Multiple sclerosis in the province of Ferrara, Italy, in 2004-13: the Emilia Romagna Multiple Sclerosis Registry (ERMeS)

GROPPO E[1,2], PASTORE M[1,2], CASETTA I[1,2], PUGLIATTI M[1,2], CANIATTI ML[3], BALDI E[3], DELLA COLETTA E[1,2], CESNIK E[1,2], GRANIERI E[1,2], and the ERMeS Group*

[1] Sezione di Scienze Neurologiche Psichiatriche Psicologiche, Dipartimento di Scienze Biomediche e Chirurgico-Specialistiche, University of Ferrara, Italy
[2] U.O. Clinica Neurologica, Azienda Ospedaliero-Universitaria , Arcispedale S. Anna, Ferrara, Italy
[3] U.O. Neurologia, Azienda Ospedaliero-Universitaria , Arcispedale S. Anna, Ferrara, Italy

***ERMeS (Emilia Romagna Multiple Sclerosis) Group**: Granieri E, Castellazzi M, Casetta I, Tola M, Fainardi E, Dallocchio F, Bellini T, Rizzo R, Rotola A, Di Luca D, Seraceni S, Contini C, Sabbioni S, Negrini M, Tognon M, Antonelli T, Groppo E, Gentile M, Baldi E, Caniatti M, Ceruti S, Manfrinato M, Trentini A, Bortolotti D, Miotto E, Ferracin M, Mazzoni E, Pietrobon S, Masini I, Rotondo J, Martini F, Baruzzi A, D'Alessandro R, Michelucci R, Salvi F, Stecchi S, Scandellari C, Granella F, Nichelli P, Sola P, Ferraro D, Vitetta F, Simone A, Bedin R, Marcello N, Motti L, Montepietra S, Guidetti D, Immovilli P, Montanari E, Pesci I, Guareschi A, Greco G, Santangelo M, Mauro A, Malagù S, Rasi F, Spadoni M, Galeotti M, Fiorani L, Neri W, Ravasio A, Pasquinelli M, Guttmann S, Monaldini C.

Introduction and Objectives

Epidemiological studies on MS are important to explaining clinical course and to going insight to disease's pathogenesis. The epidemiological studies of the last 40 years indicate that the multiple sclerosis (MS) distribution in Mediterranean countries, and in Italy in particular, is complex, particularly for incidence, and the Kurtzke's latitude-related model is not widely accepted [1-7]. Recent reports confirmed that MS incidence rate in southern Europe seems uneven, also within countries and in time [1-10]. An apparent increasing trend appears stable in the last two decades in several reports and in long surveys conducted in the same areas, both in Italy and other Mediterranean countries [1-4, 8, 13]. The province of Ferrara, Region of Emilia Romagna, northern Italy, is a high risk area for MS, with increasing temporal trends (1,4). However, due to large differences in the methods and diagnostic criteria used in past MS epidemiological surveys, it is hard to make comparisons across studies and correctly explain the relevance of an apparently increasing temporal trend reported from the same areas [5-9]. Some authors have related this trend to only an increase in the number of diagnoses of MS in the absence of biological evidences. Therefore it is not clear whether the increase indicates a change in incidence and prevalence, or reflects improved case identification and ascertainment [9,10].
We sought to update incidence of MS in this province [1-4].

Materials and Methods

We conducted a community-based intensive incidence study, by adopting a complete enumeration approach. Incidence patients were drawn from a community-based prospective multi-source registry implemented by the MS Centre of Ferrara. The Province of Ferrara, situated in northeastern Italy between 44°32' and 44°58' north and between 10°13' and 11°14' east, has a temperate climate. The area is known to been have inhabited since the Paleolithic period. According with HLA gene frequencies, the Ferrarese people are typically of Caucasian phylogenetic root. The standards of living and medical care are high. We included MS patients diagnosed according to the Mc Donald's diagnostic criteria, with disease onse in the study area, between 2004 and 2013 [15]. The mean study population for the incidence period was 355,905 (170,279 men and 185,626 women), 349,777 in 2004 and 355,334 in 2013 and served as denominator for the incidence estimation. Crude mean annual incidence rates (per 100,000) were computed based on the number of new MS cases by clinical onset as numerator. These rates were standardized to the 2009 European Population by direct method. 95% confidence interval (95% CI) was calculated assuming a Poisson distribution [14].

Results

Based on 232 patients (66 men and 166 women) with MS clinical onset in the period 2004-13, the mean crude annual incidence was 6.52 per 100,000 (95%CI: 5.75-7.39), 3.88 (95%CI: 3-4.93) for men and 8.94 (95%CI: 7.66-10.43) for women, with a female:male ratio of 2.5. The mean ± SD age at onset (range, 17-73 years) was 36.6±10.9 for both sexes and was 35.8±11 for women and 38.7±10.7 for men (p>0.05) (**Table 1**). The age- and sex adjusted rate to European population was 7.33 for both sexes, 3.87 and 10.87 for men and women, respectively. We observed an incremental trend over decades (**Figure1**). From 1990 to 2003 MS more frequent age onset is between 30-34 years for men 25-29 years for women. In our study we found a more frequent age onset between 20-34 years and confirm greater incidence rate in the age class 25-29 years for women and greater incidence rate in the age 30-34 for men (p=ns) (**Figure 2**).

In 52% of patients the onset was monosymptomatic, in 48% plurisymptomatic. Optic neuritis (19 %) and sensory disorders (14 %) were the most common presenting symptoms. The monosymptomatic pyramidal onset was associated with a greater lag time between onset and diagnosis (**Table 2**).

Table 2. Distribution (%) of symptoms and signs at clinical onset and corresponding mean diagnostic delay (years) for each clinical presentation, in the province of Ferrara, Italy, 2004-13.

Clinical onset	Prioportion of incident cases (%)	Mean (SD) diagnostic delay from clinical onset (months)
Polisymptomatic	40	8.8
Myelitis	8	12.9
Optic neuritis	19	9.1
Pyramidal	7	23.3
Sensitive	14	13.8
Brainstem /cerebellar	16	11.1
Sphyncteric	0.5	5

Figure 1. Mean annual incidence rates of MS in the province of Ferrara, Italy, 2004-13.

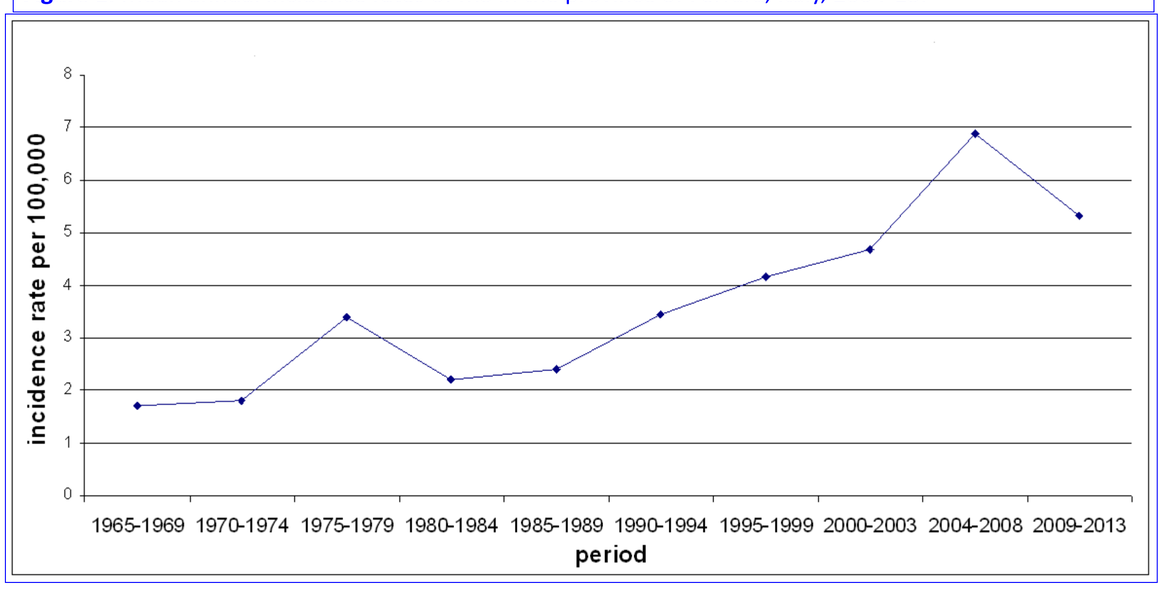
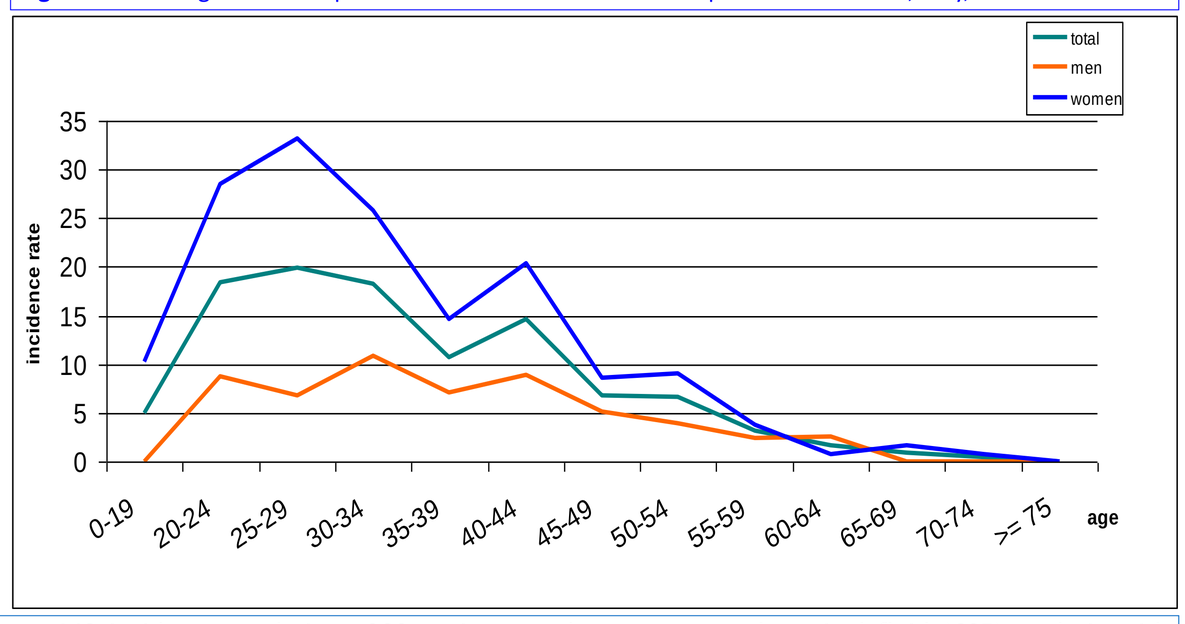


Table 1. Age- and sex-specific incidence rates of MS (per 100,000) in the province of Ferrara, Italy, 2004-13.

	N. cases			Mean annual population			Crude incidence rate		
Age	Total	Men	Women	Total	Men	Women	Total	Men	Women
0-19	6	0	6	49968	25801	24168	4.92	0	10.20
20-24	25	6	19	13565	6911	6672	18.43	8.68	**28.48**
25-29	35	6	29	17623	8883	8740	19.86	6.75	**33.18**
30-34	43	13	30	23612	11950	11662	18.21	**10.88**	**25.72**
35-39	30	10	20	27837	14165	13672	10.78	7.06	14.63
40-44	42	13	29	28783	14574	14209	14.59	8.92	20.41
45-49	19	7	12	27835	13839	13996	6.83	5.06	8.57
50-54	17	5	12	25880	12588	13292	6.57	3.97	9.03
55-59	8	3	5	25145	12101	13104	3.18	2.48	3.82
60-64	4	3	1	24234	11589	12645	1.65	2.59	0.79
65-69	2	0	2	23094	10814	12280	0.87	0	1.63
70-74	1	0	1	22132	9925	12069	0.45	0	0.83
75+	0	0	0	46253	17139	29117	0	0	0
Total	232	66	166	355961	170279	185626	6.52 *(95%CI: 5.75-7.39)*	3.88 *(95%CI: 3-4.93)*	8.94 *(95%CI: 7.66-10.43)*

Figure 2. Mean age- and sex-specific incidence rates of MS in the province of Ferrara, Italy, 2004-13.



Among our MS incident populations 202 patients underwent to cerebrospinal fluid (CSF) analysis with isoelectric focusing, as previously described and generally accepted [17]. Among these 167 (82,7%) were positive for IgG oligoclonal bands (OCB), performed with a standardized methodology [17]

Discussion and Conclusions

We adopted a complete enumeration approach on a well-defined population with suitable size to ensure accuracy (over 350,000 pop.). To minimize possible biases we adopted an intensive case collection approach and were supported by adequate expertise in epidemiological surveys [1-4, 7, 16].

The increasing incidence documented during the last decades in Italy and other European areas, highlights the importance of environmental factors related to lifestyle [7].

We confirmed, respect to previous study, the mean age at onset. Like our survey, the majority of the incidence studies on MS in Caucasian populations indicate that the distribution of incidence of the disease according to age peaks in the age-groups between 25 and 40 years [8, 11]. The mean lag time in the decade between 1965 through 1974 was 6.1 years, falling to 4.6 years between 1975 to 1984, 1.9 years between 1985 and 1994 and finally 7 months between 1994 to 2004. In others surveys the lag time between onset and diagnosis was longer [12]. In our last reports the average lag time between symptomatic onset and diagnosis resulted of 9.9 +/- 16.2 months for remitting-relapsing forms and of 11.6 +/- 17.8, including months for progressive forms too.

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As just suggested by other authors, to study valid time trends of MS incidence rates there is necessity to conduct long-term surveys and repeated surveillances. Therefore, it would be important to obtain a reinforcement of national and/or international registers and to create an implementation of strategies for the creation of clinical registers in countries where they do not have any. These would make it possible to obtain pictures of the epidemiological course of MS even over the next decades and they would provide the bases for the development of case-control studies [18].

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