Neuromyelitis optica spectrum disorder relapses and seasonal influence in an equatorial country cohort

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Introduction. Information about seasonal distribution of Neuromyelitis optica spectrum disorders (NMOSD) attacks, particularly in tropical countries, has rarely been described and the reported data are diverse.

Objective. To evaluate influence of seasonal variation in NMOSD relapses in an equatorial country.

Patients and methods. Exploratory observational, retrospective ecological study in a cohort of patients with NMOSD followed from January 2008 to December 2019. Data of demographic, clinical information, characteristics of relapses and seasonal temporal variation were recorded. Also, the annual, monthly and intra-annual seasonal variation of relapses was quantified. A negative binomial regression was used to estimate the associations between the number of relapses and climatic and temporal variables.

Results. One hundred thirteen patients were included, most of them were female (89.38%), with a mean age at NMOSD diagnosis was 44.97 (±13.98) and the median of relapses per patient were 2 relapses (IQR 1-3). The patients presented 237 relapses, most of these in AQP4 seropositive patients (87.76%) and longitudinal extensive myelitis was the most frequent type of relapse (53.59%). According to the temporal variation, relapses were more common in the second rainy season (28.69%) during November and December. However, there weren't significant differences in the number of relapses between seasons and climatic variables in the multivariable model.

Conclusion. The number of NMOSD relapses in this equatorial country cohort did not exhibit any significant associations with climatic variations, including changes in rainy or dry seasons.

Key words. Autoimmune diseases of the nervous system. Demyelinating diseases. Neuromyelitis optica. Relapses. Seasonal variations. Seasons.

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune astrocytopathy mediated by specific auto-antibodies against aquaporin 4 receptor [1,2]. Relapses may present as a severe optic neuritis, longitudinal extensive myelitis and diencephalic, area postrema or cerebral syndrome [3].

The pathogenesis of autoimmune diseases comprises a series of complex interactions between genetic, environmental and hormonal factors. The levels of vitamin D, melatonin, exposure to ultraviolet radiation and infections exhibit a seasonal pattern that may explain the variation in the incidence/prevalence of the disease activity of some autoimmune diseases during the year [4]. Seasonality of relapses has been poorly described in NMOSD cohorts since they have been studied mainly in intermediate or high latitude countries [5,6].

Countries on the equator have specific characteristics in terms of time variations. In Colombia, according to data from the Colombian National Institute of Hydrology, Meteorology and Environmental Studies (IDEAM), in tropical latitude countries, stations are classified as rainy or dry seasons depending on the millimeters of rain collected per hour. (dry season: 0-6 mm, intermediate: 6-14 mm; and rainy season: 14-20 mm.). These seasonal temporal variations are defined as first dry season (january to march), first rainy season (april to june), second dry season (july to september) and second rainy season (october to december) [7-9]. Also, there are other factors that influence interannual precipitations like *El Niño* (extreme heat) or *La Niña* (extreme cold/rain), have an impact on interannual precipitation [10].

The aim of this study was to evaluate if there is any yearly pattern in the frequency of relapses in

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patients with NMOSD in a country at the equator and its relationship with dry or rainy seasons.

Patients and methods

Location and study design

This is an observational, ecological and retrospective study that evaluated the presence of relapses, in patients with diagnosis of NMOSD, who consulted from january 2003 to december 2021 at Fundación Instituto Neurológico de Colombia, Medellín, Colombia.

Participants

We included all patients older than 18 years-old with diagnosis of NMOSD as defined by the 2015 Wingerchuck diagnostic criteria [2,11], who had relapses during january 1st 2003 to december 31st 2021. Relapses were defined as exacerbations with new symptoms or worsening attributable to a new T_2 or T_1 contrast-enhancing lesion on magnetic resonance imaging within a 30-day period. Patients with incomplete data, unavailable studies or pregnancy were excluded.

Primary outcome, covariables and data sources

The primary outcome of this study was the number of relapses per month and year presented during the follow-up period. Demographic characteristics, Antibodies to antiaquaporin 4 status and number of relapses were described. Clinical relapse features, days of hospitalization and treatment were also exhibited. Both patient and relapse characteristics were collected retrospectively from clinical records and magnetic resonance imaging findings.

The ecological variables evaluated were: temporal variation (first dry season, first rainy season, second dry season and second rainy season); mean of highest temperature per month; mean of lower temperature per month and records of annual, monthly and intra-annual seasonal and climatic, using records provided by IDEAM [12].

Statistical analysis

Relative and absolute frequencies were reported for qualitative variables and mean or median variables were estimated for quantitative variables according to their normality. Data was tested for normality using the Kolmogorov-Smirnov test. To evaluate if there were differences in the proportions of relapses between dry and rainy seasons, we performed a χ^2 test and determined if there were differences in the median of relapses between months, using Kruskal-Wallis test.

Due to the over-dispersion of the data, a negative binomial regression was used to estimate the associations between the number of relapses and climatic and temporal variables. A simple negative binomial regression model was done and the variables included in the multivariable analysis were those with $p < 0.25$. In addition, a stepwise method based on purposeful selection of variables, including statistical and biological plausibility was conducted in the multivariable analyses. The effects of modification and confounding were evaluated and the Akaike information criteria was used to select the best model that explained the outcome. Incidence rate ratio was estimated with a confidence of 95% and statistical significance $p < 0.05$. All the analysis was performed in RStudio version 4.2.2.

Results

Characteristics of participants and relapses

We included 113 patients who met the eligibility criteria, most of the patients were female (89.38%). The mean age at NMOSD diagnosis was 44.97 (±13.98), 84.07% (n = 95) of the cases were aquaporin 4 seropositive, 10.62% (n = 12) were aquaporin 4 seronegative and 5.31% (n = 6) were aquaporin 4 undetermined.

The patients presented 237 relapses, with an average of 2 relapses per patient. Most of these relapses were presented in females (91.14%), and in aquaporin 4 seropositive patients (87.76%). The most frequent type of relapse was longitudinally extensive transverse myelitis (53.59%), follow by optic neuritis (32.49%). Also, 45.57% of relapses were treated with methylprednisolone and 27.43% of the cases were treated with metil-prednisolone plus plasmapheresis (Table I).

According to the temporal variation, 23.21% (n = 55) of relapses were presented in the first dry season, 23.21% (n = 55) of in the first rainy season, 24.89% (n = 59) in the second dry season and 28.69% (n = 68) in the second rainy season. Likewise, we determined that the months with more frequency of relapses were november (n = 26) and december (n = 24) and the months with the lowest relapses were february (n = 15) and april (n = 15)

(Fig. 1). The annual frequency of NMOSD relapses between 2003-2021 is described in figure 2.

Univariate and multivariate analysis

In the bivariate analysis, significant differences were observed between the proportion of relapses reported during dry and rainy seasons (48.2%, n = 114, versus 51.8%, n = 123, p < 0.0001). However, there weren't significant differences in the median of relapses between dry or rainy seasons (p = 0.1739) and in the median of relapses between months (p = 0.5599).

In the simple negative binomial regression models, we didn`t find significant associations between co-variables and the number of relapses. The final multivariate model included the following co-variables: SDS, the months July and august. These factors were not associated with the number of relapses when their effect was adjusted in the multivariable model (Table II).

Table I. NMOSD relapse characteristics.

	n = 237 (%)
Sex	
Women	226 (91.14)
Men	21 (8.86)
Age at diagnosis ± SD	44.97 ± 13.98
NMOSD type	
AQP4 (+)	208 (87.76)
AQP4 (–)	20 (8.44)
Undetermined	9 (3.8)
Type of relapse	
ON	77 (32.49)
LETM	127 (53.59)
Brain stem	9 (3.8)
ON + LETM	20 (8.44)
LETM + brain stem	2 (0.84)
ON + LETM + brain stem	1 (0.42)
ON + LETM + brain	1 (0.42)
Acute treatment	
None	22 (9.28)
Metilprednisolone	108 (45.57)
Metilprednisolone + plasmapheresis	65 (27.43)
Plasmapheresis	1 (0.42)
Rescue plasmapheresis	2 (0.84)
Chronic treatment	
None	151 (67.11)
Azathioprine	35 (15.55)
Rituximab	14 (6.22)
Other[a]	25 (11.12)

AQP4: aquaporin 4; LETM: longitudinally extensive transverse myelitis; NMOSD: neuromyelitis optica spectrum disorder; ON: optic neuritis, SD: standard deviation. [a] Other include cyclophosphamide, prednisone, and combined treatments such azathioprine plus cyclosporine and rituximab plus cyclophosphamide.

Discussion

A variety of factors associated with multiple sclerosis attacks have been documented in the literature, including seasonality, infectious diseases, vitamin D levels and melatonin [13]. In patients with NMOSD, studies on the effect of seasonality are limited and their conclusions are mixed. In this retrospective cohort conducted in an equatorial country, we observed that NMOSD relapses tended to occur more frequently during the rainy season. However, no significant differences in median relapses were found between dry and rainy seasons, nor was there an association between the number of relapses and the climatic and temporal factors studied in the multivariate model.

Our findings align with a limited number of studies that have previously investigated the relationship between NMOSD relapses and seasonal variations [1,3,4,14]. Cohorts from Brazil, Japan, Australia and the United Kingdom, countries that are not on the equator line, demonstrated no significant association between NMOSD relapses and changes in months, weather or humidity throughout the year [1,3-5].

Despite not finding an association between the variables and the number of relapses in the present study, it is important to highlight that, by observing a higher proportion of relapses in rainy seasons, measures for the detection of relapses in these seasons should be reinforced, since their attention im-

Figure 1. Number of neuromyelitis optica spectrum disorder relapses per month.

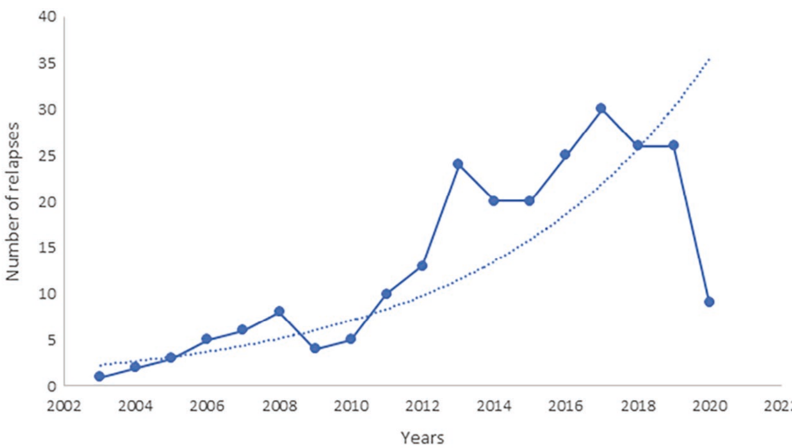
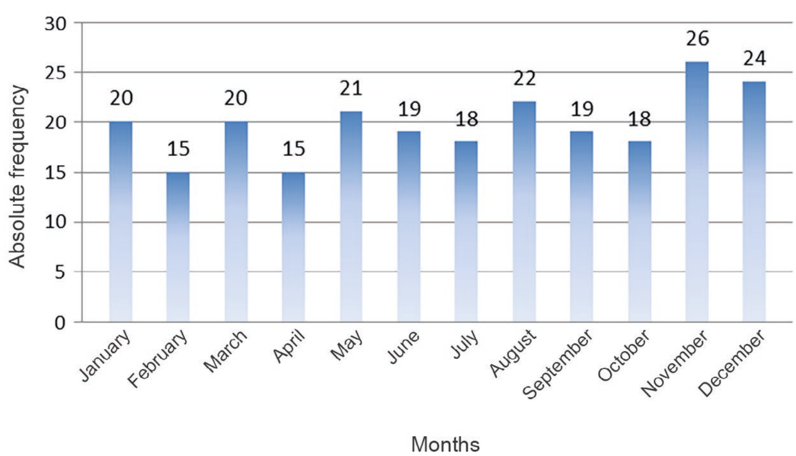


Figure 2. Annual frequency of neuromyelitis optica spectrum disorder relapses 2003-2020.



plies timely treatment to avoid the progression of the disability with the requirement of the availability of intensive care units necessary for treatment with plasmapheresis.

It is important to remark that rainy seasons in Colombia may vary according to additional phenomena like *El Niño* or *La Niña*, potentially disrupting the typical annual seasonality pattern [15-17]. Moreover, climatic factors like altitude, temperature, precipitation, cloudiness, humidity, and other variables can vary depending on the specific locations of municipalities and are measured at different climate stations. This study was done in only one city (Medellin) with an altitude of 1,495 meters, described as subtropical, humid and with an average temperature of 22 ºC [18]. These meteorological variations presented according to the geographical latitude could explain the fact that the present study didn't find associations between seasons, months and temperatures in the city of Medellin.

There was a noticeable increase in relapses between 2012 and 2019. We propose that this phenomenon may be related to the initiation of the demyelinating disease programme at our institution during this period, leading to the inclusion of a larger number of patients in our cohort. Despite the recognised influence of possible manifestations of climate change in Medellín, with increased temperatures and higher frequency of extreme precipitation [18], the data available in this study on climatic conditions were considered insufficient to explain the observed increase in relapses.

It has been suggested that in patients with NMOSD, as in patients with autoimmune diseases such as systemic lupus erythematosus and psoriasis, there may be an association with antigen mimicry generated by viral infections, influenza vaccination, and fluctuations in vitamin D and melatonin [19], which are related to seasonal patterns.

Influenza and Epstein-Barr virus have been recognized as triggers of autoimmune diseases [20]. Epstein-Barr virus has a higher prevalence during winter and has been found in greater proportions in patients with systemic lupus erythematosus relapses [19]. In this regard, two seasonal influenza peaks are usually reported in Colombia: the first, between march and july; and the second, from september until december [21]. The findings of the present study evidence a greater number of relapses during november and december; this is concordant with influenza peaks, and it could correlate with rainy seasons. Further ecological studies are needed to confirm this hypothesis. In addition, there is a case report in Korea associating seasonal influenza vaccination and a patient with a NMOSD attack [22]. In this case, it is uncertain if the NMOSD relapse was related to the Influenza virus, a vaccine vehicle or the vaccine itself. According to the World Health Organization in subtropical and tropical countries, influenza immunization is scheduled for april [23]. The Colombian National Institute of Health provides influenza vaccine to vulnerable groups like adults older than 60 years old, infants between 14 and 23 months old, pregnancy and added comorbidities [24]. This vaccination timing does not correspond to NMOSD relapses found in this study.

Table II. univariate and multivariate negative binomial regression models.

	n = 237 (%)	Crude IR (95% CI)	*p* value	Adjusted IR (95% CI)	*p* value
Temporal season					
First dry season, (IQR)	1 (1-2)	0.87 (0.64-1.16)	0.37		
First rainy season, (IQR)	2 (1-3)	0.84 (0.62-1.12)	0.9989		
Second dry season, (IQR)	2 (1-3)	1.27 (0.94-1.69)	0.106	1.21 (0.85-1.68)	0.266
Second rainy season, (IQR)	1 (1-3)	1.001 (0.75-1.32)	0.994		
Environmental temperature					
Lowest, °C ± SD	17.76 ± 0.49	1.02 (0.89-1.15)	0.766		
Highest, °C ± SD	28.13 ± 1.02	0.89 (0.67-1.15)	0.38		
Months					
January, median (IQR)	2 (1-2.5)	0.96 (0.59- 1.49)	0.874		
February, median (IQR)	1 (1-2)	0.78 (0.45-1.27)	0.361		
March, median (IQR)	2 (1-2)	0.96 (0.59-1.48)	0.874		
April, median (IQR)	1 (1-1)	0.78 (0.44 -1.27)	0.361		
May, median (IQR)	1 (1-2.5)	1.01 (0.63-1.55)	0.943		
June, median (IQR)	1 (1-2)	0.83 (0.50-1.29)	0.43		
July, median (IQR)	2 (1-3.5)	1.40 (0.84-2.19)	0.172	1.68 (0.66-2.04)	0.535
August, median (IQR)	2 (2-3)	1.33 (0.84-2.01)	0.202	1.12 (0.65-1.89)	0.666
September, median (IQR)	1 (1-2.75)	1.01 (0.61-1.57)	0.963		
October, median (IQR)	1.5 (1-2)	0.95 (0.57-1.49)	0.846		
November, median (IQR)	2 (1-3)	1.17 (0.76-1.72)	0.449		
December, median (IQR)	1 (1-3)	0.97 (0.63-1.46)	0.923		

CI: confidence interval; IQR: interquartile range; IR: incidence rate; SD: standard deviation.

The bibliography underscores the immunomodulatory role of vitamin D, as evidenced by in vitro studies revealing its capacity to inhibit the pro-inflammatory activity of $CD4^+$ Th1, thereby curtailing the production of interleukin 2, interferons gamma and tumor necrosis factor alpha [25,26]. Furthermore, vitamin D deficiency has emerged as a potential risk factor in various autoimmune disorders, specifically in relation to MS, Type 1 DM, and SLE. Multiple studies have reported a correlation between reduced vitamin D levels and an increased frequency of multiple sclerosis and systemic lupus erythematosus attacks during the winter months [13,19]. Notably, individuals with neuromyelitis optica spectrum disorder (NMOSD) have been identified with significantly lower levels of vitamin D compared to healthy controls, with an observed inverse correlation between vitamin D levels and the Expanded Disability Status Scale score [27]. Despite its tropical/subtropical location, 43% of the Colombian population is vitamin D deficient [28]. In the current study, the assessment of vitamin D levels at every relapse was not feasible, preventing the establishment of associations between vitamin D insufficiency and the frequency of relapses.

Melatonin, an indoleamine, exhibits antioxidant properties by stimulating various antioxidant enzymes in tissues, safeguarding lipids, proteins, and DNA from oxidative damage. Beyond its roles melatonin has been identified for its ability to impede the differentiation of T_H17 cells, leading to a reduction in interleukin 17 and cytokines [29]. Melatonin follows a circadian rhythm synchronized with the light/dark cycle, peaking during the dark phase [30]. While its circadian effects undergo adaptations in response to seasonal variations, recent studies have revealed an inverse correlation between melatonin levels and multiple sclerosis activity [31]. In this study we couldn't reaffirm this hypothesis, therefore its association with NMOSD remains to be determined.

Studying potential triggers of NMOSD relapses is essential to prepare the organization of resources and health institutions in order to prevent, diagnose and treat relapses. Also, consideration of possible environmental risk factors could provide clues about the risk factors and pathogenesis of this complex disease.

This study is subject to several limitations that warrant consideration within the scientific discourse. Firstly, there exists a potential for information bias due to the measurement of climatic variables at different weather stations. To address this, we took measures to minimize variability by specifically selecting the nearest climate station to Medellin city. Unfortunately, the incomplete data in the IDEAM registry prohibited the inclusion of certain climatic variables such as humidity, precipitation, and cloudiness in our analysis. The inability to estimate the annualized relapse rate resulted from the lack of detailed tracking of exactly when relapses occurred within each year, making it impossible to specific patterns in relapse occurrence. Another limitation stems from the study's non-probabilistic sampling approach, leading to a selection bias as the participants were confined to residents of Medellin city. Consequently, the generalizability of the findings may be constrained. Finally, caution is advised in interpreting results, because the ecological study design may distort inferences based on climatic aggregated data. It is crucial to consider individual variability and not rely solely on averages or aggregated data for a comprehensive understanding of the findings.

Conclusion

The number of NMOSD relapses within this equatorial country cohort showed no associations with climatic variations, including shifts between rainy and dry seasons. Future studies should delve into potential environmental risk factors that might serve as triggers for relapses and could be anticipated for preventive measures.

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Recaídas del trastorno de espectro de la neuromielitis óptica e influencia estacional en una cohorte de un país ecuatorial

Introducción. La evidencia sobre la distribución estacional de las recaídas del trastorno del espectro de la neuromielitis óptica (NMOSD), especialmente en países tropicales, es limitada y diversa.

Objetivo. Evaluar la influencia de las variaciones estacionales en las recaídas del NMOSD en un país localizado sobre la línea ecuatorial.

Pacientes y métodos. Se llevó a cabo un estudio ecológico, con información retrospectiva de una cohorte de pacientes con NMOSD atendida entre enero de 2003 y diciembre de 2020 en Medellín, Colombia. Se recolectaron datos demográficos y clínicos de los pacientes, así como información sobre variables estacionales y climáticas. Se calculó la frecuencia de recaídas por estación, mes y año, y se realizó una regresión binomial negativa para evaluar la asociación entre el número de recaídas, y las variables estacionales y climáticas.

Resultados. Se incluyó a 113 pacientes, de los cuales el 89,38% eran mujeres, con una edad media en el momento del diagnóstico de NMOSD de 44,97 (±13,98) años y una mediana de tres recaídas (rango intercuartílico: 1-2). Se registraron 237 recaídas, la mayoría en pacientes seropositivos para anticuerpos antiacuaporina 4 (87,76%) y con mielitis longitudinal extensa como la presentación clínica más común (53,59%). Las recaídas se presentaron con mayor frecuencia durante la segunda temporada lluviosa (28,69%; *n* = 68), y en los meses de noviembre y diciembre. Sin embargo, en la regresión binomial negativa no se observó una asociación significativa entre el número de recaídas y las variables climáticas y estacionales, los meses y los años.

Conclusión. Las variables climáticas y los patrones estacionales no muestran una asociación significativa con cambios en el número de recaídas del NMOSD en pacientes residentes en un país localizado sobre la línea ecuatorial.

Palabras clave. Enfermedades autoinmunes del sistema nervioso central. Enfermedades desmielinizantes. Estaciones. Neuromielitis óptica. Recaídas. Variaciones estacionales.