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Abbreviations:
CCSS; Caja Costarricense de Seguro Social.
EDSS; Escala del Estado de Discapacidad Ampliada de Kurtzke.
EM; Esclerosis múltiple.
HSC; San Carlos Hospital.
HSJD, San Juan de Dios Hospital.
HSRA; San Rafael Hospital in Alajuela.
CSF; Cerebrospinal fluid.
OCT; Optical coherence tomography.
RM; MRI

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Original

Epidemiological study of multiple sclerosis in Central America and the Caribbean (ENHANCE study): partial results from Costa Rica

Epidemiological study of multiple sclerosis in Central America and the Caribbean (ENHANCE study) partial results of Costa Rica

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Abstract

Aim: This study aimed to describe the incidence and analyze the main demographic, epidemiological, clinical, diagnostic and treatment characteristics, as well as the presence of known risk factors and prognoses in Costa Rican patients with multiple sclerosis, treated in three hospitals, and who participated in the international study called ENHANCE.

Methods: The study was observational in nature, the medical records of patients over 18 years of age diagnosed with multiple sclerosis treated in three hospitals of the Costa Rican Social Security Fund, specifically the San Juan de Dios Hospital, the San Rafael de Alajuela Hospital and the San Carlos Hospital, during the period between January 2014 and December 2019, were retrospectively analyzed. All cases were used to determine clinical and sociodemographic characteristics, while only new cases from the study period were taken into account for incidence calculations. Clinical and treatment outcomes were obtained from a subset of patients with active follow-up of at least 5 years.

Results: A total of 147 cases were registered, of which 72 were new in the study period and 75 were incident or prevalent in 2014 that had documented follow-up of at least 5 years. The mean age at symptom onset was 31.9 years and 35.0 years at diagnosis. A predominance of cases was found in the female sex 69.4% (n=102) and the patients presented a variable score on the Extended Disability Scale that ranged from 0 to 8.5. The annual incidence in the population analysed varied between 0.32 and 1.28 cases per 100,000 inhabitants. The main clinical form identified was relapsing-remitting 87.8% (n=129) and the main reported impairments were motor and sensory. The most frequent central lesions documented in magnetic resonance imaging were periventricular lesions (35% (n=45) and it was found that most patients had low levels of vitamin D. In relation to therapeutic management, a decrease in the use of traditional treatments (commonly called first-line) and an increase in the use of new or second-line alternatives, such as ocrelizumab and natalizumab, were observed.

Conclusion: The data obtained in the present study suggest that the population analyzed behaves in a similar way to what has been reported in other international studies and does not differ considerably from what has been previously reported in the country.

Keywords: multiple sclerosis, incidence, population characteristics, diagnosis, therapeutics.

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Multiple sclerosis in Costa Rica Multiple sclerosis is a chronic, inflammatory and demyelinating disease[1]; it mainly affects women and compromises a wide spectrum of neurological functions: sensory, motor, autonomic and cognitive[2]. In turn, it is the non-traumatic pathology that produces the highest degree of disability in young adults[3-5]. Although its origin is unknown, genetic factors have been identified that, together with environmental components, such as levels of vitamin D, exposure to ultraviolet radiation, infections by specific pathogens (Epstein-Barr virus) and lifestyles (smoking, obesity), could influence the susceptibility to suffer from the disease[4,6,7].

MS is reported to affect approximately 2.8 million people worldwide[8,9] and its prevalence varies across geographic regions. High incidence rates are generally recorded in North America and Europe[10], while in East Asia, Sub-Saharan Africa and Latin America, lower figures are reported[11,12]. In Latin America, the reported prevalence ranges from 0.83 to 38.2 cases per 100,000 inhabitants, while the estimated incidence is between 0.15 and 3.0 cases per 100,000 person-years[13]. In Central America, although reports have increased in recent years, they remain scarce and a crude prevalence ranging from 1.0 to 7.1 cases per 100,000 inhabitants has been reported[14]; while in the Caribbean region the figures tend to be higher, reaching between 8.5 and 21.0 cases per 100,000. Differences that could be at least partially attributed to the absence of updated records and underreporting[14,15].

Due to the fact that in recent years there has been a general increase in the number of cases of MS[16], this study framed within an international proposal (ENHANCE) aimed to analyze the main demographic, clinical, epidemiological, diagnostic and treatment characteristics, as well as the main risk factors and known prognoses in patients with MS in three hospitals of the Costa Rican Social Security Fund during the period between January 2014 and December 2019.

The statistical analysis was descriptive, for which the SPSS program for Windows (IBM Corp. 2016, Version 24.0 Armonk, NY) was used. The main variables of the present research were: age, sex, race or ethnicity, diagnostic criteria used, time elapsed between the first symptoms and diagnosis, classification of MS, among others.

This study was approved by the Central Scientific Ethics Committee of the Costa Rican Social Security Fund (CEC-Central-CCSS) under protocol number: R022-SABI-00299.

Methods

An observational study was carried out with a follow-up cohort based on the retrospective review of the records of patients with a diagnosis of MS seen during the period between January 2014 and December 2019 at the San Juan de Dios Hospital (HSJD), the San Rafael de Alajuela Hospital (HSRA) and the San Carlos Hospital (HSC), all of the CCSS. This study was part of an international initiative promoted by the Central American and Caribbean Forum on Multiple Sclerosis (FOCEM). Adult patients over 18 years of age with a confirmed diagnosis of MS, with no restriction by sex or ethnicity, were included in the study. Specifically, a total of 147 MS patient records that met the inclusion criteria and lacked exclusion criteria were analyzed.

The incidence (number of new cases in the participating centers/population assigned to these centers) was determined considering all new diagnoses according to the McDonald 2010 or 2017 criteria, during the period from 2014 to 2019. On the other hand, for the determination of the main clinical and sociodemographic characteristics, the aforementioned group was used plus patients with an incident and prevalent diagnosis of MS in 2014 with at least one annual follow-up visit for 5 years. The latter, in turn, were subject to assessment of clinical and treatment outcomes.

Results

During the study period, 147 records of patients diagnosed with MS were identified. Of these, 72 data correspond to new cases between 2014 and 2019, and 75 to incident or prevalent patients in 2014, with documented follow-up of at least once a year for 5 years.

The sex distribution identifies 69.4% (n=102) of women and 30.6% (n=45) of men, which generates a female:male ratio of 2.3:1. In 92.5% (n=136) of the cases analyzed, ethnicity was not recorded, and the rest were Latino.

Of the total number of participants, 87.8% (n=129) had the relapsing-remitting clinical form, 4.1% the primary progressive variant, 3.4% the secondary progressive form, and only 2.7% were classified as clinically isolated syndrome (course of the disease according to Lublin et al 2014)[17] (Figure 1).

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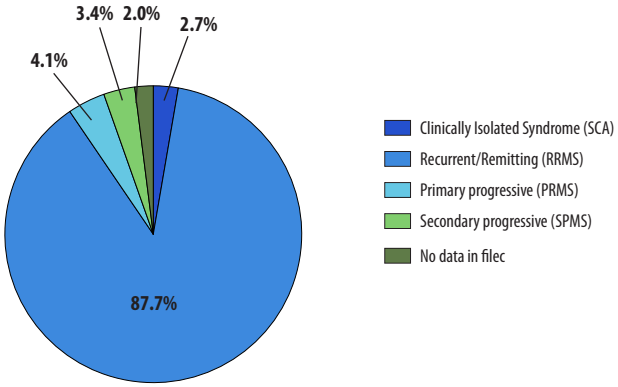

Figure 1. Distribution of participants according to the form of presentation of the pathology, n= 147 in the HSJD, HSRA and HSC hospitals of the CCSS during the period 2014-2019.
CCSS: Costa Rican Social Security Fund; HSJD: San Juan de Dios Hospital; HSRA: San Rafael Hospital in Alajuela; HSC: Hospital de San Carlos.

Symptom onset occurred at a mean age of 31.9 ± 10.9 years, while the mean age of diagnosis was 35.0 ± 11.2 years. At the time of data collection, the minimum age identified in the patients was 20 and the maximum was 80 years, with a range of 60 and a mean of 45.0 ± 12.7. The average time elapsed from the onset of symptoms to the date of diagnosis was 2.83 ± 5.43 years.

Regarding the existence of a family history of MS, 95.9% (n=141) of the participants did not register MS.

This precedent is true, while the remaining 4.1% (n=6) do report it, which are distributed in degrees of consanguinity ranging from the second to the fourth.

At the time of diagnosis, the functional status of 104 patients (70.8%) assessed using the Expanded Disability Status Scale (EDSS) ranged from 0 to 8.5 (Figure 2). Considering the disability values as: mild (0-3.0), moderate (3.5-6) and severe (⩾6.5), it is observed that at the time of diagnosis in 73.1% of the cases the level of disability was mild.

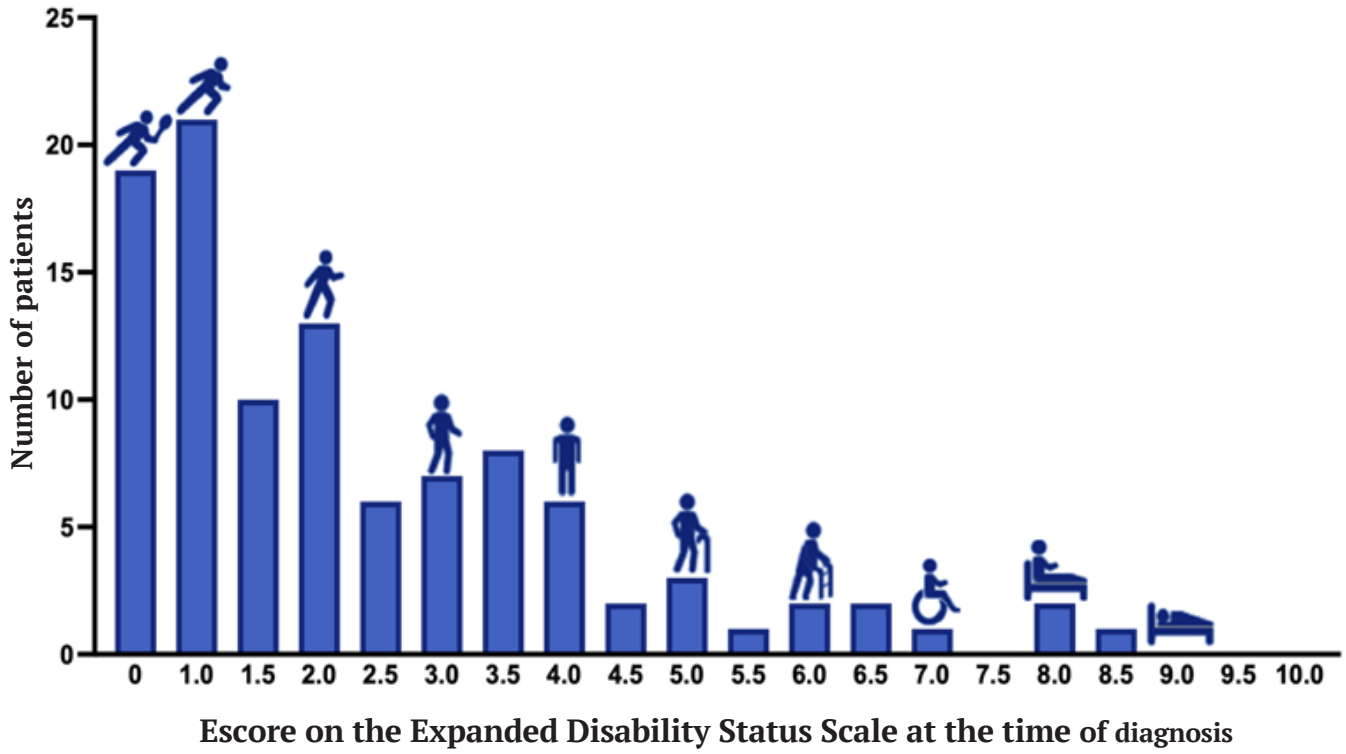

Figure 2. Distribution of patients with Multiple Sclerosis according to the result of the clinical evaluation using the Expanded Disability Status Scale at the time of diagnosis, n=104 in the HSJD, HSRA and HSC hospitals of the CCSS during the period 2014-2019.
CCSS: Costa Rican Social Security Fund; HSJD: San Juan de Dios Hospital; HSRA: San Rafael Hospital in Alajuela; HSC: Hospital de San Carlos.

Also, only records of vitamin D determinations were identified in 30 patients, where low values are evident in the majority. 50% (n=15) of the patients with this determination showed levels between 20.1 – 39.9 ng/mL, in 40% (n=12) of the cases the levels were less than 20 ng/mL and in the remaining 10% (n=3) the determinations showed levels greater than 40 ng/mL.

Magnetic resonance imaging reports of 131 patients at the time of diagnosis showed abnormal results in 99% (n=130) of the cases; revealed mainly periventricular lesions in 35% (n=45) of patients, cortical and periventricular lesions in 15% (n=19), and infratentorial and periventricular lesions in 11% (n=14) (Table 1).

The annual incidence in the population analysed ranged between 0.32 and 1.28 cases per 100,000 inhabitants; that is, they showed the maximum value during 2014 (Table 2). According to the healthcare center, in the HSJD there was an incidence between 0.32 and 1.90 cases per 100,000 during the years studied, while in the HSRA between 0.30 and 1.20 cases per 100,000 were identified in the HSRA. 100,000 inhabitants and in the HSC this value was between 0.37 and 1.50 cases per 100,000 inhabitants.

In relation to the clinical and treatment results obtained from the subset with active follow-up of at least 5 years, it is observed that over the years, the number of vitamin D determinations in the study population increased considerably; Thus, for the first year of follow-up, documents are 16 determinations were made, of which 30.8% showed levels below 20 ng/mL, 61.5% were between 20.1 and 39.9 ng/mL and the remaining 7.7% were greater than 40 ng/mL; while for the last year of follow-up, the more than twice the number of determinations of this vitamin, of which 21.2% showed levels below 20 ng/mL, 66.7% were between 20.1 and 39.9 ng/mL and 12.1% were greater than 40 ng/mL (Figure 3).

Table 1. Distribution of lesions according to anatomical region identified in n = 130 patients by magnetic resonance imaging at the time of diagnosis of multiple sclerosis, performed in the HSJD, HSRA and HSC hospitals of the Costa Rican Social Security Fund, period 2014-2019

Finds	Quantity (*n*)
Periventricular lesions	45
Cortical and periventricular lesions	19
Periventricular and infratentorial injuries	14
Cortical, periventricular and infratentorial lesions	12
Periventricular and spinal cord injuries	10
Periventricular injury, infratentorial and spinal cord injuries	9
Cortical, periventricular lesions, infratentorial lesions and spinal cord injuries	5
Cortical and spinal cord injuries	4
Cortical lesions	3
Cortical, periventricular and spinal cord injuries	3
Spinal cord injuries	2
Infratentorial injuries	2
Cortical, infratentorial and spinal cord injuries	1
Infratentorial and spinal cord injuries	1
Cortical and infratentorial lesions	0

HSJD: San Juan de Dios Hospital; HSRA: San Rafael Hospital in Alajuela; HSC: Hospital de San Carlos.

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Table 2. Incidence of multiple sclerosis identified between 2014 and 2019 in the HSJD, HSRA and HSC hospitals of the Costa Rican Social Security Fund

Year	Number of cases (*n*)	Incidence (cases per 100,000 inhabitants)
2014	22	1,28
2015	14	0,83
2016	7	0,44
2017	13	0,76
2018	16	0,91
2019	6	0,32

HSJD: San Juan de Dios Hospital; HSRA: San Rafael Hospital in Alajuela; HSC: Hospital de San Carlos.

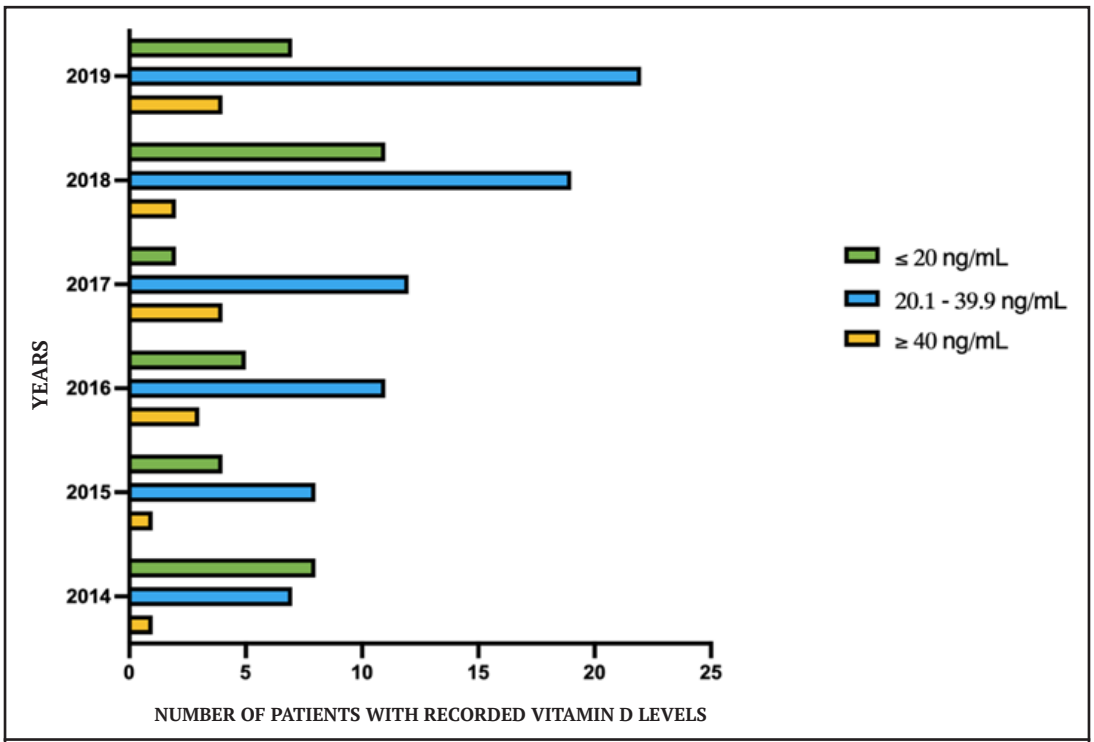

Figure 3. Distribution of vitamin D levels in patients with Multiple Sclerosis, n=75 in the HSJD, HSRA and HSC hospitals of the CCSS during the period 2014-2019.
CCSS: Costa Rican Social Security Fund; HSJD: San Juan de Dios Hospital; HSRA: San Rafael Hospital in Alajuela; HSC: Hospital de San Carlos.

In this follow-up cohort that included 75 patients followed for 5 years, baseline EDSS scores were recorded in 56 patients, with a median of 3.0 points. At 5 years of follow-up, this determination was recorded in 61 patients and showed an increase in both the median value (3.5 points) and the reported upper limit (9.0 vs 8.5 points). It is also evident that initially the majority of the population under study (50%) had a mild disability and that only 10.7% had severe disability; however, after 5 years of follow-up, 44.3% had mild disability and an increase of almost 10% in the proportion of patients in the severity stage (19.7%) was observed, which shows an increase in disability at 5 years.

In relation to the presentation of seizures (episodes of neurological deficit lasting >24 hours), during the first year of follow-up, 45.3% (n=34) of the patients had at least one crisis, of which 24 required acute treatment with intravenous corticosteroids and in one case immunoglobulin was used. In the second year, 22 patients with seizures were registered and 15 of them, 68.2%, required an approach with intravenous corticosteroids. By the third year, 59 patients presented seizures and 9 of them, 56.3%, required intravenous corticosteroids, while by the fourth year, 24 patients experienced seizures and all were treated with corticosteroids, in addition 14 of them received immunoglobulins. Finally, in the last year, 22 patients presented seizures and 18 of them, 81.8%, were treated with corticosteroids.

The highest percentage of relapses (41.3%) was recorded during the year of diagnosis. Approximately one third of the patients experienced relapses during the entire study period, for the first year of follow-up 29.3% of relapses were reported, in the second 30.7%, in the third 26.7%, in the fourth 30.7%, while in the last year of follow-up a decrease in the percentage of patients who suffer relapses is observed. that is, equivalent to 21.3%.

Of the diagnoses made in 2014 (applicable to the follow-up cohort), magnetic resonance imaging was performed in 52% of the patients, which showed that 48.7% of them had lesions in 2 different locations of the central nervous system (see classification for affected anatomical regions in Table 1), 23.1% had lesions in 1 region, 20.5% had lesions in 3 locations and 7.7% had lesions in 4 locations. At the end of the follow-up of these same patients (5 years later), imaging results were reported in 37.3% of the patients, of which: 53.6% had lesions in 2 locations, 25.0% had lesions in 3 locations, 17.9% had lesions in 1 location, and 3.6% had lesions in 4 locations.

In addition, different neurological compromises were recorded in the patients involving motor, cerebellous, bladder, spinal cord, sensory, cerebral and optic neuritis (Figure 4), of all these, motor, sensory and bladder impairments are the most frequent; and spinal cord and brainstem compromises are the least common. Despite this, In general terms, the frequency throughout the follow-up period remained relatively constant; except for a decrease in the frequency of optic neuritis in the first year, an increase in sensory impairment in the same period and a transient reduction at the level of the brainstem during the third year.

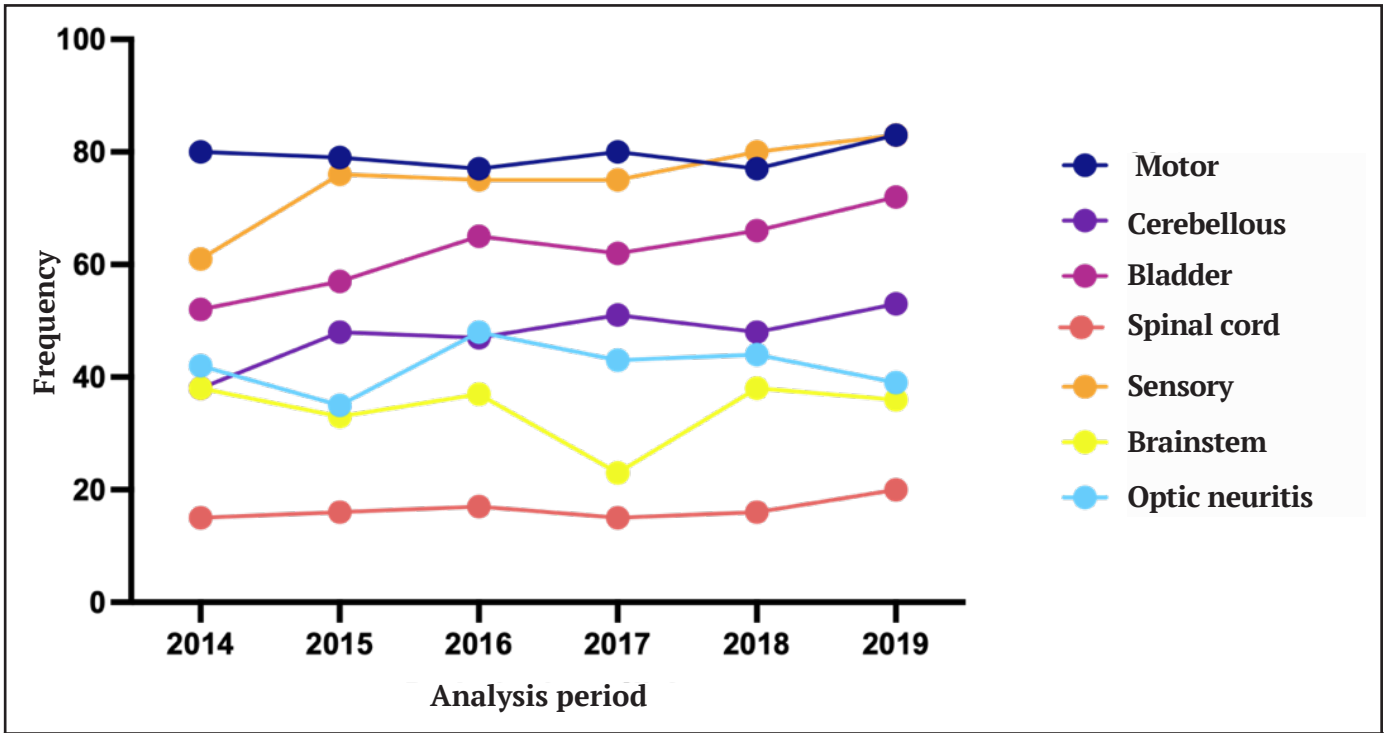

Figure 4. Type and frequency of clinical and neurological involvement presented by patients with Multiple Sclerosis, n=75, in the HSJD, HSRA, and HSC hospitals of the CCSS during the period 2014-2019. CCSS: Costa Rican Social Security Fund; HSJD: San Juan de Dios Hospital; HSRA: San Rafael de Alajuela Hospital; HSC: San Carlos Hospital.

During the study period, a total of 63 optical coherence tomography (OCT) scans were performed. There is an upward trend in the amount of OCTs over time, with a maximum of 14 (18.7%). Of all the tests carried out, 44.4% showed abnormal findings (Table 3). On the other hand, the determination of oligoclonal IgG bands was carried out in 22 cases during the follow-up period, which generated a positive response in 20 of them (90.9%) (Table 4).

Table 3. Number of patients in the follow-up cohort (n=75) who underwent optical coherence tomography (OCT) and results obtained between 2014 and 2019 at the HSJD, HSRA, and HSC hospitals of the CCSS

Year	Number of OCTs performed	Percentage of OCT performed	Finds	
			Normal	Abnormal
2014	5	6,7%	4	1
2015	10	13,3%	5	5
2016	12	16%	4	7
2017	10	13,3%	7	3
2018	12	16%	7	5
2019	14	18,7%	7	7

CCSS: Costa Rican Social Security Fund; HSJD: San Juan de Dios Hospital; HSRA: San Rafael Hospital in Alajuela; HSC: Hospital de San Carlos; OCT: Optical Coherence Tomography.

Table 4. Number of patients in the cohort who underwent analysis of oligoclonal IgG bands in CSF and results obtained between 2014 and 2019 at the HSJD, HSRA and HSC hospitals of the CCSS

Year	Oligoclonal IgG Bands	Findings	
		Normal	Abnormal
2014	15	13	2
2015	1	1	0
2016	1	1	0
2017	1	1	0
2018	1	1	0
2019	3	3	0

CCSS: Costa Rican Social Security Fund; HSJD: San Juan de Dios Hospital; HSRA: San Rafael Hospital in Alajuela; HSC: Hospital de San Carlos; CSF: Cerebrospinal fluid.

In relation to treatments, in the first year of follow-up, 93.2% (n=69) of the patients received interferon beta, 2.7% used fingolimod or natalizumab, and 1.4% were treated with azathioprine. To Throughout the follow-up period, there was a marked increase in the use of fingolimod, as well as a decrease in the frequency of other treatments, specifically interferon beta (Figure 5).

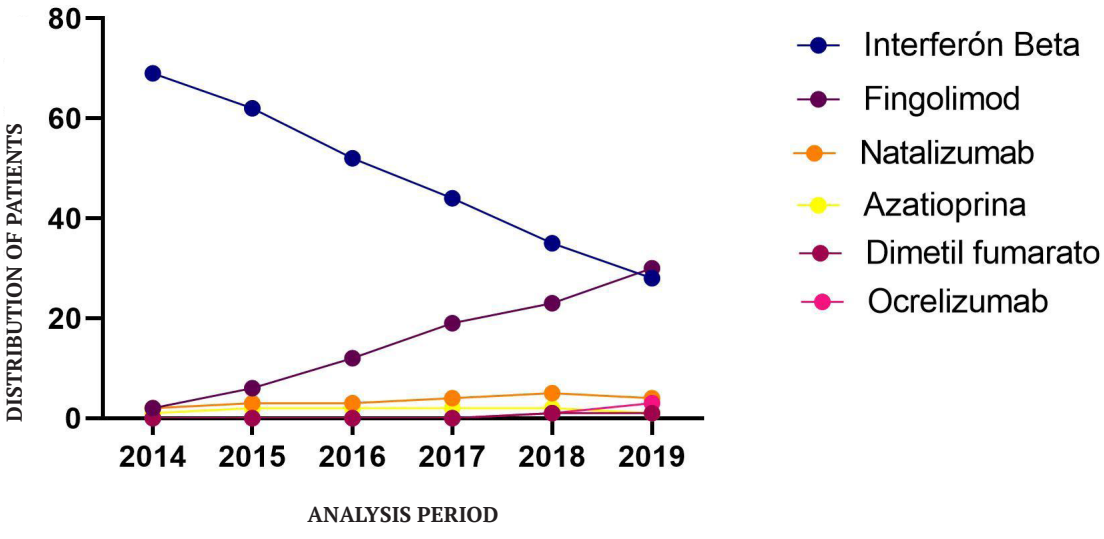

Figure 5. Distribution of patients with multiple sclerosis according to the treatment used, n=75 in the HSJD, HSRA and HSC hospitals of the CCSS during the period 2014-2019.
CCSS: Costa Rican Social Security Fund; HSJD: San Juan de Dios Hospital; HSRA: San Rafael Hospital in Alajuela; HSC: Hospital de San Carlos.

Discussion

Identifying the main characteristics of the MS population is essential to optimize the clinical management of this disease, as it favors the taking of specific measures and the appropriate clinical approach to it. In the present study, it is established that the population analyzed maintains the sex ratio previously identified by other authors[4,18], where there is a predominance of cases in the female sex. Previous research has determined that this difference could be related to the presence of endogenous sex hormones in the female sex; the which can influence the predisposition and severity of the disease, given their role in modulating the immune system[5,18]. The gender proportion identified in this study is similar to that reported in countries such as Nicaragua, Guatemala, Ecuador, and some regions of the Valencian community[12,19,20]. This could be related to genetic and environmental aspects common among populations[21]. However, the proportion identified differs from that reported in countries such as China and Japan, where the sex ratio is higher[22]. This predominance could be explained by environmental risk factors that mainly affect this group and could be related to aspects such as: birth and birth control, obesity, occupation and smoking[1], although the influence of non-modifiable factors such as genetics cannot be ruled out.

The prevalence and incidence of MS varies in different regions of the world[23], and it has been reported that the greater the distance from the Equator, the incidence rate tends to increase[24]. In accordance with the above, the incidence identified is lower than in other latitudes such as Spain, the United States, and Canada[19,25], and is similar to that previously reported in another national study[26]. It should not be forgotten that in the case of developed countries, incidence data could be higher due to greater availability of diagnostic tools and greater access to specialized consultations[12,22].

The age of onset of symptoms of the patients, as well as the age at diagnosis, is consistent with what has been reported both nationally[26] and in a study conducted in Mexico[6] and other existing studies[14]. The time from the onset of symptoms to the diagnosis of MS has been decreasing over the years. It is currently established that in European countries it is approximately 1.5 years[27-30], while in the United States it is 1.1 years[31]. This reduction in the time to diagnosis is also observed in Latin America, where, thanks to the new diagnostic criteria and their revisions, as well as the greater number of personnel familiar with the pathology, the delay in the diagnosis of MS has decreased[32]. In Argentina, the maximum time reported in 2021 was 15 months[33]. In this study, the time identified coincides with that reported in other countries such as Panama, Cuba, Nicaragua, and Brazil[14,34]. The variability observed between countries can be attributed to a variety of factors, such as levels of health literacy among populations, differences in referral processes, robustness and accessibility to specialized health care facilities, and the use of different diagnostic criteria and methods such as NMR and BOC[30]. Unlike the cases of a family history of MS reported in Mexico and Europe, in this study a lower percentage of this condition is reported (less than 5%), which could suggest the importance of non-modifiable risk factors such as genetics in the risk of developing the pathology[6], as well as the need to increase the size of the analysis in the present study. In relation to the low number of determinations of oligoclonal IgG bands, it should be noted that they are included as a complement to the diagnostic criterion of MS until 2017[1] and initially, at the level of the CCSS, they were performed only in a hospital center, so they were not always requested or available.

According to the Manual of Clinical Practice in Multiple Sclerosis, NMO and MOGA of the Spanish Society of Neurology (SEN) 2023, BOCs are an immunological biomarker of great clinical relevance for diagnosis as they represent the local synthesis of immunoglobulins in the central nervous system, which reflects chronic inflammatory activity. In addition, they also have prognostic value, as studies have suggested that patients with BOC have a more aggressive or active course of the disease.

At the international level, it has been shown that patients with MS generally have low levels of vitamin D[35,36], which is consistent with what was identified in the participants of thisstudy[37,38]. Although information on vitamin D levels is limited in Costa Rica, a high prevalence of 25-hydroxyvitamin D insufficiency and deficiency is also reported for the general population[39].

In accordance with what has been reported in the literature, it is identified in the present study that the most common form of clinical presentation of multiple sclerosis is RRMS[6,12,19]. Likewise, a higher frequency of the Primary Progressive form (PPMS) has been observed compared to the Secondary Progressive form (SPMS), a finding that differs from other studies[12,14]. This discrepancy could be attributed to the need to incorporate a larger population into the analysis of this study.

In relation to the treatment of MS, it is important to note that at the beginning of the study period, it was evident that most patients with this disease received treatment with interferon beta. At that time, during 2014, this was the only therapy available at the CCSS level that could be prescribed without the need to carry out an additional administrative purchase procedure[26]. However, over the years, for the pathology in question there is a greater availability of options and a change in

the therapeutic choice. Thus, there is a marked decrease in the frequency of patients treated with interferon beta and an increase in the number of patients receiving more recently approved drugs such as fingolimod. The latter, being an oral medication, has probably improved levels of adherence to treatment among patients[40]. In addition, it has been described as a reasonable therapeutic option both for the initial treatment of the disease and for those patients who have demonstrated an inadequate response to previous treatments or have experienced poor tolerance[41,42]. Because this drug poses a risk of developing macular edema, several studies emphasize the importance of regular ophthalmological examinations[40], which is why there is an increase in the number of optical computed tomography scans in the MS population over time[43]. Coinciding with what was observed in this study.

OCT has become an essential tool in MS due to its ability to detect and monitor both inflammatory and neurodegenerative damage early and accurately. Its clinical use allows for better risk stratification, monitoring Multiple sclerosis in Costa Rica more detailed disease progression and a objective evaluation of the efficacy of treatments[1].

This study has inherent limitations to observational initiatives based on retrospective review of documents, maintains the dependence on medical records for data collection, possibility of information biases and confusion. Likewise, obtaining data from only three hospitals of the Social Security of Costa Rica limits the representativeness of the sample and could make it difficult to extrapolate the findings identified to the entire national population because there are other hospitals with specialized neurology care where this pathology is treated and managed.

Finally, the incidence and prevalence of multiple sclerosis is increasing in both low-income and high-income countries. It is estimated that more than 2.8 million people are living with MS worldwide. Hence, it is the non-traumatic pathology that generates the greatest disability in the population of young adults (only surpassed by traffic accidents), it is necessary to know the behavior of this in our reality. The present research reaffirms that the clinical and sociodemographic characteristics of this population in three hospitals in Costa Rica are consistent with those observed in other studies. Thus, the annual incidence, the predominance of females, the average age at onset of symptoms, and the most common clinical manifestations, which include motor and sensory impairments, are aligned with global patterns. The growing adoption of new therapies underscores the evolution in disease management and other identified aspects such as low vitamin D levels in most patients could open up new opportunities for future research and treatment approaches. The findings identified not only emphasize the need for continuous follow-up of patients, but also highlight the importance of implementing intervention strategies adapted to the specific characteristics of a population, as well as the implementation of research projects in the area.

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