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Absence of latitudinal gradient in oligoclonal bands prevalence in Argentina

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ABSTRACT

Background: Like MS prevalence, oligoclonal bands (OCB) frequency seems to follow a latitudinal gradient. Argentina is extensive, latitude-wise, and previous studies have not found an MS prevalence latitudinal gradient. Our aim is to describe OCB prevalence in MS, clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS) patients included in the Argentinean MS and NMOSD registry (RelevarEM) and to investigate if it follows a latitudinal gradient. **Methods:** For each province, an average latitude was calculated, and OCB frequency was investigated. Multivariate logistical regression analysis and linear correlation were performed. Statistical analysis was repeated after excluding patients from centers using isoelectric focusing (IEF) in less than 95% of patients (CwIEF<95). **Results:** We included 2866 patients. OCB were positive in 73.9% of patients. No association or correlation were found between OCB and latitude of residence, even after excluding patients from (CwIEF<95). **Conclusion:** OCB positivity does not follow a latitudinal gradient in Argentina. Also, OCB positivity is lower than described in other world regions.

1. Introduction and objectives

Multiple sclerosis (MS) is a multifactorial disease. Both genetic and environmental factors play relevant roles in its pathogenesis and epidemiology. As with MS prevalence, it has been suggested that oligoclonal bands (OCB) prevalence follows a latitudinal gradient being more frequent farther away from the equator (Dobson et al., 2013). Latitude is associated with several environmental factors, such as UV radiation (and indirectly vitamin D levels) and infections (Negrotto and Correale, 2018). Importantly, the influence of latitude is not restricted to environmental factors, and there are marked regional differences in the genetic composition of the population due to admixture of ethnic ancestry (Negrotto and Correale, 2018). However, most studies assessing OCB prevalence included patients from the northern hemisphere or only few patients from scarce regions of the southern hemisphere (Dobson et al., 2013; Lechner-Scott et al., 2012; Peña-Sánchez et al., 2020). Although OCB positivity is expected in approximately 90% of MS patients (Dobson et al., 2013), the reported prevalence in some regions from the southern hemisphere, such as Brazil and Australia, has been much lower (Lechner-Scott et al., 2012).

Previous epidemiological studies from Argentina have not found an MS prevalence latitudinal gradient (Melcon et al., 2008). Argentina has several particularities that are relevant to MS epidemiology. First, it is an extensive country latitude-wise, extending from 21°46'S to 66°13'S. Furthermore, there is a complex ethnic admixture contributing to the genetic heterogeneity of the population (Avena et al., 2012). Finally, most MS referral centers are concentrated in a few provinces. Therefore, the location where the patients reside and where they are treated does not often coincide. Thus, previous OCB prevalence reports collecting data from these centers (Dobson et al., 2013; Lechner-Scott et al., 2012; Peña-Sánchez et al., 2020) may have mistakenly located patients at a different latitude from where they reside.

OCB play a central role in MS diagnosis and differential diagnosis,

and in fact have been included as an alternative to dissemination in time in the last revision of the McDonald criteria (Thompson et al., 2017). Accordingly, current recommendations suggest considering alternative diagnosis in OCB negative patients to avoid misdiagnosis (Solomon, 2019). It follows that knowing the real OCB prevalence in a certain population has important implications for MS diagnosis and treatment and that extrapolation of data from other world regions is not always correct.

The aim of the present study is to describe the prevalence of OCB in CSF in patients with MS, CIS and RIS included in the Argentinean MS and NMOSD registry (RelevarEM, NCT 03,375,177) and to investigate if the prevalence follows a latitudinal gradient.

2. Methods

RelevarEM is a longitudinal, observational MS and NMOSD registry in Argentina. Detailed methodology of RelevarEM has been previously published elsewhere (Rojas et al., 2019). Validated criteria (McDonald 2010 or 2017 criteria) were used to diagnose MS (Rojas et al., 2019). Ethics committee approval was obtained for each participating center. For each province, an average latitude was calculated using extreme N and S latitudes obtained from Google Maps. Regarding OCB, pattern II or III were considered as positive. The frequency of OCB was calculated for each diagnostic category (MS, CIS, RIS) and for each province. Statistical analysis was carried out using SPSS v22. Graphs were created on Graph Pad Prism 5 and Excel. Multivariate logistic regression analysis was performed considering OCB as a dichotomous dependent variable and latitude as an ordinal independent variable, adjusted by clinically relevant variables. Also, the percentage of patients OCB positive for each province was calculated, and linear correlation was tested for.

Although OCB technique was not originally collected in the RelevarEM registry, participating centers were asked to complete an online questionnaire indicating the percentage of patients in which OCB were

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tested using isoelectric focusing followed by immunofixation or immunoblotting IgG (IEF) or other methods, including “unknown” as an option. Statistical analysis was repeated after excluding patients from participating centers that reported IEF in less than 95% (CwIEF<95) of patients (including those with unknown testing methodology).

3. Results

We included 2866 patients from different locations in Argentina (92.4% MS, 5.8% CIS and 1.8% RIS) (Table 1). The mean age at diagnosis (SD) was 32.7 (11.2), 35.2 (10.7) and 40.7 (11.2) for MS, CIS and RIS patients, respectively. Lumbar puncture (LP) was performed in 54.6%, 63.9%, and 43.4% of MS, CIS and RIS patients, respectively. OCB were positive in 75.4%, 55.7% and 60.9% of MS, CIS and RIS patients, respectively. Province of residence and treating center differed in 33.6% of patients.

After excluding patients from CwIEF<95, 2359 patients were included. OCB were positive in 76.5%, 53.9% and 61.1% of MS, CIS and RIS patients, respectively.

No association was found between OCB positivity and latitude of residence, adjusted by gender, age at diagnosis and diagnostic category (OR 0.987 (CI95% 0.958–1.017); $p = 0.398$). No linear correlation was found between the percentage of OCB positive patients and latitude of residence (Fig 1). Notably, after excluding patients from CwIEF<95, the lack of association or correlation remained invariable (OR 0.984 (CI95% 0.952–1.017); $p = 0.333$).

4. Discussion

Similarly to what has been described regarding MS prevalence, OCB positivity does not seem to follow a latitudinal gradient in Argentina. Also, OCB positivity in our study is lower compared to previous reports from other world regions.

The main limitation of the present study is the information gap on technique used to determine OCB in each patient. However, OCB positivity was similar after excluding CwIEF<95 and no latitudinal gradient was found after exclusion of those patients. Furthermore, a previous

meta-analysis has shown only small differences in OCB prevalence when including only studies using IEF or including all studies regardless of the technique used (87.7% vs 84.3 in MS patients and 68.6 vs 67.5% in CIS patients) (Dobson et al., 2013). The main strengths of this study are the representation of patients from all the provinces of Argentina, which is an extensive region, latitude-wise, in the southern hemisphere, and the large number of patients included. Importantly, in 33% of our patients the province of residence and the province of the treating center differ showing that previous reports suggesting a latitudinal effect on OCB prevalence including patients from Argentina should be taken with caution.

The most likely explanation for the low OCB positivity and lack of latitudinal gradient are differential environmental and genetic factors in our population. The ethnic background of Argentina's population results mainly from the admixture of European Caucasian and Native American ancestry with a lower contribution of African ancestry. The presence of protective genetic factors from Native American ancestry has been previously suggested (Negrotto and Correale, 2018). There are also considerable regional differences in the ethnic background within the country (Avena et al., 2012). Also, the contribution of misdiagnosis cannot be completely ruled out. Misdiagnosis has been reported in up to 30% of patients in MS specialized centers. Although the prevalence of MS misdiagnosis in Argentina has not been systematically studied throughout the country, a recent communication from a referral center found misdiagnosis in 16% of patients who came for a second opinion with “definite MS” diagnosis (Gaitán et al., 2019). Furthermore, LP was performed in only half of the patients, probably conditioning a selection bias since typical patients fulfilling McDonald criteria are less likely to undergo LP. Additionally, although OCB positivity is stable over time and rarely affected by MS treatments, some exceptions have been recently described, such as natalizumab, cladribine and hematopoietic stem cell transplant (Larsson et al., 2019), which can negativize OCB in a proportion of patients. In our population LP is usually performed to establish the diagnosis and prognosis, before initiating disease modifying treatments, and it is only exceptionally repeated. Therefore, we estimate that the contribution of the effect of MS treatments on OCB positivity to our results is extremely low. Finally, the effect of the

Table 1
Demographic and clinical characteristics of patients according to province of residence.

Province	Average latitude (°S)	N	Gender (% F)	Age at diagnosis*	Diagnosis (%)			LP (%)	OCB (%)
					MS	CIS	RIS		
Jujuy	23.2	6	83.3	30.7 (12.2)	66.7	33.3	0	16.7	100
Salta	24.2	96	62.5	30.2 (9.8)	89.6	9.4	1	16.7	62.5
Formosa	24.7	3	66.7	31 (10.6)	100	0	0	66.7	50
Chaco	26.1	14	42.9	31.7 (12.8)	85.7	14.3	0	71.4	70
Misiones	26.8	28	67.9	29.4 (9.5)	89.3	10.7	0	27.5	73.3
Tucuman	27.1	96	79.2	30.5 (9.9)	91.7	6.3	2.1	45.8	81.8
Catamarca	27.6	12	41.7	27.8 (12.8)	100	0	0	66.7	100
Santiago del Estero	28	23	56.5	33.5 (10.2)	100	0	0	34.8	62.5
Corrientes	29	16	62.5	34.4 (9.3)	93.8	0	6.3	50	62.5
La Rioja	29.9	9	100	37 (12)	88.9	11.1	0	77.8	100
San Juan	30.1	30	60	31.8 (12)	93.3	6.7	0	50	60
Santa Fe	31.2	201	69.2	32.6 (10.3)	93	3.5	3.5	42.8	58.1
Entre Rios	32.1	64	54.7	32 (11.1)	96.9	3.1	0	59.4	73.7
Cordoba	32.3	450	69.3	33 (10.3)	95.1	4.9	0	60.4	79.4
San Luis	34	20	75	31.7 (7.1)	85	15	0	85	70.6
CABA	34.6	781	64.7	33.8 (12)	91.3	6.3	2.4	58.3	75.6
Mendoza	34.8	91	58.2	30.9 (8.9)	92.3	6.6	1.1	27.5	80
Buenos Aires	37.2	804	63.7	33.3 (11.7)	93.3	5.3	1.4	59.8	72.6
La Pampa	37.2	16	50	31.1 (17.3)	100	0	0	50	87.5
Neuquén	38.6	10	70	38.4 (13)	80	10	10	60	50
Rio Negro	39.8	12	75	35.5 (6.1)	75	25	0	25	100
Chubut	44	58	70.7	34.3 (10.5)	77.6	6.9	15.5	48.3	57.1
Santa Cruz	44.2	11	45.5	34.4 (9.8)	90.9	0	9.1	54.5	50
Tierra del Fuego	53.8	15	73.3	28.3 (10.7)	93.3	6.7	0	93.3	78.6
TOTAL		2866	65.4	33 (11.2)	92.4	5.8	1.8	54.9	73.9

* Mean age in years (SD). N: number. F: female. MS: multiple sclerosis. CIS: clinically isolated syndrome. RIS: radiologically isolated syndrome. LP: lumbar puncture. OCB: oligoclonal bands. CABA: Ciudad Autónoma de Buenos Aires.

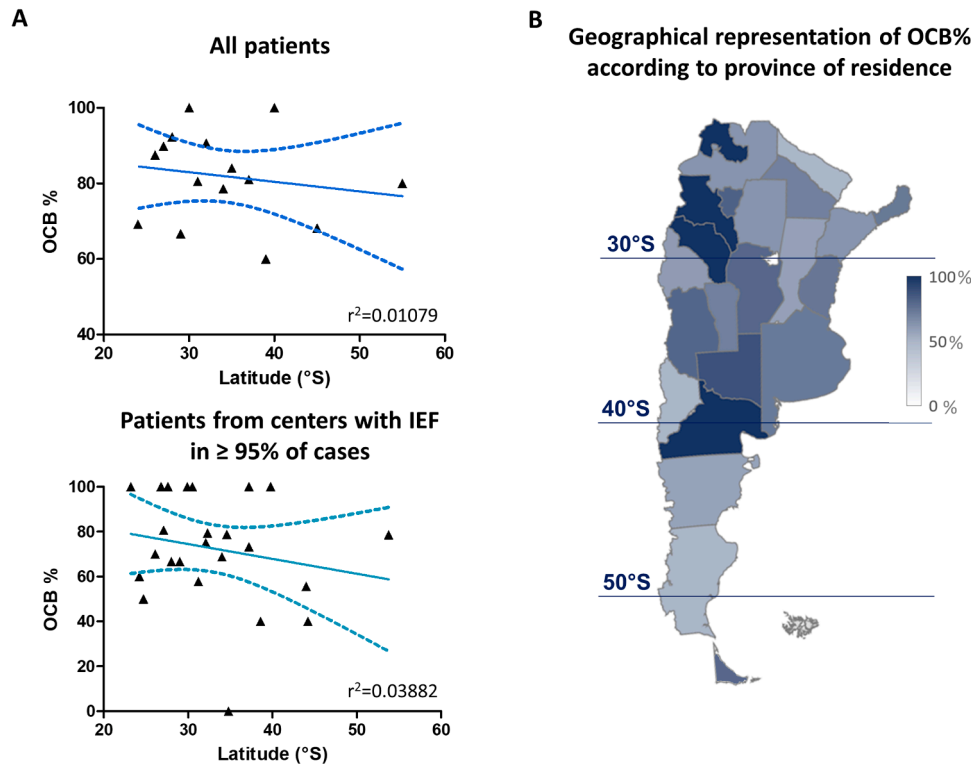


Fig. 1. Representation of OCB positivity according to latitude of residence of patients. **A:** Scatter plot showing linear correlation with 95% confidence intervals. **B:** Geographic representation using color scale to indicate OCB positivity.

country's domestic north-to-south migration must be considered.

It is extremely relevant for the management of MS patients in our region to know the real prevalence of OCB, to avoid delaying the diagnosis in otherwise typical MS patients only due to absence of OCB in CSF based on data extrapolated from other world regions. This warrants further studies to clarify the reasons behind the lack of latitudinal gradient in MS prevalence and OCB frequency in MS patients in Argentina.

Declaration of Competing Interest

All authors declare they have no conflict of interest.

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