Multiple Sclerosis and Related Disorders 47 (2021) 102652

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Epidemiological findings of neuromyelitis optica spectrum disorders in a Venezuelan study

Soto de Castillo Ibis [a,*], Molina Omaira [a], Soto Arnoldo [b], Armas Elizabeth [c], Mendoza Sandra [d], Castillo Maria Carlota [a], Castro Elizabeth [a], Vink Laura [e], Leon Rosalba [c], Valbuena Oscar [f], Del Moral Luisa [g], Acosta Nahir [h], Freda Hernandez [a]

[a] Department of Neurology. Hospital Universitario de Maracaibo, Maracaibo, Venezuela
[b] Department of Neurology. Centro Medico Docente La Trinidad, Caracas, Venezuela
[c] Department of Neurology. Hospital Universitario de Caracas, Caracas, Venezuela
[d] Department of Neurology. Ciudad Hospitalaria "Dr. Enrique Tejera", Valencia, Venezuela
[e] Department of Neurology. Hospital Juan Daza Pereira, Barquisimeto, Venezuela
[f] Department of Pediatric Neurology, Hospital de especialidades pediátricas, Maracaibo, Venezuela
[g] Centro Medico de Cabimas, Cabimas, Venezuela
[h] Research Center, Instituto Cardiovascular del Cesar, Valledupar, Colombia

ARTICLE INFO

Keywords:
Neuromyelitis optica spectrum disorders
epidemiology
relative frequency
MS/NMOSD ratio
Venezuela

ABSTRACT

Background: Neuromyelitis optica spectrum disorders (NMOSD), is a rare autoimmune inflammatory disease of the central nervous system. Since the countries of Latin America (LATAM) show contrast in geographic, social, environmental factors, and genetic heterogeneity, the information about NMOSD epidemiology in the region allows a better understanding of the disease and its clinical outcome.
Objectives: To determine the prevalence, relative frequency (RF), and clinical characteristics of NMOSD in a multiethnic Venezuelan cohort of patients with demyelinating disorders.
Methods: We conducted a retrospective descriptive multicenter study of hospital case records of individuals with an established diagnosis of MS and NMOSD in the National Program for Multiple sclerosis (MS) from 2011 to 2018. We selected those NMOSD cases based on the 2006 Wingerchuck and the 2015 International panel for the diagnosis of Neuromyelitis optica (IPND) criteria.
Results: We identified 249 patients with NMOSD. The prevalence was 2.11 per100,000 individuals (95% confidence interval (CI)1.85 2.37), the RF was 23%, and the MS/NMOSD ratio was 3.2:1. The average disease onset occurred by the fourth decade of life (34±14.8 years of age); with a strong female predominance (female to male ratio: 4:1). Mestizos constituted 86,7% of this cohort. Most of the patients presented initially with simultaneous optic neuritis (ON) and acute transverse myelitis (ATM) and a recurrent course was registered in 82.3% of cases. The mean of the expanded disability status scale (EDSS) was 3.5 (IQR 2-7). Abnormal brain and spine MRI were present in 47.8% and 81.1% of patients, respectively. Antibodies against aquaporin-4 (AQP4) which were measured through a cell-based assay were positive in 55.3% of the individuals tested. The most used immunosuppressant agent was Azathioprine (57.4%).
Conclusion: NMOSD in Venezuela affects mainly young Mestizo women and shows one of the highest relative frequency in the region. Planning and developing healthcare programs for underserved populations as well as more comprehensive LATAM studies are required to identify the distribution and variations of its epidemiological picture.

Abbreviations: NMOSD, Neuromyelitis optica spectrum disorders; MS, Multiple Sclerosis; IPND, International panel for the diagnosis of neuromyelitis optica; ON, Optic Neuritis; ATM, Acute Transverse Myelitis; APS, Area postrema syndrome; MRI, magnetic resonance imaging; VEP, Visual evoked potentials; CNS, central nervous system; LATAM, Latin America; SA, South America.

* Corresponding Author: Department of Neurology. Hospital Clinico. Urbanizacion La Trinidad. Maracaibo, Venezuela
E-mail address: ibissotodecastillo@gmail.com (S.C. Ibis).

https://doi.org/10.1016/j.msard.2020.102652
Received 30 July 2020; Received in revised form 17 November 2020; Accepted 23 November 2020
Available online 26 November 2020

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune inflammatory demyelinating disease of the central nervous system (CNS) that affects mainly the optic nerves and the spinal cord (Wingerchuk et al., 2006). Once thought to be a form of multiple sclerosis (MS), it is now considered a distinct autoimmune entity with different underlying pathogenesis and more severe course (Jarius et al. 2014; Pittock, 2008; Wingerchuk et al., 2007). The discovery of a highly specific aquaporin-4 (AQP4) autoantibody (NMO-IgG) has updated the diagnostic criteria and expanded the spectrum of NMO-related conditions (Fujihara et al., 2012; Lennon et al., 2004, 2005; Pittock et al., 2006; Wingerchuk et al., 2006). NMOSD, a term proposed for the International consensus diagnostic criteria in 2015, involves a variation of the classical picture with a broader range of symptoms (Wingerchuk et al., 2015). These include typical NMOSD brain lesions (hypothalamus, corpus callosum, brainstem, periventricular) or a more limited presentation, such as isolated transverse myelitis or optic neuritis, with or without detectable AQP4 autoantibody (Bienia & Balabanov, 2013; Pandit et al., 2015; Wingerchuk et al., 2007, 2015).

Although cases of NMOSD have been described throughout the world, epidemiological studies regarding this disease are still scarce in many countries (Alvarenga et al. 2017; Etemadifar et al., 2015; Pandit et al., 2015). In the United States, Europe, and Asia NMOSD prevalence has been reported to be less than 5 cases per 100,00 inhabitants (Asgari et al., 2011; Etemadifar et al., 2014; Cossburn et al., 2012; Marignier et al., 2008; Mealy et al., 2012; Sahraian et al., 2010; Pandit & Kundapur, 2014). In one study from Australia and New Zealand, NMOSD is three times more prevalent in individuals with Asian ancestry than in the rest of the population of predominantly European descent (Bukhari et al., 2017). However, new and more robust population-based studies in Caucasians show that NMOSD seems to be more common than earlier believed (Cossburn et al., 2012; Jacob et al., 2013; Jonsson et al, 2019).

In LATAM countries, where the racial mix is common, the NMOSD prevalence has ranged from 0.37 to 4.2/100,000 affecting predominantly African descents, including mestizo and Afro-Caribbean people (Bichuetti et al., 2009; Cabre et al., 2001; Cabrera-Gomez et al., 2009; Rivera et al., 2008). A trend of a higher relative frequency (RF) of NMOSD to MS in areas where non-white descendants predominate is common in this region (Alvarenga et al., 2017; Correa Diaz et al., 2020; Papais-Alvarenga et al., 2015). These findings have been attributed to many factors, including population genetic composition, geographical or environmental factors. LATAM studies on NMOSD also show a female predominance affecting mainly young patients between 30-40 years with ON and ATM being the most frequent symptoms. Limited information exists about NMOSD epidemiology and its clinical course in Venezuela. In this study, we aimed to determine the prevalence, relative frequency, and clinical characteristics of NMOSD in a Venezuelan cohort.

2. Patients and Methods

2.1. Setting

Located at the northernmost end of South America within a latitude and longitude of 8^0 0' N and 66^0 0' W, Venezuela is the sixth-largest country in LATAM with a total multiethnic population of about 31,017,064 (INE, 2015) and considered a low prevalence MS zone. The patients in this study resided in the Venezuelan West and Central regions that include the Capital, Central, and Central West political administrative districts; it has an area of 176,224 Km^2 with a population of 11, 770,529 inhabitants (INE, 2015). All Venezuelan patients with CNS demyelinating disorders are registered in a database of the National Program for Multiple Sclerosis (National Registry) which is administrated by the Venezuelan Institute of Social Security (IVSS, Caracas). These registries facilitate the distribution of immunosuppressive therapies among Venezuelan patients, and the treatment is free of charge.

2.2. Data source

The primary data source was the medical records of patients with the diagnosis of NMOSD and MS followed from 2011 to the end of 2018. The records from each institution were cross-checked with information from the National Registry to verify that each patient appeared just once in the study, avoiding duplication of data (Fig 1). The patients were collected from the following hospitals: 1) Hospital Universitario from Maracaibo, 2) Centro Medico La Trinidad from Caracas, 3) Hospital Enrique Tejera from Valencia, 4) Hospital Juan Daza Pereira from Barquisimeto, 5) Hospital de Especialidades Pediatricas from Maracaibo, 6) Hospital Universitario from Caracas, 7) Centro Medico from Cabimas.

2.3. Study design

We conducted a retrospective descriptive multicenter study of NMOSD by reviewing the medical records and getting information through questionnaires that included general information, clinical examination, and paraclinical studies of all cases with this diagnosis. For each patient, we collected demographic data including sex, age, ethnicity (Mestizos, Amerindians, African Venezuelans, and Caucasians) (Rivera & Cabrera, 2001) at onset and follow-up; first symptom (classified ON, ATM, brainstem syndrome, area postrema [APS], or cerebral syndrome); disability score (Expanded Disability Status Scale (EDSS); monophasic or recurrent course; laboratory data (NMO-IgG, classified seropositive, seronegative or unknown); MRI data (classified normal or abnormal); visual evoked potentials, and type of treatment. Serum samples were analyzed using a cell-based assay for the NMO-IgG antibody in the Mayo Clinic Neuroimmunology Laboratory. Since the anti-myelin oligodendrocyte glycoprotein (MOG) antibody test is not available in our country, we did not include MOG seropositive patients.

2.4. Diagnosis

We retrospectively identified patients with clinical features of NMOSD at onset and follow-up using the 2006 and the 2015 criteria and validated the diagnosis of the entire cohort based on the 2015 IPND criteria (Wingerchuk et al. 2006, 2015). The whole dataset (clinical record, neuroimaging, and laboratory data) was reviewed by a panel of neurologists to agree on the final diagnosis.

2.5. Statistics

We calculated the prevalence using the number of patients with NMOSD per 100,000 individuals (with 95% confidence intervals for this proportion) and the relative frequency (RF) by the quotient involving the total cases of NMOSD divided by the sum of cases MS and NMOSD (Alvarenga et al., 2017) The qualitative variables were expressed in frequency and percentages. The quantitative variables were evaluated for their mean or median with their respective standard deviation and interquartile range depending on whether they met the normal distribution. The association of qualitative variables was analyzed with the chi-square test and the mean difference using the Mann-Whitney U test. Analyses were performed with the SSPS statistical software. The study was approved by the ethical committee of each of the participant hospitals.

3. Results

The National Registry held records of 1069 patients. From this group, we identified 820 (76.7%) patients with MS and 249 (23.2%) NMOSD patients meeting the 2006 and 2015 NMOSD criteria. The prevalence was 2.11 per 100,000 (95% confidence interval (CI)1.85 2.37), the RF

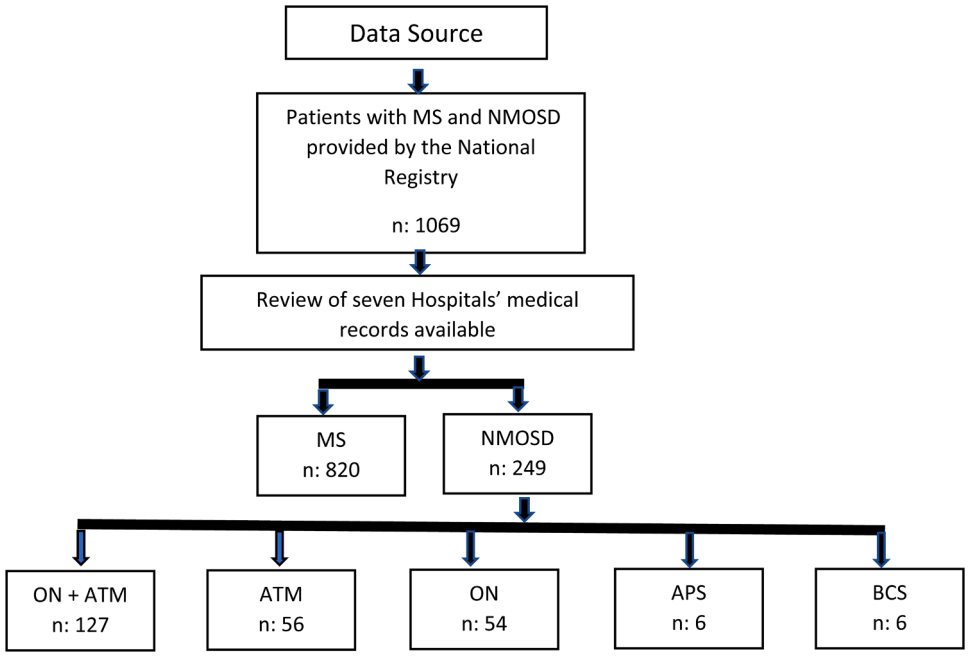

Fig. 1. Sampling and review process.
Abbreviations: NMOSD: Neuromyelitis optica spectrum disorders; MS: multiple sclerosis; ON: optica neuritis; ATM: acute transverse myelitis; APS: area postrema syndrome; BCS: brainstem/ cerebral syndrome.

was 23%, and the MS/NMOSD ratio was 3.2:1. The sex distribution was strongly skewed toward female (82.7%), with a female to male ratio of 4:1. Patients' demographics characteristics, clinical, and paraclinical findings are exhibited in **Table 1.** The average disease onset occurred in the fourth decade of life (34±14.8) years of age. Mestizo patients constituted the largest race group (86.7%), and the disease course was recurrent in 82.3% of patients. Most of the patients (51%) presented initially with ON and ATM followed by isolated ATM (22.4%), and ON (21.6%), while 2.4% presented with brainstem/cerebral and area postrema syndrome (APS), respectively. A recurrent course was registered in 82.3%. The average time between the first and second relapse was 12 months (range 0-366). Abnormal brain and spine MRI were present in 47.8% and 81.1% of patients, respectively. AQP4-IgG antibodies were measured in 141(56.6%) patients, 57.4% of the cases had positive antibodies (78/141), and 44.6% of the cases were negative (63/141). There was no association between gender and the result of AQP-4 IgG (p=0,052*)*. The mean EDSS score was 3.5 (IQR 2-7) at the debut of the disease. There were no statistical differences in the mean EDSS by gender (female =3,5; male = 2,25; p = 0,456); evolutionary course (monophasic = 2,5; recurrent = 4,0; p= 0,08) or AQP-4 IgG (positive = 3,5; negative = 3, 0; p = 0,821).

In the acute setting, the most common drug given was methylprednisolone treatment (IVMP) and 5.2% received plasmapheresis at least once. Azathioprine was used as the immunosuppressant drug in 57.4%. Few patients were treated with mycophenolate mofetil (3.2%), while only 0.8% of patients received Cyclophosphamide and Rituximab, respectively.

4. Discussion

The prevalence of NMOSD was estimated to be 2.1 per 100,000 individuals in this Venezuelan study. This number is in line with previous reports in the literature from Europe, Asia, the United States, and LATAM (Asgari et al., 2011; Bukhari, et al., 2017; Jacob et al., 2013). A review of those studies shows variable criteria, methodology, and limited geographic region indicating that the prevalence is mainly crude rates and will probably increase in future reports. Since the National Registry received all the patients with this diagnosis, and we sampled the whole number of known cases at the time of the study, we consider this as the best estimate of the actual prevalence of NMOSD in Venezuela. Case ascertainment in NMOSD represents a significant factor affecting demographics.

NMOSD has been reported from different countries with diverse ethnicities. Some studies show an NMOSD ethnical preference for non-whites; for instance, NMOSD is diagnosed in 15 to 57% of African-American, Japanese, and Indian populations with CNS demyelinating disorders while in less than 2% of Caucasians (Etemadifar et al., 2015; Cabre et al., 2001; Kira, 2003; Wu et al.,2008). More evidence indicating that NMOSD is uncommon in Caucasians comes from studies analyzing the MS to NMOSD ratio and the RF. In one study in Florence, Italy, a high MS prevalence area, the MS/NMOSD ratio was 79.1 (for each NMOSD patient 79 were MS) (Bizzoco et al., 2009). Conversely, in the Southeast of Brazil study, this ratio was 4:1 in Rio de Janeiro and 13:1 in São Paulo (Papais-Alvarenga et al., 2014). And another recent report from Ecuador showed a ratio of 5.2:1 (Correa Diaz et al., 2020). The ratio of 3.2:1 found in our study is close to that of Rio de Janeiro and Ecuador. Taken together, the high frequency of NMOSD among African descents and mestizos in these LATAM regions adds credence to the hypothesis of an ethnic connection with this disease.

Ethnicity also plays a consistent role in determining the frequency of occurrence of NMOSD across a few LATAM reports available. One recent study showed that RF is higher in cities with a high proportion of non-whites living in areas with a low prevalence of MS (Alvarenga et al., 2017; Papais-Alvarenga et al., 2015). For example, the RF was 27% in Martinique, 8% in Mexico, 20.5% in Rio de Janeiro, and 15.9% in Ecuador compared to 2.1% in Argentina whose proportion of non-whites is 1% (Cabrera-Gomez et al., 2009; Flanagan et al., 2016; Gracia, et al., 2014; Rivera et al., 2008; Correa Diaz et al., 2020). The RF in our work is one of the highest in the region and close to those from high non-white populations. Interestingly, one study relates RF to geographic latitude and ethnicity in that the overall RF increases on a South-North gradient (Bukhari et al., 2017; Alvarenga et al., 2017). As these LATAM countries show geographic, social, environmental, and ethnic differences, a combination of risk factors may influence their RF. Some authors, point

Table 1
Demographic, Clinical, and Paraclinical Characterization of NMOSD patients.

Demographic	Patients
(n: 249)	
Age at onset, mean ± SD	34 (14.8)
Sex, n (%)	
Female	206 (82.7)
Male	43 (17.3)
Female to male ratio	4:1
Ethnicity, n (%)	
Mestizo	216 (86.7)
Caucasian	18 (7.2)
	12 (4.8)
Amerindian	12 (4.8)
African Venezuelan	3 (1.2)
Clinical	
Disease course, n (%)	
Monophasic	44 (17.7)
Recurrent	205 (82.3)
Initial clinical event, n (%)	
Simultaneous ON + ATM	127 (51)
ATM	56 (22.4)
ON	54 (21.6)
Area postrema syndrome	6 (2.4)
Brainstem/cerebral syndrome	6 (2.4)
EDSS median (IQR)	3.5 (2-7)
Paraclinical	
AQP4-IgG, n (%)	141 (56.6)
Seropositive	78 (57.4)
Seronegative	63 (44.6)
Unknown	108 (43.4)
Brain MRI, n (%)	
Normal	86 (34.5)
Abnormal	119 (47.8)
Unknown	44 (17.7)
Spine MRI, n (%)	
Normal	21 (8.4)
Abnormal	202 (81.1)
Unknown	18 (7.2)

Abbreviations: NMOSD: neuromyelitis optica spectrum disorders; n: number; SD: standard deviation; ON: optic neuritis; ATM: acute transverse myelitis; EDSS: expanded disability status scale; IQR: interquartile range; AQP4-IgG: aquaporin-4 Immunoglobulin G antibody; MRI: magnetic resonance imaging.

out that the ethnic and socioeconomic profile, the low income, and the type of medical care for these patients are associated with these differences in the frequency of NMO (Alvarenga et al., 2017) (Papais-Alvarenga et al., 2015).

The claim that NMOSD has an ethnical preference for non-whites has been recently revisited (Jonsson et al., 2019). New studies suggest that NMOSD frequency in Caucasians is higher than what was initially considered (Asgari et al., 2011; Cossburn et al., 2012). Almost 90% of the patients included in a Sweden study were of Caucasian origin; therefore population-based studies using single diagnostic criteria and long follow-up will assist identify demographic variations in this disease (Etemadifar et al., 2015; Jonsson et al., 2019).

As an uncommon entity, the clinical features of NMOSD are still being characterized. The demographic features of this sample are comparable to those of other cohorts, the median age at onset of 34 years, and most of the cases are female. In some prevalence studies in the region, the age at onset varies between the third and fourth decade of life, but NMOSD can affect both young and older adults (Cabre et al., 2001; Del Negro et al., 2017; Rivera et al., 2008). In the Cuban study, blacks were older than non-blacks at disease onset (Cabrera-Gomez et al., 2009). The female to male ratio in our series was 4:1 for the entire group. NMOSD is more prevalent in women than men, with a female predominance of up to 9:1, which is higher than that observed in MS (2:1 to 3:1) (Flanagan et al., 2016; Mealy et al., 2012; Dilokthornsakul et al., 2016). Most of the patients in our cohort were mestizos probably reflecting the ethnic characteristics of our country.

We found a high rate of simultaneous ON and ATM as the first event (51%), followed by isolated ATM and isolated ON. Other LATAM studies show ON as the initial presentation in 29 to 57% (Carnero Contentti et al., 2020; Del Negro et al., 2017; Rivera et al., 2008) while isolated ATM is reported in 29-to 46 % of patients (Correa Diaz et al., 2020; Carnero Contentti et al.,2020). Simultaneous ON and ATM (also known as Devic Syndrome) are less common. Del Negro et al., in their series of 34 patients, reported that only 23.5 % of their patients had this presentation at disease onset (Del Negro et al., 2017). More recently, in one multiethnic retrospective study with 603 patients, this phenotype was observed in only 4% (Kim et al., 2018). Few patients in the current series had brainstem and area postrema (APS) syndrome as the first presentation which is similar to described in other studies (Carnero Contentti et al., 2020; Correa Diaz et al., 2020). As expected, most of our patients had abnormal spine MRI showing longitudinally extensive lesions which is one of the criteria for NMOSD (Wingerchuk et al., 2015). About 48 % had a brain MRI with findings not consistent with MS. Direct comparison with other studies is difficult due to methodological differences among case definitions and patient ascertainment. AQP4-IgG antibodies were measured in 141 patients (56.6%) being positive in 78 (57.4%). One study by Jiao et al. (Jiao, 2013), found that the sex ratio (female to male) was 1: 1 in seronegative patients and 9: 1 for seropositive ($p < 0.0001$). In our study, although the female: male ratio was 4: 1 in seronegative patients and 9: 1 in seropositive patients, this difference was also not statistically significant ($p = 0.052$). Jiao et al. mention other factors that might contribute to diverse seronegativity rates for NMOSD including diagnostic inaccuracy, clinical and demographic differences, and timing of blood samples. Like in other reports on NMOSD, relapses occurred in the majority of our patients, but we did not find any association between the disease course and the result of AQP4-IgG. The average EDSS was 3.5. There were no statistical differences in the mean EDSS by gender, evolutionary course, or AQP-4 IgG. It is of clinical interest to evaluate which clinical predictors are related to a greater disability; for example, Altintas et al., in a Turkish cohort, found similar results to ours since they did not find differences by sex or by the presence of antibody against AQP-4 (Altintas, 2015).

Almost 60% of our NMOSD patients used azathioprine as the immunosuppressant drug because of its cost and availability. Few individuals were treated with Mycophenolate Mofetil and only two were treated with Rituximab. In Venezuela, there is a significant lack of resources for early diagnosis and medical care of NMOSD patients who exhibit high morbidity (Carnero Contentti et al., 2020; (Papais-Alvarenga et al., 2015).

The results of this study need to be interpreted with caution. The prevalence rate of NMOSD in Venezuela of 2.1/100.000 might be an underestimation since the sample does not cover all the cases diagnosed, documented, and registered in the country at the time of the study. The case-ascertainment method can have left out those patients who are not being identified as NMOSD, and those receiving diagnosis and treatment in other institutions. However, we considered it as the best current estimation of prevalence and epidemiological data of NMOSD in Venezuela.

5. Conclusions

NMOSD in Venezuela represents a significant proportion of all demyelinating disorders affecting primarily adult females and non-white populations. This systematic study shows the prevalence and the MS/NMOSD ratio close to those reported in LATAM. We found one of the highest RF in the region which might be related to ethnicity, among other factors. A clinical pattern characterized by simultaneous ON and ATM was the most frequent initial event with a predominantly recurrent course. Planning and developing healthcare programs for underserved populations as well as more comprehensive LATAM studies are required to identify the distribution and variations of its epidemiological picture.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgment

The authors thank Dr. J. Pena for his assistance in the English revision and edition of the manuscript.

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