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Multiple sclerosis prevalence and incidence in San Vicente del Raspeig, Spain

Natalia Perez-Carmona[a], Juana Gimenez-Martinez[b], Cristina Borrego-Honrubia[c], Angel P. Sempere[b,*]

[a] Neurology Section, Hospital San Vicente del Raspeig, Spain
[b] Neurology Service, Hospital General Universitario de Alicante, Alicante 03010, Spain
[c] Health Psychology Department, University of Alicante, Alicante, Spain

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ABSTRACT

Background: Changes in the demographic epidemiology of multiple sclerosis (MS) may challenge the view of a latitudinal gradient in the distribution of MS. The objective of this study was to assess the incidence and prevalence of MS in addition to information on MS phenotypes and the use of disease modifying therapies (DMTs) in San Vicente del Raspeig in south eastern Spain.

Methods: This was a prospective epidemiological study of MS in San Vicente del Raspeig (population of 57,175 inhabitants based on the 2017 census) from 2005 to 2018. Multiple sources were used to identify MS cases. We considered as prevalent and incident cases all patients who satisfied either the criteria of Poser for clinically or laboratory-supported definite MS, or McDonald criteria. MS phenotypes were defined according to the 2013 revisions.

Results: For the prevalence data, 64 patients were identified. The non-adjusted prevalence was 111.9 (95% CI: 87.7–142.9) cases per 100,000 inhabitants; the prevalence was 159.3 cases per 100,000 inhabitants for women and 63.6 cases per 100,000 inhabitants for men. The female-to-male ratio was 2.6:1. The age-adjusted prevalence for the European standard population was 107 cases per 100,000 inhabitants. During the study period, the incidence was 5 cases per 100,000 inhabitants per year. Most patients were being treated with DMTs (81.3%). MS was active in at least 12.5% of patients.

Conclusions: The results are consistent with the increased risk of MS in Spain observed over the last three decades, with growing prevalence rates that place the country in the high-risk prevalence zone.

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS). The disease course can be extremely variable across individual patients, and although significant treatment advances have been made in recent years, MS remains one of the most frequent causes of neurological disability in young people (Oh et al., 2018).

Epidemiological studies performed in different areas of Spain have shown increasing prevalence rates, but there is no clear evidence of a true increase in the incidence of MS (Modrego and Pina, 2003; Otero-Romero et al., 2013; Izquierdo et al., 2015). The emergence of increasingly effective biological therapies and an active approach for treating MS are changing the long-term outcome for people with MS (pwMS) (Dobson and Giovannoni, 2019). However, few epidemiological studies have evaluated the use of disease modifying therapies (DMTs).

Phenotypic descriptions based on the clinical course of the disease are important for communicating, determining prognoses and making treatment decisions. Although a new classification of MS phenotypes that includes considerations of disease activity and disease progression is currently available (Lublin et al., 2014), no epidemiological study conducted in Europe has yet analysed the MS phenotypes according to the 2013 revisions.

Our study was designed to measure the incidence and prevalence of MS in addition to information on MS phenotypes and the use of DMTs in south eastern Spain.

* Corresponding author.
E-mail addresses: angel.perezs@umh.es, aperezs@mac.com (A.P. Sempere).

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Table 1
Prevalence of MS in San Vicente del Raspeig by age and sex.

Age (years)	Population			MS patients			Prevalence/100,000		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
≤14	5193	4798	9991	–	–	–	–	–	–
15–24	2952	2936	5888	–	–	–	–	–	–
25–34	3697	3792	7489	2	7	9	54.1	184.6	120.2
35–44	5615	5442	11,057	7	12	19	124.7	220.5	171.8
45–54	4391	4377	8768	5	18	23	113.9	411.2	262.3
55–64	2969	3208	6177	4	5	9	134.7	155.9	145.7
≥65	3486	4319	7805	0	4	4	0	92.6	51.2
Total	28,303	28,872	57,175	18	46	64	63.6	159.3	111.9

2. Methods

2.1. Study population

We performed a prospective epidemiological study of MS in San Vicente del Raspeig between December 31, 2005 and December 31, 2018. San Vicente del Raspeig is a town located in south eastern Spain in the province of Alicante at a latitude of 38° 23′ North. San Vicente del Raspeig has a Mediterranean climate, with an annual mean temperature of 17.7 °C. The total population based on the 2017 census was 57,175 inhabitants (28,303 males and 28,872 females), with a 5.6% immigrant population, mainly from Europe and Latin America. The total population at the beginning of the study, based on the 2005 census, was 46,034 inhabitants.

Healthcare is provided by the only general hospital located in the nearby city of Alicante, a long-term care hospital located in the city of San Vicente del Raspeig, and two primary health care centres. MS-specialized healthcare is provided by the MS unit at the general hospital. The healthcare system in Spain is free to access and universal.

2.2. Case definition and data collection

Only patients who satisfied either the Poser criteria for clinically or laboratory-supported definite MS or the McDonald criteria were included (Poser et al., 1983; Polman et al., 2005). Prevalent cases were defined as MS-confirmed patients who were living in San Vicente del Raspeig on the prevalence day, 31 December 2018. Patients residing in San Vicente del Raspeig on a temporary basis were excluded. The incidence was studied for the 2005–2017 period. Incidence was based on the year of the clinical onset of MS.

Data were retrieved from the following sources: 1) Abucasis, the computerized primary care medical records system, 2) the database of the MS unit at the general hospital, and 3) the local association of patients with MS. Demographic data were obtained from the Spanish National Statistics Institute (www.ine.es).

Information was recorded for the following variables: sex; year and age at onset; and age, use of DMT, disability and MS phenotype at last follow-up. Disability was assessed by the Expanded Disability Status Scale (EDSS) score (Kurtzke, 1983). All EDSS assessments were performed by trained and certified examiners (www.neurostatus.net). MS phenotypes were defined according to the 2013 revisions (Lublin et al., 2014). Informed consent was required for participation in the study. The study protocol was approved by the ethical committee of the Hospital Marina Baixa.

2.3. Statistical analysis

Age- and gender-specific as well as age-adjusted prevalence rates according to the 2013 European standard population (Eurostat, 2013) were calculated using the direct method. Rates with their 95% confidence intervals were expressed per every 100,000 inhabitants. The Wilson method was used to calculate confidence intervals. Quantitative variables are described using the mean ± standard deviation (SD) or median and range. Qualitative variables are presented as absolute numbers and percentages. Differences in numeric variables between patient groups were analysed by independent *t*-tests or the Mann–Whitney *U* tests and Kruskal–Wallis tests as appropriate.

3. Results

On the prevalence date, 64 patients were identified (46 women and 18 men). All patients satisfied both the McDonald criteria and the Poser diagnostic criteria for clinically or laboratory-supported definite MS. The non-adjusted prevalence was 111.9 (95% CI: 87.7–142.9) per 100,000 inhabitants; the prevalence was 159.3 per 100,000 inhabitants (95% CI: 119.5–212.4) for women and 64.9 per 100,000 inhabitants (95% CI: 40.2–100.5) for men (Table 1 and Fig. 1). The ratio of female-to-male patients with MS was 2.6:1. The age-adjusted prevalence per 100,000 inhabitants for the European standard population was 107 cases per 100,000 inhabitants. During the study period, the incidence was 5 cases per 100,000 inhabitants per year (95% CI: 3.6–7.1).

The mean age on the prevalence date was 46 years (SD: 10.9; range: 25–72), with no significant difference between women and men ($p = 0.53$). The mean age at onset was 32.3 years (SD: 10.4; range: 13–62). The mean duration of the disease on the prevalence date was 13.7 years (SD = 7.3), with no significant difference between women and men (mean disease duration of 14.3 years for women and 12.5 years for men, $p = 0.35$).

All patients had at least one clinical evaluation in the past 12 months. A brain magnetic resonance imaging (MRI) scan was performed in the current year in 58 of the 64 patients (91%). The MS phenotypes on the prevalence date are outlined in Table 2. The mean EDSS score was 2.6 (SD: 2.3, range: 0–9). Patients with progressive MS were older than patients with relapse-remitting MS (RRMS) (54.3 vs 43.9 years, $p < 0.01$), and the mean EDSS score of patients with progressive MS was higher than that of patients with RRMS (5.9 vs 1.8,

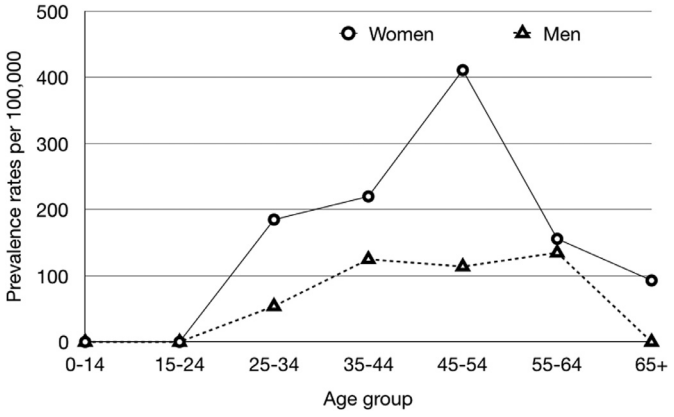

Fig. 1. Prevalence of multiple sclerosis in San Vicente del Raspeig, Spain, by sex and age groups.

Table 2
MS clinical types at the prevalence date.

Relapsing-remitting	51 (79.7%)
Active	6 (9.4%)
Inactive	42 (65.6%)
Indeterminate	3 (4.7%)
Secondary progressive	8 (12.5%)
Active and with progression	2 (3.1%)
Not active and without progression	4 (6.3%)
Indeterminate activity and with progression	2 (3.1%)
Primary progressive	5 (7.8%)
Not active and without progression	4 (6.3%)
Indeterminate activity and with progression	1 (1.6%)

$p < 0.01$).

Most patients were being treated with DMTs (81.3%), which included the following: IFN-β (11/52, 21.2%), glatiramer acetate (10/52, 19.2%), rituximab/ocrelizumab (9/52, 17.3%), dimethyl fumarate (9/52, 17.3%), fingolimod (7/52, 13.5%), azathioprine (3/52, 5.8%), natalizumab (2/52, 3.8%) and teriflunomide (1/52, 1.9%). The median delay between diagnosis and the start of the first DMT was 3 months.

4. Discussion

In this study, we identified an MS prevalence of 111.9 cases per 100,000 inhabitants in south eastern Spain, which is higher than the figures obtained from previous studies performed in Spain (Modrego and Pina, 2003; Otero-Romero et al., 2013; Izquierdo et al., 2015; García et al., 1989; Matias-Guiu et al., 1990; Bufill et al., 1995; Fernandez et al., 1994; Sempere et al., 1995; Uria et al., 1997; Pina et al., 1998; Pardo et al., 1997; Casquero et al., 2001; Mallada-Frechin et al., 2000; Tola et al., 1999; Benito-Leon et al., 1998; Hernandez, 2002; Aladro et al., 2005; Garcia-Gallego and Morera-Guitart, 2002; Ares et al., 2007; Candeliere-Merlicco et al., 2016; Bartulos Iglesias et al., 2015; Otero-Romero et al., 2015; Carreon-Guarnizo et al., 2016) (Table 3) and similar to the estimated prevalence rate in Malaga using the capture-recapture method (Fernandez et al., 2012). Repeated investigations in the same areas have shown a clear increase in MS prevalence in Spain over the last decades (Modrego and Pina, 2003; Otero-Romero et al., 2013; Izquierdo et al., 2015).

This increase in prevalence could have resulted from a rise in incidence or from longer survival time. The incidence of MS ranged from 2.2 to 3.8 cases per 100,000 inhabitants in studies conducted in Spain before 2000 and from 3.6 to 5.8 cases per 100,000 inhabitants in studies conducted after 2000 (Table 3). In our study, we found an MS incidence of 5 cases per 100,000 inhabitants, which is twice as high as that found in a previous study in the same province (Matias-Guiu et al., 1990). This increase in incidence may be due to a greater ascertainment of diagnosed patients or a higher disease risk. Differences in case ascertainment are unlikely because MRI has been widely available since the early 1990s, and the health system in Spain has not changed in recent decades. The increasing incidence points to the growing influence of environmental changes in people genetically susceptible to the disease (Goodin, 2016).

The increased incidence and prevalence of MS in Spain is in agreement with the observed changes in demographic epidemiology of MS over the past decades (Koch-Henriksen and Sorensen, 2010; GBD 2016 Multiple Sclerosis Collaborators, 2019). A recent systematic analysis revealed a strong latitude gradient for the prevalence of MS and suggested that the distribution of MS may still be generally described as having three zones of frequency or risk (GBD 2016 Multiple Sclerosis Collaborators, 2019). However, other authors have challenged the theory of a latitudinal gradient of MS in Europe and North America (Koch-Henriksen and Sorensen, 2010). The estimated prevalence of MS in the south eastern region of Spain, based on our data and the study by Malaga, is higher than 100 cases per 100,000 inhabitants, placing Spain in the high-risk zone, which is in disagreement with the north to south gradient.

Another important change in the demographic epidemiology of MS is the increase in MS incidence in women in many places, leading to higher female-to-male sex ratios over time (Koch-Henriksen and Sorensen, 2010). We found a female-to-male ratio of 2.6, which is similar to the ratio identified in other European studies (Ajdacic-Gross et al., 2017; Kingwell et al., 2013). Except for one study, there was no

Table 3
Incidence and prevalence of MS in Spain (1987–2018).

Province	Latitude	Study	Prevalence date	Prevalence (95% CI)	Age-adjusted prevalence*	Incidence (95% CI)	Female:male ratio
Canary Islands	28°	(Garcia et al., 1989)	1987	15 (8.4–24.7)	–	–	1:2
Alicante	38°	(Matias-Guiu et al., 1990)	1988	17.2 (11.4–25.8)	18.9	2.2	2.8:1
Barcelona	41°	(Bufill et al., 1995)	1991	58 (43.1–78.9)	62	–	2:1
Malaga	36°	(Fernandez et al., 1994)	1991	53 (32–82)	–	–	2.2:1
Segovia	40°	(Sempere et al., 1995)	1994	56 (36–76)	–	3.2 (2–4.6)	3.3:1
Asturias	43°	(Uria et al., 1997)	1994	65.1 (37.9–92.3)	59.3	3.7 (1.4–7)	1.2:1
Zaragoza	41°	(Pina et al., 1998)	1995	58 (39–78)	–	2.6	2:1
Teruel	39°	(Modrego Pardo et al., 1997)	1996	32 (22.8–41.3)	35.5	2.2	1.7:1
Balearic Islands	39°	(Casquero et al., 2001)	1996	68.6 (50.3–91.6)	75.5	3.4 (2.2–5.3)	2.3:1
Alicante	38°	(Mallada-Frechin et al., 2000)	1997	41.3 (31–53,6)	45	2.8 (2.1–3.8)	3.1:1
Valladolid	41°	(Tola et al., 1999)	1997	58.3 (43.7–75.7)	51.6	–	2:1
Madrid	40°	(Benito-Leon et al., 1998)	1998	43.4 (34.7–53.7)	52	3.8 (2.7–5.3)	1.6:1
Canary Islands	28°	(Hernandez, 2002)	1998	41.7 (29.8–58.4)	–	2.25	2.7:1
Alicante	38°	(Garcia-Gallego and Morera-Guitart, 2002)	2001	40.3 (30.6–52.7)	–	–	2.4:1
Canary Islands	28°	(Aladro et al., 2005)	2002	77.5 (59.7–98.9)	69.7	4.1 (2.4–6.6)	3.1:1
Coruña	42°	(Ares et al., 2007)	2003	78.7 (60.4–97)	71.1	5,3 (3.2–7.5)	1.6:1
Teruel	39°	(Modrego and Pina, 2003)	2003	75 (52–97)	–	4,6 (2.8–6.5)	1.9:1
Barcelona	41°	(Otero-Romero et al., 2015)	2008	79.9 (66.3–95.6)	80.4	–	1.4:1
Murcia	37° – 38°	(Candeliere-Merlicco et al., 2016)	2010	71.9 (60–85)	80.6[a]	–	2.6:1
Sevilla	38°	(Izquierdo et al., 2015)	2011	90.2 (75.6–104.8)	–	4,6 (4.1–5.1)	2.5:1
La Rioja	41–42°	(Bartulos Iglesias et al., 2015)	2011	65 (56–74)	62.2	3,5 (2.8–4.2)	2:1
Girona	42°	(Otero-Romero et al., 2015)	2013	–	–	3.6 (2.4–5.3)	1.5:1
Murcia	37° – 38°	(Carreon-Guarnizo et al., 2016)	2014	88 (76–100)	82.9	5.8 (2.9–8.7)	2.1:1
Alicante	38°	Present Study	2018	111.9 (87.7–142.9)	107	5 (3.6–7.1)	2.6:1

(*) Where age-specific data were available, age-standardised prevalence was calculated by the direct method using the 2013 European standard population.
[a] Age-standardised prevalence only available for the Spanish-born population.

evidence of a trend towards an increasing incidence in women compared to the incidence in men in Spain over the past decades (Izquierdo et al., 2015).

Early treatment with DMTs is associated with prolonged survival (Goodin et al., 2012). Survival time and incidence rate are the two most important components of prevalence. Since survival may be influenced by the use of DMTs, epidemiological studies should evaluate their use in the studied populations. A large proportion of patients were being treated with DMTs in our study (81.3%). Information about the use of DMTs is available in only three other epidemiological studies conducted in Spain. The use of DMTs increased from 29.6% in 2001 (Garcia-Gallego and Morera-Guitart, 2002) to 52.4% and 63.5% in 2011 (Izquierdo et al., 2015; Otero-Romero et al., 2015). Information about the use of DMTs in different countries is scarce, but a survey among European neurologists highlighted the variability in many aspects of MS disease management (Fernandez et al., 2017).

Accurate phenotypic descriptions are needed to characterize the clinical course of pwMS and allow for a better comparison between different populations. This is the first epidemiological study in Europe that uses the 2013 MS phenotypic descriptions. Despite the high use of DMTs in pwMS in our study, active MS was present in a significant number of patients.

Our study was limited to a small geographical area, which restricts the generalizability of the findings. There are several factors that may contribute to an underestimation of prevalence such as the delay between onset and diagnosis and the possibility that a few MS patients with mild attacks did not seek medical attention. It is also possible that the primary care physician did not refer a patient with MS to the neurologist because this diagnosis was unsuspected.

The results support the observation of the increased risk of MS in Spain observed over the last three decades with increasing prevalence rates that place our country in the high-risk prevalence zone. We also provided information about the distribution of MS phenotypes and the use of DMTs, which may help to study possible differences across populations.

Declaration of Competing Interest

Natalia Perez-Carmona has received personal compensation from Biogen Idec, Merck Serono, Sanofi-Aventis and Teva for consulting, serving on a scientific advisory board or speaking. Juana Gimenez-Martinez has received speaker honoraria from Almirall, Biogen Idec and Sanofi-Aventis. Cristina Borrego-Honrubia reports no disclosures. Angel P Sempere has received personal compensation from Almirall, Biogen Idec, Bayer Schering Pharma, Merck Serono, Novartis, Roche, Sanofi-Aventis and Teva for consulting, serving on a scientific advisory board or speaking.

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