos:** Estudio observacional descriptivo longitudinal, pacientes con diagnóstico de NMO según criterios de Wingerchuck 2015, valorados en el HUSI, del 2006-2017. Se realizó análisis de variables cuantitativas con promedio, desviación estándar, mediana y percentil 25-75, las variables cualitativas con frecuencia absoluta y porcentajes. Se realizó prueba de Wilcoxon Sign-rank sum test para datos pareados para evaluar la correlación entre agudeza visual (AV) y escala de discapacidad de EDSS (Escala Expandida del Estado de Discapacidad) de ingreso y egreso posterior al tratamiento.

**Resultados:** 37 pacientes participaron. La edad promedio fue de 42 años. La forma de presentación fue neuritis óptica (NO) en el 81,1% de los casos. En los pacientes que se presentaron como NO fue típica en el 21,6%, atípica en 43,2% y bilateral 18,9% de los casos. Se realizó un promedio de 4,6 plasmaféresis (PMF), al egreso el 45,9% presentaron una agudeza visual (AV) menor de 20/800. EDSS de ingreso promedio 2,8 y el de egreso posterior a tratamiento fue de 2,2.

**Conclusión:** Existe variabilidad fenotípica, cada vez mas frecuente, en los pacientes con NMOSD. Incluyendo una mayor frecuencia de neuritis óptica bilateral, menor numero de pacientes con bandas oligoclonales patrón II positivas y con lesiones típicas de EMN en RMN con NMO seropositiva y una mayor presentación de casos debutando con mielitis parcial de segmento corto

PALABRAS CLAVE: Acuaporina 4. Enfermedades Autoinmunes, CNS. Enfermedad de Devic. Mielitis Transversa. Neuromielitis Óptica (DeCS)

## INTRODUCTION

Neuromyelitis Optica (NMO) also known as Devic's Disease is a central nervous system (CNS) autoimmune inflammatory disorder with a variable clinical presentation, with a monophasic course or in relapses, which predominantly affects the optic nerve and the spinal cord (SC) (1-3). NMO is more prevalent in women than in men, ratio 3-6:1, with an average age of 35-45 years-old (4-6). The prevalence of NMO varies geographically, from 0.52 per 100,000 people in countries such as Cuba, 4.4 cases per 100,000 people in southern Denmark to 10 per 100,000 people in Martinique (7-12). The number of cases reported has varied with the change in clinical criteria; in Latin America, the largest cohort of NMO patients is from Brazil, Bichuetti published 41 cases in 2009. In Colombia there is a high prevalence of NMO, although it has not yet been estimated; the first study published in our country described the characteristics of 22 patients in three centers. The new Wingerchuck et al diagnostic criteria have increased the recognition of the spectrum of NMO disorders, incorporating IgG-NMO positivity as one of the pillars that support the diagnosis; the protein water channel in astrocytes, called aquaporin 4 (AQP4) has been identified as target of the attack. It is strongly expressed in astrocytes in the brain, spinal cord and optic nerve, but also in the epithelial cells outside the CNS, such as the kidney and stomach (13, 14).

Traditionally, NMO was considered a monophasic disease, with simultaneous involvement of bilateral optic neuritis and longitudinally extensive transverse myelitis (LETM) (15-19). One of the greatest advances was the discovery that the majority of NMO patients have AQP4-IgG, thus becoming a disease-specific biomarker. The term NMOSD was introduced in 2007 and in the 2015 update to include patients with seropositive NMO, including phenotypes different from ON and LETM, such as area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy/acute diencephalic syndrome and symptomatic brain syndrome; in addition to seropositive patients with coexisting autoimmune diseases (e.g., systemic lupus erythematosus and Sjögren's syndrome) (20-35).

We report the demographic, clinical, imaging, and cerebrospinal fluid (CSF) cytochemistry characterization in patients diagnosed with NMOSD at the Hospital Universitario San Ignacio (HUSI), Bogotá, Colombia, during 2006-2017.

## MATERIALS AND METHODS

### Participants

A retrospective descriptive observational longitudinal study

**Inclusion criteria:**

Patients evaluated at the HUSI during 2006-2017, diagnosed with NMOSD according to The International consensus diagnostic criteria for neuromyelitis optica spectrum disorders 2015 (1), classifying them as seropositive or seronegative NMOSD:

*- Seropositive NMOSD (must meet all of the following criteria):*

1. At least 1 characteristic clinical core: optic neuritis, longitudinally extensive acute transverse myelitis or area postrema syndrome
2. Positive serum AQP4-IgG
3. Exclusion of alternative diagnoses

*- Seronegative NMOSD (must meet all of the following criteria):*

1. At least 2 characteristic clinical cores that occur as a result of 1 or more clinical attacks and that meet all of the following criteria:

A. At least 1 characteristic clinical core: optic neuritis, longitudinally extensive acute transverse myelitis or area postrema syndrome.

B. Dissemination in space (2 or more different characteristic clinical cores)

C. Meets imaging criteria in magnetic resonance imaging (MRI)

(i) Acute optic neuritis: normal brain MRI or T2 lesion or contrast enhancement with extension > 50% of the length of the optic nerve, or compromise of the optic chiasm.

(ii) Acute myelitis: spine MRI with longitudinally extensive intramedullary lesion (>=3 contiguous segments) or focal spinal atrophy in patients with a clinical history compatible with acute myelitis.

(iii) Area postrema syndrome: requires spinal cord injury/area postrema.

(iv) Acute brain stem syndrome: requires periependymal brainstem lesions

2. Serum AQP4-IgG-AB test negative or not available
3. Exclusion of alternative diagnoses

Additionally, patients should have the following data in the clinical history:

1. Demographic variables
2. Clinical characteristics (visual acuity at admission and discharge)
3. EDSS (Expanded Disability Status Scale)
4. Cerebrospinal fluid cytochemistry
5. Oligoclonal bands
6. Treatment received for acute attack

The basic data of the patients were taken from the Neurology Service database, search of medical records in the HUSI SAHI system. Through the DISEARCH system, the user request and access key was made through the institutional form for requesting information on medical record code EYA-R-18.





The demographic data for each patient were recorded in a database (age at diagnosis, race, sex, years of follow-up, diagnosis of the clinical presentation), brain MRI with number and location of lesions, anti AQP4 AB, and in case of having it, information on its positivity or negativity, result of cerebrospinal fluid cytochemistry including: cellularity (absolute count), differential count (lymphocytes, neutrophils, eosinophils), proteinorrachy in mg/dL, glycorrhachia in mg/dL, oligoclonal bands, number and type of relapses, EDSS score at admission and discharge, treatment received (type and number).

**Exclusion criteria:**

Patients with a medical records lacking the aforementioned data were excluded.

Patients were recruited at the Hospital Universitario San Ignacio, Bogotá, with the authorization of the Research and Ethics Committee, in accordance with the ethical standards of the Declaration of Helsinki of 1964, clinical research must conform to the moral and scientific principles that justify medical research, no risk given that a review of clinical histories was carried out.

**Statistical analysis**

A 95% confidence interval was used, significant p value < 0.05, variables according to nature: sex; continuous variables: age, cellularity value, specific count, proteinorrachy (mg/dL), glycorrhachia (mg/dL); discrete or count variables: EDSS score at admission and discharge, associated systemic autoimmune diseases; categorical variables: classification by sub-groups according to the EDSS score (mild, moderate or severe disability). The quantitative variable analysis was performed with mean, standard deviation, median and interquartile range, the qualitative variables with absolute numbers and percentages. Wilcoxon sign-rank sum test was performed for paired data to evaluate the correlation between visual acuity (VA) and EDSS disability scale at admission and discharge after treatment. All analyses were performed with R statistical package, version 3.4.4.

## RESULTS

### Sociodemographic characteristics

37 patients participated, with an average age of 42 years old (IQR 29-51 years), 78.4% were women, most of urban origin (94.6%), high school education (43.2%), and employed 83.8%. (table 1)

### Clinical characteristics

The initial clinical presentation in 81% of the patients

**Table1. Demographic characteristics**

| Variable | Count | % |
|---|---|---|
| **GENDER** | | |
| Female | 29 | 78.4 |
| Male | 8 | 21.6 |
| **ORIGIN** | | |
| Urban | 35 | 94.6 |
| Rural | 2 | 5.4 |
| **LEVEL OF EDUCATION** | | |
| Elementary school | 3 | 8.1 |
| High school | 16 | 43.2 |
| Technical school | 9 | 24.3 |
| University | 9 | 24.3 |
| **OCCUPATION** | | |
| Student | 3 | 8.1 |
| Employed | 31 | 83.8 |
| Unemployed | 2 | 5.4 |
| Retired | 1 | 2.7 |

was optic neuritis (ON); 16% debuted with acute longitudinally extensive transverse myelitis (LETM), and 3% with ON and LETM (Figure 1). At admission, VA was lower than 20/800 in 46%, and after treatment 54% were discharged with VA higher than 20/800.

Given the association of NMOSD with autoimmune comorbidities, autoimmune diseases simultaneous with NMOSD were recorded in 5 patients (13.5%), the most frequent being myasthenia gravis (N=2 - 5.4%) and the others evenly divided (2.7%) among Sjögren's syndrome, rheumatoid arthritis and differentiated connective tissue disease.

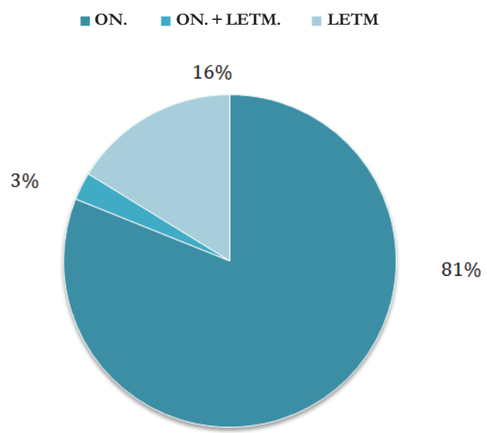


**Figure 1. Clinical variables of the first attack**
**ON (optic neuritis) ON+LETM (acute longitudinally transverse myelitis) LETM**

Of those patients whose first attack was ON, 81% were unilateral and 19% bilateral. being atypical with VA greater than 20/800 in 24.3%. The 21.6% debuted with typical ON with VA lower than 20/800, the 18,9% does not perceive light bilateral and unilateral.

## Laboratory characteristics

In cerebrospinal fluid (CSF) studies, the mean leukocyte count was 2.8 leukocytes/mm3, the average differential leukocyte count was: lymphocytes 9.9%, eosinophils 6.3%, and neutrophils 3.5%, with normal proteinorrachy and glycorrhachia. In the study of oligoclonal bands (OCBs) by isoelectric focusing the majority of the patients had pattern I (62.2), followed by pattern II (8.1%).

## Imaging characteristics

In single and contrast MRI studies of orbits with a protocol for demyelinating diseases, the involvement of the optic nerve had an average extension of 15.9 mm (IQR 12.5 – 20 mm), table 2.

63% of the patients met Wingerchuck's radiological criteria for longitudinally extensive ON and 37% for non-longitudinally extensive ON. The location was retrobulbar in 40,5% and anterior in 18,9%, simultaneous compromise of anterior and retrobulbar segment in 5.4%, equal percentage in retrobulbar + optic chiasm and optic chiasm + optic tract, 5.4% in optic chiasm.The anatomic location was distributed as follows: 40.5% intracisternal, 18.9% intraorbital and intracanalicular.

Single and contrast MRI studies were normal in 37.8%. Among the abnormal results non specific white matter lesions were obserber in 35.1%, typical of NMOSD in 16.2% and 8.1% had typical lesions that meet the Barkhof criteria for Multiple Sclerosis (MS).

MRI studies of the cervical/thoracic spine were normal in 32.4%. Among the abnormal findings 27% presented LETM in the cervical region and 2.7% LETM in the thoracic region, cervical centromedullary 13.5%, and we were struck by the fact that 5.4% had cervical eccentric short segment myelitis, 2,7% thoracic eccentric short segment myelitis.

AQP4-IgG ABs by ELISA method were positive in 40.5% in the first sampling, it was repeated in 17 patients with clinical suspicion after discharge in a minimum time of 1 month, being positive in 35,1% of them.





**Table 2. Imaging characteristics**

| Variables | Mean | Standard deviation | Minimum | Maximum | Median | Percentile 25 | Percentile 75 |
|---|---|---|---|---|---|---|---|
| Extension length of ON involvement (mm) | 15.9 | 6.8 | 3 | 30 | 16.5 | 12.5 | 20 |

## Therapeutic characteristics

Twenty three patients (62.2%) received treatment for the attack with a combination of methylprednisolone and PPH, and 8.1% of the patients (3) only received methylprednisolone. On average, the number of PPH was 4.6. In relation to immunomodulatory maintenance management the most common treatment was prednisolone and azathioprine (56.8), followed by rituximab in 40.5% of the patients.

## Wilcoxon sign-rank sum test for paired data

The Wilcoxon rank test was performed to evaluate statistically significant differences between visual acuity or EDSS at admission and discharge and treatment with plasmapheresis. Table 3.

## DISCUSSION

The epidemiology of NMOSD has been based on international studies of relatively small populations; many early studies have shown demographic, clinical, laboratory and radiological variability. This variability is due to confounding factors, including the use of non-standardized diagnostic criteria, variability in anti-AQP4 antibody assay techniques, studies with small cohorts, and the potential for selection bias. The epidemiological characteristics of patients in Colombia differ in some criteria from the usual presentation known worldwide; this makes it necessary to describe our own epidemiology and the characteristics of patients with NMOSD in Colombia.

The advent of more specific diagnostic criteria, improved tests and diagnostic methods, and a better understanding of the basic immunology of NMO and NMOSD have made it possible to talk more homogeneously about patients with NMOSD. Given the heterogeneity of the populations, it is particularly important to describe the clinical, neuroimaging and laboratory characteristics, that are particular to the Colombian population. It is striking to note the frequency of AQP4-IgG seroconversion to positivity and the frequency of association with other autoimmune comorbidities; the prevalence worldwide is 20-30%, and in our study autoimmune comorbidities were reported in 13.5% of the population.

It is interesting that the demographic variables of our study are very similar to those reported in other studies; the clinical presentation has a heterogeneity, and we emphasize that of the patients who debuted with optic neuritis in the first attack, up to 19% was bilateral, compared to the world population, which is only 5%. In paraclinical variables, three patients (8.1%) with seropositive NMOSD had oligoclonal bands pattern II, compared to the world population, which reports up to 20%. Regarding the characteristics of the cerebrospinal fluid cytochemistry, the literature reports that

**Table 3: Wilcoxon sign-rank sum test for paired data**

| | Admission Median | Discharge n | Median | n | Z(*) | p value |
|---|---|---|---|---|---|---|
| PPF (plasmapheresis)=1 | | | | | | |
| VA | 2 | 23 | 1 | 23 | 2.8 | 0.0048 |
| EDSS | 3 | 20 | 2 | 23 | 3.3 | 0.0011 |
| PPF (plasmapheresis)=2 | | | | | | |
| VA | 1.5 | 8 | 1 | 8 | 1.4 | 0.1573 |
| EDSS | 2 | 8 | 1.5 | 8 | 2.0 | 0.0455 |
| TOTAL | | | | | | |
| VA | 2 | 31 | 1 | 31 | 3.2 | 0.0016 |
| EDSS | 3 | 28 | 2 | 31 | 3.8 | 0.0001 |

35% of patients present pleocytosis of less than 50 cells/mL with a differential count of 44% neutrophils and 10% eosinophils (30,33); in our study, 29.7% had mild pleocytosis with lymphocytic (9.9%), eosinophilic (6.3%) and neutrophilic (3.5%) predominance.

It is striking that in radiological studies, up to 8.1% presented lesions typical of multiple sclerosis according to the Barkhof criteria, compared to 16% in the world population; unlike the world population, which reports a 7-14% short segment partial acute myelitis presentation, we noted a higher frequency in our study (21.6%) (16-25). In addition, in studies worldwide, the most common form of spinal involvement is longitudinally extensive acute transverse myelitis (80%); in our study it was not as frequent, as it was only evidenced in 29.7%. EDSS was statistically significantly lower at discharge compared to admission among patients treated with plasmapheresis (Z= 3.8, p 0.0001).

Differences were compared to the study by Reyes et al, were the most frequent first attack was optic neuritis and autoimmune systemic diseases, lower percentage of patients with MRI with typical lesions of MS and number of patients with BOG positive pattern II. Regarding the treatment received in the attack, the majority of patients were treated with plasmapheresis and methylprednisolone; they had a better outcome, with better visual acuities and EDSS of 3 or less, with statistically significant differences.

In conclusion, although our study had a small sample which limits the extrapolation of the results to other Colombian populations. It is important to know the characteristics of our NMOSD population. This will make it possible to suspect and diagnose the disease in a timely manner in difficult cases, in order to prevent the accumulation of disability in a young working population.

## CONCLUSION

In Colombia there is only one study of 22 patients in 3 hospital centers. There are no more epidemiological data specific to our population, being this the first characterization of the largest number of patients NMOSD patients recruited in a single hospital in Bogotá. We want to emphasize that we found some differences in the presentation in comparison with the available data in the literature. However, studies with a larger number of patients are required to draw conclusions regarding differences in clinical, imaging and laboratory variables in our population.

## Conflicto de interes

There is no conflict of interest regarding the publication of this article.

## REFERENCES


1. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85:177-89.
2. Wingerchuk DM, Lennon VA, Pittock SJ,Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology, 2006;66(10):1485-9.
3. Reyes MA, Navas Granados AV, Ramírez SF. Spectrum of optic neuromyelitis in Colombia, first characterization clinical and radiological in three centers of Bogotá. Acta Neurol Colomb. 2016;32(3):190-202.
4. Melamed E, Levy M, Waters PJ, et al. Update on biomarkers in neuromyelitis optica. Neurol Neuroimmunol Neuroinflamm.2015;2(4):e134.
5. Mata S, Lolli F. Neuromyelitis optica: an update.J Neurol Sci. 2011;303(1-2):13-21.
6. Lennon PVA, Wingerchuk DM, Kryzer TJ. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet. 2004;364(9451):2106-12.
7. Drori T, Chapman J. Diagnosis and classification of neuromyelitis optica (Devic's Syndrome). Autoimmun Revi 2014;13:531-3.
8. Pereira WL, Reiche EM, Kallaur AP, Kaimen-Maciel DR. Epidemiological, clinical, and immunological characteristics of neuromyelitis optica: A review. J Neurol Sci. 2015;355(1-2):7-17
9. Etemadifar M, Nasr Z, Khalili B. Epidemiology of neuromyelitis optica in the world: A systematic review and meta-analysis. Mult Scler Int.2015;2015:174720.
10. Asgari N, Lillevang ST, Skejoe HP, Falah M, Stenager E, Kyvik KO. A population-based study of neuromyelitis optica in Caucasians. Neurology. 2011;76(18):1589-95.
11. Flanagan E, Cabre P, Weinshenker BG, et al. Epidemiology of aquaporin-4 autoimmunity and neuromyelitis optica spectrum. Ann Neurol. 2016;79(5):775-83.
12. Cabre P, Gonzalez-Quevedo A, Lannuzeletal A.Descriptive epidemiology of neuromyelitis optica in the Caribbean basin. Rev Neurol. 2009;165-(8-9):676-83.
13. Jacob A, Panicker J, Lythgoe D, et al. The epidemiology of neuromyelitis optica amongst adults in the Merseyside county of United Kingdom.J Neurol. 2013;260(8):2134-7.
14. Cabrera-Gómez JA, Kurtzke JF, Gonzalez-Quevedo A, Lara-Rodrıguez R. An epidemiological study of neuromyelitis optica in Cuba.J Neurol, 2009:256(1),35-44.
15. Rivera JF, Kurtzke JF, Booth VJ, Corona VT. Characteristics of Devic's disease (neuromyelitis optica) in Mexico.J Neurol. 2008; 255(5):710-5.
16. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med 2005;202(4):473-7.
17. Varrin-Doyer M, Spencer CM, Schulze-Topphoff U et al. Aquaporin 4-specific T cells in neuromyelitis optica exhibit a Th17 bias and recognize Clostridium ABC transporter. Ann Neurol 2012;72:53-64.
18. Sellner J, Hemmer B, Muhlau M. The clinical spectrum and immunobiology of parainfectious neuromyelitis optica (Devic) syndromes. J Autoimmun 2010;34(4):371-9.
19. Bennett JL, Lam C, Kalluri SR et al. Intrathecal pathogenic anti- aquaporin-4 antibodies in early neuromyelitis optica. Ann Neurol 2009; 66(5):617-29.
20. Popescu BF, Lennon VA, Parisi JE et al. Neuromyelitis optica unique area postrema lesions: nausea, vomiting, and pathogenic implications. Neurology 2011; 76(14):1229-37.
21. Ghezzi A, Bergamaschi R, Martinelli V, et al. Clinical characteristics, course and prognosis of relapsing Devic's neuromyelitis optica. J Neurol 2004; 251(1):47-52.
22. Verkman AS. Aquaporins in clinical medicine. Annu Rev Med 2012;63:303-16.
23. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet Neurol 2007;6(9):805-15.
24. Jarius S, Ruprecht K, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A multicentre study of 175 patients. JNeuroinflammation. 2012;Jan 19;9:14.
25. 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(8):1135-43.
26. Pandit L, Asgari N, Apiwattanakul M, et al. Demographic and clinical features of neuromyelitis optica: A review. Mult Scler J. 2015; 21(7):845-53.
27. Matiello M, Lennon VS, Jacob A, et al. NMO-IgG predicts the outcome of recurrent optic neuritis. Neurology 2008;70(23):2197-200.
28. Sellner J, Hemmer B, Mühlau M. The clinical spectrum and immunobiology of parainfectious neuromyelitis optica (Devic) syndromes. J Autoimmun. 2010;34(4):371-9.
29. Jarius S, Wildemann B.The history of neuromyelitis optica. JNeuroinflammation 2013; Jan 15;10:8.
30. Kira J-I. Multiple sclerosis in the Japanese population. Lancet Neurol. 2003;2(2):117-27.
31. Jacob A, Mckeon A, Nakashima I, et al. Current concept of neuromyelitis optica (NMO) and NMO spectrum disorders. J Neurol Neurosurg Psychiatry 2013;84(8):922-30.
32. Di Pauli F, Mader S, Rostasy K, et al. Temporal dynamics of anti-MOG antibodies in CNS demyelinating diseases. Clin. Immunol. 2011;138(3):247-54.
33. Akmar-Demir G, Tuzun E, Waters P, et al. Prognostic implications of aquaporin-4 antibody status in neuromyelitis optica patients. J Neurol 2011;258(3):464-70.
34. Wang H, Dai Y, Qiu W,, 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(1-2): 181-4.
35. Weinshenker BG, Wingerchuk DM, Vukusic S, et al. Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis. Ann Neurol. 2006;59(3):566-9.