



Onset-adjusted incidence of multiple sclerosis in the Girona province (Spain): Evidence of increasing risk in the south of Europe



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ABSTRACT

Background: Recent studies show an increasing incidence of multiple sclerosis (MS) in southern Europe. Although by its geographical location and genetic characteristics Spain is expected to be similar to other southern European regions, data on incidence are scarce. The aim of this study was to determine the onset-adjusted incidence of MS in the Girona province in Catalonia (Spain).

Methods: A prospective incidence study pooling data from the population-based Catalonia MS Registry was performed. Incident cases were defined as patients who had the onset of symptoms compatible with a clinically isolated syndrome (CIS) suggestive of MS in 2009 and fulfilled McDonald-2005 criteria during follow-up. Age- and sex-specific incidence rates were obtained.

Results: The Registry included 182 patients residing in Girona that presented a CIS from January 2009 to December 2013. Fifty one patients had the onset of symptoms in 2009, of whom 27 patients fulfilled the diagnostic criteria, giving an incidence of 3.6 per 100,000 (CI 95% 2.4–5.3) inhabitants; 4.3 (CI 95% 2.5–7.1) for women and 2.9 (CI 95% 1.4–5.2) for men. The age-adjusted incidence rate for the European population was 3.29 (CI 95% 3.2–3.3).

Conclusion: The incidence estimation derived in this study is consistent with recent epidemiological data of MS in southern Europe suggesting an increase in incidence in this region.

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1. Background

The early descriptive epidemiological studies on multiple sclerosis (MS) showed an uneven distribution of the disease throughout the globe. Lower latitude areas were perceived to be at lower risk for the disease as compared to northernmost regions. This has changed over the years and incidence has increased, as showed by recent population-based studies performed in southern European countries and other lower latitude areas [1,2]. This is the case of Sicily where incidence of MS has increased from 1.3 per 100,000 inhabitants and year during 1975–1999 to 7.0 during 2000–2004 and Greece with incidence rising from 2.7 in 1984–1989 to 10.7 in 2002–2006 [3,4]. Despite possible methodological explanations (improved study methodology,

changes in diagnostic criteria, improved diagnostic tools and case ascertainment) an actual increase in the risk for developing the disease cannot be ruled out. These southern regions become of key importance when describing the changes in the environmental risk factors and their interaction with the genetic background that could be driving the observed increasing trend.

By its geographical location and genetic characteristics, the epidemiological pattern of MS in Spain is expected to be consistent with other southern European regions. In fact, recent prevalence studies show values ranging from 79 to 125 cases per 100,000 inhabitants [5–7], a figure similar to those reported in Italy and Greece [3,8,9]. However, incidence data are very limited in our milieu, based only on four studies published in the past 15 years using hospital sources at city or regional scale (La Palma island, Santiago de Compostela, Las Palmas de Gran Canaria and Bajo Aragón) [5,10–12]. These studies were primarily designed to obtain prevalence estimates and incidence data were obtained retrospectively. This made it difficult to determine the exact

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date of onset, which is paramount to capturing the etiological relevance of this measure [13]. In the present study we aim to determine for the first time in the Girona province the onset-adjusted incidence of MS, based on a prospective population-based registry.

2. Methods

2.1. Study design and setting

We performed a prospective incidence study of MS in the province of Girona, following patients from the onset of symptoms until diagnostic confirmation to obtain an accurate onset-adjusted incidence rate. Girona is a geographically and administratively defined area located in north-eastern Catalonia (Spain) with a total extension of 5754 km² (Fig. 1). It has a well established open access public healthcare system provided by a tertiary care hospital, 8 local hospitals and 49 primary health care centers. The total population according to the 2009 census was 747,782 inhabitants (368,153 women and 379,629 men) representing 10% of the total population of Catalonia [14].

2.2. Case definition and selection criteria

Incident cases were defined as confirmed MS patients who had the onset of symptoms compatible with a clinically isolated syndrome (CIS) suggestive of MS between 1st January 2009 and 31st December 2013, while residing in Girona. CIS was defined as neurological symptoms of a monophasic presentation with a suspected underlying CNS process of the inflammatory-demyelinating type, with a minimum duration of 24 h in the absence of fever or infection. CIS patients were followed over a 5-year period (2009–2013) to confirm the diagnosis according to the McDonald 2005 criteria, which were those in use at the time of registry implementation [15]. Probable MS cases were defined as those fulfilling either dissemination in space (DIS) or in time (DIT) according to the Barkhof-Tintoré MRI criteria [16]. We excluded patients who were residents on a temporary basis (defined as not registered in the census or residing in the study area for less than 6 months per year, according to official data from the Spanish National Institute of Statistics).

2.3. Sources of information and data collection

Cases were obtained from the Catalonia MS Registry (www.epidemcat.cat). The registry started in January 2009 and prospectively includes patients residing in Catalonia presenting with a CIS followed

until diagnosis of MS is confirmed. The Registry is designed to achieve a maximum diagnosis homogeneity and accuracy of the declared cases. The notifying neurologists are required to report the information needed to verify the McDonald 2005 criteria [15]. As such, information about relapses (date, topography and clinical evidence of one or more lesions), baseline and follow-up MRI (total number of T2 lesions, lesion topography, presence of new T2 lesions and gadolinium enhancing lesions) as well as presence of oligoclonal bands is required. Based on the reported data, the registry software performs an automatic verification to detect whether there is sufficient evidence to conclude dissemination in time and/or space as established in the 2005 McDonald criteria. This information is double-checked by the registry coordinator. Further details of its implementation process and main features can be found elsewhere [17,18].

A total of 21 hospitals throughout Catalonia take part in the registry, including the three main hospitals for the care of patients with MS in the Girona region (Hospital Universitari Doctor Josep Trueta, Hospital Santa Caterina de Salt and Hospital de Figueres). The smaller hospitals in Girona were also contacted and confirmed to be participating in the Registry by referring their incident patients to the main hospitals, ensuring a complete geographical coverage in the region.

Because of health care administration features and geographical conditions, it is unlikely for a patient resident in Girona to resort to clinics with dedicated MS units other than those in Girona or in Catalonia (mainly in the capital, Barcelona). Therefore, we searched the MS Registry database for patients with continuous residency in Girona, regardless of the hospital they were recorded into the registry from. In case of missing data in the registry, we asked for necessary blank fields to be filled in by the neurologist actually seeing the patient. Demographic, clinical, MRI and Cerebrospinal fluid (CSF) data were collected for each patient. The study protocol was approved by the research ethics committee of Vall d'Hebron University Hospital (Barcelona) as the reference committee.

2.4. Statistical analysis

Age- and gender-specific as well as adjusted incidence rates according to the 2009 European standard population [19] using the direct method were calculated. Rates were expressed per every 100,000 inhabitants and the 95% confidence intervals were calculated assuming a Poisson's distribution. Quantitative variables were described using mean \pm standard deviation (SD) or median and range. The Student's *t* test was used to compare arithmetic means and the Chi-squared test was used to compare proportions.

3. Results

Over the period January 2009–December 2013, 186 patients presenting a CIS while residing in the province of Girona were recorded into the registry. They were reported from 7 hospitals (3 in the province of Girona and 4 in the province of Barcelona) with a median time from onset of symptoms until registration of 2 months (interquartile range [IQR] 1–7.25 months). Three patients were excluded from the study database because they were duplicates from two different hospitals, therefore obtaining a final cohort of 183 patients. Fig. 2 shows the case ascertainment flow diagram. In January 2014 the whole cohort was reviewed to check for fulfillment of diagnostic criteria. At that stage, an additional patient was excluded because of a confirmed alternative diagnosis. Table 1 shows the demographic and clinical characteristics of the remaining 182 patients.

From the final cohort of 182 patients, 51 had the onset of disease in 2009. Of the 51, 53% were women, with a mean age at onset of 36.1 years (standard deviation [SD] 10.9). During the follow-up period (median of 50 months; IQR 46–54) 27 patients fulfilled the McDonald 2005 diagnostic criteria, and were therefore incident cases, according to case definition for the present study. There were no statistically



Fig. 1. Geographical representation of the Girona province within Catalonia (Spain).

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