Original Research Paper

Prevalence of multiple sclerosis in Cuenca, Ecuador

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Abstract

Background: Cuenca, a city in the Andean Region of southern Ecuador, has 591,996 inhabitants. A decade-old study showed the prevalence of multiple sclerosis in Cuenca was 0.75 cases per 100,000 inhabitants but no new epidemiological studies in this city have been performed since then. The aim of this study, conducted in 2016, was to update the prevalence records of multiple sclerosis in Cuenca.

Methods: We performed a descriptive cross-sectional study in which we investigated prevalence rates in November of 2016. We estimated the prevalence of multiple sclerosis by cross-matching registries from the two neurological referral hospitals in Cuenca.

Results: A total of 23 records were obtained from the two sources. The estimated prevalence was 3.88 per 100,000 inhabitants (95% confidence interval: 3.83–3.94). The disease was predominant among women (60%). The mean age of this cohort was 37 years (standard deviation ±12.4). Of the cases, 78% were relapsing–remitting multiple sclerosis. The mean Expanded Disability Status Scale score was 2.5.

Conclusions: This study is an update to the first study conducted 10 years ago and shows the prevalence of multiple sclerosis in Cuenca has increased. However, the prevalence of multiple sclerosis is still low and very similar to that reported in neighbouring countries.

Keywords: Prevalence, multiple sclerosis, Cuenca, Latin America

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Introduction

Multiple sclerosis (MS) is an inflammatory, degenerative and demyelinating disease of the central nervous system that affects young adults.[1–3] The prevalence of this entity in the world is heterogeneous and Latin America (LA) is no exception. Thus, there are LA cities in which prevalence ranges between 25 to 30 cases per 100,000 inhabitants, as is the case in Nuevo León, Mexico and Buenos Aires, Argentina. There are cities such as Quito and Lima with low prevalence rates of MS (5.05 and 7.6 cases per 100,000 inhabitants, respectively).[4–8] In recent years there has been an increase in the prevalence of MS in certain regions of LA and Europe. However, an increase in prevalence has not been demonstrated in every study.[9–12]

In Ecuador a cross-sectional study conducted a decade ago showed that MS prevalence in Cuenca was 0.75 cases per 100,000 inhabitants.[8] Since then, new epidemiological studies have not been carried out and we do not know if this prevalence has increased as it has in other regions of the world. The objective of this study is to update the prevalence of MS in Cuenca and compare these results with those published in the previous study.

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Materials and methods

Setting

Cuenca is the third-largest city in Ecuador. The population of Cuenca in November 2016 was 591,996 according to the National Institute of Statistics and Census (INEC). Cuenca is located in the Andean region at an altitude of 2800 meters, latitude 2° South and longitude 79° West. It lies 432 km south of Quito, the capital of Ecuador, latitude 0° (Figure 1).[8–13] The ethnic composition of this city has a majority of mestizos, followed by Caucasians and a minority composed of Amerindians and Afro-Ecuadorians (Figure 1).[13]

In Cuenca, the healthcare system is made up of three providers: the Social Security Fund, which covers 50% of the work force and their beneficiaries; the private healthcare service, which covers 3% of workers with medium and high incomes; and the Ministry of Health, which covers the rest of the population. The healthcare institutions serving in Cuenca are classified into three levels of complexity, ranging from the simplest, which are the first-level hospitals staffed by general practitioners, to the most complex, the third-level hospitals attended by specialists and equipped with high-level technology.

Citizens who reside in Cuenca have access to both the public healthcare system and private health system. The MS patients in this study were being treated at tertiary hospitals, across which there are radiologists and 11 neurologists, two of whom are experts in neuroimmunology (able to diagnose and treat MS). These hospitals are also equipped with magnetic resonance imaging (MRI) machines. Patients from both private and public hospitals had access to disease modifying therapies such as interferon and fingolimod.[14,15]

Selection criteria

We conducted a descriptive cross-sectional study. All patients were evaluated by authors of this manuscript who have expertise in the diagnosis of MS. Patients were included in the study based on three diagnostic criteria: (a) they met the McDonald 2010 diagnostic criteria (which include clinically isolated syndrome (CIS) and MS);[16] (b) they were born in or had resided in Cuenca for at least 1 year; and (c) they were alive in the prevalence month (November 2016). Those patients who did not meet the diagnostic criteria or lived in other cities of Ecuador were excluded from the study.
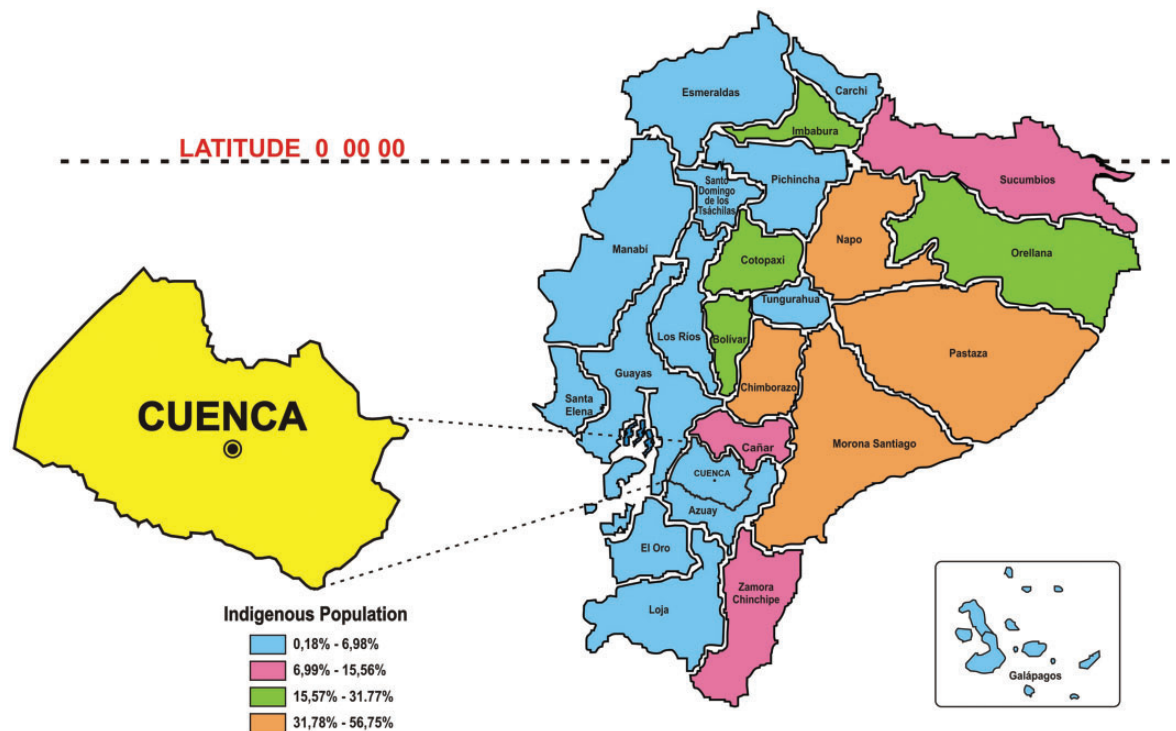

Figure 1. Area of investigation: geographic location of Cuenca, Ecuador.

Identification of cases

The register of patients in the Ecuadorian Health System is based on the 10th edition of the International Classification of Diseases (ICD-10). Data were retrieved from the electronic databases by tracking the ICD codes of the following hospitals: (a) Vicente Corral Moscoso Hospital; (b) Jose Carrasco Arteaga Hospital (both of which are tertiary-level public hospitals that represent referral centres); (c) Hospital del Rio; (d) The Santa Ana clinic; and (e) The Monte Sinaí clinic (private tertiary level hospitals in Cuenca). The study was approved by the bioethics committee of each of the participating institutions.

We reviewed the electronic medical record of the cases to verify the diagnosis. Additionally, we used a questionnaire to collect data that included the following aspects: general information (age, sex and place of birth); family and personal history; clinical findings; degree of disability; diagnostic studies such as oligoclonal bands (OCBs) in the cerebrospinal fluid (CSF) and brain and spinal MRI; differential diagnosis with other diseases; clinical type of MS; and treatment. Before the application of this questionnaire, a procedure manual on how to use the questionnaire was prepared. Patients had previously signed a consent form and confidentiality of information was respected.

According to the clinical course, patients were classified into one of the following categories: CIS, relapsing–remitting MS (RRMS), primary progressive MS (PPMS) or secondary progressive MS (SPMS).[17] We reviewed the results of brain and spinal cord MRIs at the time of initial presentation and in selected cases we reviewed additional MRI studies.

Statistical method and data analysis

We created a database that contained demographics, initial clinical findings (optical neuritis, motors, cerebellar and others), disability (measured through the Expanded Disability Status Scale (EDSS) score), time since disease diagnosis, clinical type and treatment. Patients with identical names and the same national identification number were considered overlaps. Data were analysed in a descriptive manner by measuring central tendency (average) and dispersion measures (confidence interval (CI) and standard deviation (SD)) for analysing age. We used proportions for the analysis of categorical variables.

Crude prevalence was calculated as the number of MS cases divided by the total number of subjects living in the area of focus for the date of prevalence study. The prevalence was adjusted to the population of Cuenca in 2016.[13] Additionally, age standardization to world population was performed.[18] A 95% CI of the prevalence was calculated. The statistical analysis was carried out through the statistical program Microsoft Excel.

Results

In Cuenca, we identified a total of 36 patients with MS; however, 13 of them were not residents in Cuenca and therefore excluded from the analysis. Of the 23 valid patients, 95.7% (22 patients) were treated in Jose Carrasco Arteaga Hospital and one patient was treated in the Hospital del Rio. Considering the population estimated by the INEC in November 2016, which was 591,996 inhabitants, the estimated prevalence was 3.88 per 100,000 inhabitants (95% CI, 3.83–3.94). Age-adjusted prevalence is shown in Table 1 and revealed that the prevalence was almost three times higher (11.25 per 100,000 inhabitants; $p = 0.0024$) in people between 35 and 44 years old (Table 1).

Of the 23 patients, 14 were women (60.9%), the female/male ratio was 1.5: 1. The mean age at the time of estimating the prevalence was 37 years (SD $\pm$ 12.4; 95% CI 31.8–42.6), 39 years for women and 34 for men. In contrast, the mean age of patients during the first symptoms was 31.5 years (SD $\pm$ 9.6; 95% CI 27.4–35.7), 32 years for women and 30 years for men. We did not identify children with MS. The mean disease duration was 4.1 years (SD $\pm$ 3.6; 95% CI 2.6–5.7) and fluctuated between 1 month and 16 years. The mean duration of the disease from the onset to the prevalence day was 5.74 years (SD $\pm$ 4.94; 95% CI 3.5–7.9). We did not find familial MS. All but one patient, who was second-generation European, were mestizos.

In total, 18 cases were RRMS (78.3%), two cases were CIS (8.7%) and PPMS (8.7%) and one case was SPMS (4.3%). The most frequent clinical manifestations reported at the onset of MS were optic neuritis (39.1%) follow by motor and sensory symptoms (47.8% and 37.1% respectively). Brain and spinal cord MRIs were performed in all cases the location of the lesions is presented in Table 2. Overall, 78% (18/23) met the criteria for dissemination in time and 95% (22/23) dissemination in space

Table 1. Age-adjusted prevalence of multiple sclerosis patients born or resident in Cuenca, Ecuador in 2016.

Age at prevalence month (years)	Cases	Population	Rate per 100,000 inhabitants (95% CI)	Standard population (WHO)[18]	Age-standardized rate per 100,000 inhabitants
1–4	0	57.521	–	0.08	–
5–9	0	56.998	–	0.0869	–
10–14	0	56.057	–	0.086	–
15–19	1	55.978	1.79 (1.67–1.90)	0.0847	0.151309443
20–24	3	55.886	5.37 (5.17–5.56)	0.0822	0.441255413
25–29	2	52.410	3.82 (3.65–3.99)	0.0793	0.302614005
30–34	4	45.748	8.74 (8.47–9.02)	0.0761	0.665384279
35–39	4	38.539	10.38 (10.05–10.70)	0.0715	0.7421054
40–44	4	32.557	12.29 (11.90–12.67)	0.0659	0.809656909
45–49	2	28.342	7.06 (6.74–7.37)	0.0604	0.426222567
50–54	0	25.063	–	0.0537	–
55–59	2	21.666	9.23 (8.82–9.64)	0.0455	0.420012923
60–64	0	18.106	–	0.0372	–
65–69	1	14.921	6.70 (6.28–7.12)	0.0296	0.198378125
70–74	0	11.953	–	0.0221	–
75–79	0	8.906	–	0.0152	–
>80	0	11.345	–	0.01545	–
TOTAL	23	591.996	3.88 (3.83–3.94)	0.99175	3.853108805

CI: confidence interval; WHO: World Health Organization.

(DIS). OCBs were performed in only 11 patients (47.8%) and were positive in five patients (45.4%). The average EDSS was 2.5 (ranging from 1 to 7.5). A total of 60% of patients (14/23) had an EDSS <2, 17% (4/23) had an EDSS between 2.5–4, 14.3% had an EDSS greater than 6.5. And 62% of patients (14/23) received treatment based on interferon, 29% (7/23) fingolimod and 9% (2/23) did not receive treatment (Table 2).

Discussion

The present study demonstrates a five-fold increase in the prevalence of MS in Cuenca with a range of 3.83 to 3.94 compared to a previous study published a decade ago.[8] This is in keeping with the increase in the prevalence of MS that has been observed in other regions of the world. Hirst et al.[19] demonstrated an increase in the prevalence of MS in East Wales from 101 to 146 cases per 100,000 inhabitants. In LA, through a capture-recapture method Cristiano et al.[20] demonstrated an increase in the prevalence of MS in Buenos Aires from 25 to 38.2 cases per 100,000 inhabitants over a period of 20 years. A possible explanation for the increase in the prevalence of MS in Cuenca could be because

neurologists have a better understanding of the disease and there is now greater access to MRI. Rotstein et al.[21] found the increase of prevalence of MS in Ontario, Canada appeared to be largely attributable to declining mortality rates. In this study the highest prevalence was in patients older than 50 years. In our study we found similar findings, the highest prevalence of MS was in groups of patients older than 50 years old, which is consistent with results from a previous study from Canada.

The current study also shows that the prevalence of MS in Cuenca, Ecuador, is still low and is very similar to that reported in cities of neighbouring countries such as Bogotá, 4.41 per 100,000, Lima, 7.69 per 100,000 and Panama, 5.27 per 100,000. In contrast, the prevalence of MS in Cuenca is lower if compared to cities such as Buenos Aires and Sao Paulo in which the prevalence is between 15–38.2 cases per 100,000 (Table 3).[3,4,20] Abad et al. 10 years ago showed that the prevalence of MS in the three main cities in Ecuador (Cuenca, Guayaquil and Quito) was low (between 0.75 to 5.05 cases per 100,000 inhabitants).[8] Correa et al.[22] carried out an epidemiological study in the Andean Region, which showed that the epidemiological behaviour of MS in

Table 2. Distribution of patients with multiple sclerosis according to their demographic, clinical, laboratory and radiological factors.

	$n = 23$	%
Gender		
Female	14	60.9
Male	9	39.1
Onset age (years)		
10–20	2	8.6
21–30	8	34.78
31–40	10	43.47
41–50	2	8.6
>50	1	4.3
Disease course		
RRMS	18	78.3
SPMS	1	4.3
PPMS	2	8.7
CIS	2	8.7
Clinical manifestations during the first symptom		
Optic neuritis	9	39.1
Double vision	3	13.04
Motor symptoms	11	47.82
Sensory symptoms	9	39.13
Cerebellar symptoms	2	8.69
Bladder and bowel dysfunction	1	4.34
EDSS		
(Prevalence month)		
0–2	14	60
2.5–4	4	17
4.5–6	3	14.3
>6.5	2	8.7
Oligoclonal bands		
Positive	5	21.7
Negative	6	26.1
Not done	12	52.2
Brain and spinal cord MRI characteristics		
DIT	18	78.3
DIS	22	95.7
Location of the lesions		
Periventricular	23	100
Yuxtacortical	7	30.4
Brainstem	11	56.5
Spinal cord	16	69.6
Disease-modifying therapies		
Interferons	14	62
Fingolimod	7	29
None	2	9

RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; CIS: clinically isolated syndrome; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; DIT: dissemination in time; DIS: dissemination in space.

this region was heterogeneous. The provinces with the highest concentration of Caucasian and Mestizo populations have the highest number of MS cases, as was the case in the Andean provinces of Pichincha and Azuay. These provinces had the highest MS diagnosis rate (4.49 and 4.08 per 100,000 inhabitants respectively). On the contrary, provinces in which the concentration of Amerindian population is higher and the Caucasian population is lower have a decreased number of cases of MS as was the case of the Andean provinces of Bolívar and Cotopaxi (0.75 and 0.64 respectively). Therefore, we believe the results of this study cannot be extrapolated to other cities or provinces in Ecuador due to the diverse distribution of mestizo, Amerindian and Caucasian populations in every province.

Populations in LA vary considerably from an ethnic and a genetic point of view. The largest number of people with European ancestry in LA are concentrated in Argentina, South of Brazil and Uruguay; coincidentally, these countries have the highest prevalence of MS. In contrast, countries such as Mexico, Bolivia, Peru and Ecuador have the highest concentration of mestizo and indigenous populations and the lowest prevalence of MS.[3] Flores et al. showed the Lacandon population (an Amerindian ethnic group in Mexico) did not have signs or symptoms consistent with MS.[3] It is well established that the HLA-DRB*1501 allele is associated with susceptibility to developing MS in Caucasian populations.[23] In LA, genetic studies have shown the presence of the DRB1*15 allele was more frequent in Caucasian and White populations (33.9% and 24.7% respectively) who came from Argentina and Brazil.[24,25] Additionally, there was no presence of the HLA-DRB*15 allele in the Brazilian Amerindian population.[26] In LA there is a trend towards an increase in the prevalence of MS due to genetic introduction of European HLA-DRB*15 allele.[27] Therefore, these results can explain why prevalence of MS in Cuenca is still low as there is a large number of mestizo and Amerindian populations. However, genetic studies to confirm this theory are necessary in Ecuador.

Regarding the influence of environmental factors on the risk of MS, studies from European/North American countries have shown an association between low levels of vitamin D and the risk of developing MS.[3] However, in Ecuador, we still do not know what the role of the insufficiency of vitamin D has on the risk of developing MS. Zambrano et al.[28] showed a high prevalence of vitamin D

Table 3. Prevalence of multiple sclerosis in Cuenca and other Latin American cities.[3,4,20]

Location	Latitude/ longitude	Prevalence observed per 100,000 inhabitants	Prevalence estimated by capture - recapture per 100,000 inhabitants
Argentina			
Buenos Aires (1996)	34° S 58° W		18.5
Buenos Aires (2016)	34° S 58° W		38.2
Patagonia (20029	55° S 36° W	7	17.2
Brazil			
Belo horizonte (2012)	19° S 43° W	18.1	
Botucatu (2002)	22° S 48° W	17	
Cuiabá (2008)	5° S 56° W	4.41	
Distrito Federal (2004)	15° S 45° W	5.85	
Florianópolis (2004)	27° E 48° W	12.2	
Londrina (2005)	23° E 47° W	14.84	
Marília (2006)	22° S 49° W	6.04	
Recife (2004)	8° S 34° W	1.36	
Rio de Janeiro (2000, 2012)	23° S 46° W	4.27–15	
Santa María (2014)	29° E 53° W	27.2	
Santos (2007, 2012)	23° S 45° W	15.54–15.5	
Sao Paulo (1992, 1997)	23° E 46° W	4.27–15.0	
Sorocaba (2004)	23° S 47° W	16.2	
Uberada (2011)	19° S 45° W	12.5	
Volta Redonda (2013)	22° S 44° W	15.3	30.7
Colombia			
Antioquia (1995–2000)	4° N 10° W		3.2
Caldas Santander (1995–2000)	72° E 77° W	0.1 - 2.21	1.48–4.98
Bogotá (2002)	4° N 74° W	4.41	
Costa Rica (2010)	10° N 84° W		6
Cuba (2008)	21° N 80° W	10–25.5	
Chile (2001–2006)	17° S 56° W	11.7	
Ecuador (2006)			
Cuenca	2.53° S 79° W	0.75	
Guayaquil	2.15° S 79° W	2.2	
Quito	0.15° S 78° W	5	
Ecuador (2016)			
Cuenca[a]	2.53° S 79° W	3.88	
Lima (2009)	12° S 77° W		7.6
México			
Guadalajara (2007)	96° N 106° W	1.5–13	
San Pedro Garza (2003)	25° N 100° W	30	
Monterrey (2002)	25° N 100° O	7.5	
Panamá (2000-2005)	8° N 25° W	5.24	
Uruguay (1997)	34° S 56° W		20.9

N: North; S: South; W: West.
[a]Current study.

insufficiency in MS patients in Quito (latitude zero) when compared to that of healthy individuals (42% vs 46% respectively). In addition, Orces showed a high prevalence (68.7%) of vitamin D insufficiency in older adults living on the Ecuadorian coast and in the Andean Region.[29,30] These results are contrary to the notion that geographical proximity to more tropical latitudes plays a role in determining optimal vitamin D levels. Powe et al.[31] showed in community-dwelling adults that the levels of vitamin

D and the vitamin D-binding protein were lower in Black Americans in comparison with White Americans. Contradictory, Black Americans had higher bone mineral density, higher calcium levels and slightly higher levels of parathyroid hormone levels, which suggest the concentrations of estimated bioavailable vitamin D were higher in Black Americans. A likely explanation for this observation is that racial differences had an influence on the prevalence of common genetic polymorphisms in vitamin D-binding proteins. It is crucial to study the role of these genetic polymorphisms in vitamin D-binding proteins in Mestizo populations because the Ecuadorian population, as well as European populations, has low levels of vitamin D, suggesting vitamin D is not the main driver of the low prevalence of MS in Ecuador. Other environmental or genetic factors may be responsible for the low prevalence of MS in Ecuador and it is necessary to develop studies that demonstrate the impact of these factors on the prevalence of this disease.[32,33]

The methodologies used in epidemiological studies of LA are mainly based on hospital records, neurologists and patient associations. The capture and recapture method allows for the control of the cases that have been omitted, this method is based on the overlapping of different data sources.[34] However, overlap between sources was not found in our study because almost all MS patients in Cuenca (22/23) were referred to the Jose Carrasco Hospital, a tertiary referral centre. Therefore, the prevalence calculation of MS was based on the totality of cases found. Recently, a new way to estimate the new prevalence of neurological diseases has been developed, based on a four-step approach. First, identify administrative health claim databases that cover publicly and privately insured populations. Second, develop and validate a highly accurate case-finding algorithm that can be standardly applied to all databases. Third, apply a case definition algorithm to estimate the prevalence of a neurological disease in each population. Fourth, combine prevalence estimates into a single estimate of prevalence, weighted according to the number of insured persons in each health insurance segment.[35] This new approach has been applied in the United States to estimate the new prevalence of MS. This four-step approach resulted in high sensitivity and specificity of 86–92% and 66–83% respectively.[36] This new approach may be a mechanism for finding further cases in the clinics and hospitals in our country.

The demographic characteristics of our study were very similar to those found in European cohorts. Our study showed a greater number of cases in the female sex with a female to male ratio of 1.5:1, which is slightly lower than that shown in other European studies of 2.4:1 (Norway, Switzerland and Wales)[37–39] and those reported in other cities in Ecuador (Quito and Guayaquil), which showed a ratio of 2.1–2.2:1.[8,40] The average time from the onset of symptoms to the time of diagnosis was 5.4 years. These results are similar to the results reported in other studies conducted in Italy, Wales and Scotland (5–6 years).[39,41,42] The average age was 37 years and is similar to that found in Iceland (36 years),[12] Scotland (39 years)[39] and Wales (37 years).[42] In our study we found that 8.7% of the cases were PPMS similar to that found in Iceland and Wales (7% and 8% respectively).[12,42] In general, these results demonstrate a demographic behaviour of MS that is very similar to that found in other regions of the world with a clear difference in relation to prevalence.

Intrathecal detection of oligoclonal immunoglobulins is a diagnostic aid in the detection of MS. The new McDonald 2017 diagnostic criteria have recommended that the presence of OCBs in the CSF allows for the diagnosis of MS in patients with CIS who meet DIS in MRI.[43] Additionally, OCBs in CSF are biomarkers the presence of which is an indicator of disability progression.[44] In our study, OCBs were performed in 47.8% of the patients and were positive in 45.4% of them, which shows a low frequency of positive OCBs in the CSF of our patients. Studies have shown that the prevalence rate of OCBs is not similar among the populations studied, for example: Scandinavian populations have high prevalence rates (90–95%). On the contrary, the presence of OCBs is low in populations such as China, Japan and India where prevalence ranges from 30% to 60%.[45] In Latin America studies from Brazil and Colombia have shown a low prevalence of OCBs in patients with MS between 50% and 54%.[45–47] This could be explained by the influence that ethnicity may have on the pathophysiology of the disease and inflammatory markers. Therefore, it could explain the low positivity of OCBs in our study, but more studies are necessary in Latin America and Ecuador.[46]

This study has limitations because the all the patients included in the study came from tertiary level centres in Cuenca and no other registers exist. Also, this study was conducted in a city in the Andean Region where there are data on the

prevalence of MS, nevertheless, the prevalence of MS in other cities of Ecuador is still unknown. More epidemiological studies are necessary to obtain prevalence data on MS in other cities.

Conclusion

Our study shows the prevalence of MS in Cuenca has increased in relation to a previous study published a decade ago. The prevalence is still low and very similar to that reported in neighbouring countries of South America. The demographic characteristics of the population are very similar to those found in European and North American studies. The increase in the prevalence of MS in Cuenca may be due to neurologists in Ecuador having better knowledge of the disease than they had during the previous study 10 years ago and that they have more access to MRI.

Author contributions

Edgar Correa participated in designing the project, evaluating and registering patients with MS and writing the manuscript. Angélica Ortiz, Fernando Guillen, Ariana García, Guillermo Baño, Carolina Jácome, Germaine Torres, Andrés Ortega, Eugenia Buestán and Andrés Murillo evaluated and registered patients with MS and wrote the manuscript. Enrique Terán analysed the database and wrote the manuscript. Ana Toral, Daniel Ontaneda and Praneeta Raza wrote the manuscript. All authors have revised the manuscript and approved the manuscript for submission.

Conflicts of Interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Daniel Ontaneda has received research support from National Multiple Sclerosis Society, National Institutes of Health, Patient Centered Research Institute, Race to Erase MS Foundation, Genentech, Novartis and Genzyme. He has also received consulting fees from Biogen Idec, Genentech/Roche, Genzyme, and MERCK. The other authors have no conflicts of interest to declare.

Statement of ethics

The study protocol was approved by the José Carrasco Arteaga Hospital ethics committee. Written informed consent of participation was obtained from the patients with MS.

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