

High Prevalence and Fast Rising Incidence of Multiple Sclerosis in Caltanissetta, Sicily, Southern Italy

Luigi M.E. Grimaldi^a Barbara Palmeri^b Giuseppe Salemi^b Giuseppe Giglia^b
 Marco D'Amelio^b Roberto Grimaldi^a Gaetano Vitello^a Paolo Ragonese^b
 Giovanni Savettieri^b

^aUnità Operativa di Neurologia, Fondazione Istituto San Raffaele G. Giglio, Cefalù, e

^bDipartimento di Neuroscienze Cliniche, Palermo, Italia

Key Words

Multiple sclerosis incidence • Prevalence, Sicily

Abstract

Background: Epidemiological studies conducted in Sicily and Sardinia, the two major Mediterranean islands, showed elevated incidence and prevalence of multiple sclerosis (MS) and a recent increase in disease frequency. **Objective:** To confirm the central highlands of Sicily as areas of increasing MS prevalence and elevated incidence, we performed a follow-up study based on the town of Caltanissetta (Sicily), southern Italy. **Methods:** We made a formal diagnostic reappraisal of all living patients found in the previous study performed in 1981. All possible information sources were used to search for patients affected by MS diagnosed according to the Poser criteria. We calculated prevalence ratios, for patients affected by MS who were living and resident in the study area on December 31, 2002. Crude and age- and sex-specific incidence ratios were computed for the period from January 1, 1993, to December 31, 2002. **Results:** The prevalence of definite MS rose in 20 years from 69.2 (retrospective prevalence rate) to 165.8/100,000 population. We calculated the incidence of definite MS for the period 1970–2000. These rates calculated for 5-year periods increased from 2.3 to

9.2/100,000/year. **Conclusion:** This survey shows the highest prevalence and incidence figures of MS in the Mediterranean area and confirms central Sicily as a very-high-risk area for MS.

Copyright © 2007 S. Karger AG, Basel

Introduction

Epidemiological studies conducted in Sicily and Sardinia, the two major Mediterranean islands, have consistently shown elevated incidence and prevalence of multiple sclerosis (MS) and a recent increase in disease frequency [1–3]. The prevalence of MS reaches 151.9/100,000 in rural areas of central Sardinia [4], and 120.2/100,000 in the central and hilly Sicilian town of Enna [1]. The most recent incidence rates range from 5.7 (Sicily) to 6.4/100,000/year (Sardinia) [1, 3].

The first survey of MS prevalence performed 21 years ago in Caltanissetta, a town located 35 km east of Enna, unexpectedly demonstrated a high prevalence [5]. To confirm the central highlands of Sicily as areas of elevated MS prevalence and in which the incidence may be increasing, we performed a follow-up study in Caltanissetta.

Materials and Methods

Area of Investigation

The city of Caltanissetta is located in central Sicily, at approximately 567 m above sea level. The population size on December 31, 2002, was 60,919 inhabitants compared to 60,713 inhabitants on December 31, 1981 (prevalence day of the previous study), indicating a stability of the population of this community in the last 20 years.

The level of public medical care is relatively high in Caltanissetta where a community-based department of neuroscience and a general hospital with a neurology unit have worked in conjunction until recently.

Case Collection and Ascertainment

We used the previous prevalence study as the foundation for the present survey. We made a formal diagnostic reappraisal of all surviving patients from the 1981 prevalence study and of all patients traced during the present survey. Personal contacts were undertaken with all general practitioners and neurologists working in the study area. The local branch of the Italian MS Association (AISM) was also involved in the study. Archives of the Department of Neuroscience of the 'Azienda Unità Sanitaria Locale' No. 2, of the Neurological Unit of the Caltanissetta Hospital, of the Department of Neurology of the University of Palermo and of two major Italian MS centers (Gallarate and Milano San Raffaele) were searched. The retrospective prevalence for the 1981 series was estimated including patients who had had onset of MS before the prevalence day but were diagnosed subsequently (onset-adjusted prevalence rate) [6]. Patients were classified according to the criteria of Poser et al. [7].

As onset of the disease was considered the year of appearance of the first symptom or symptoms attributable to MS.

Data Analysis

To calculate prevalence rates, we searched for patients affected by MS resident in the study area on December 31, 2002. Crude as well as age- and sex-specific prevalence ratios were calculated. Clinical features were also recorded. Crude and age- and sex-specific incidence ratios, based on the reported first symptom of MS, were computed for the period from January 1, 1993, to December 31, 2002.

Results

On December 31, 2002, 101 clinically definite MS patients (31 men, 70 women) were resident in the study area. Thirteen of them were the survivors of the 31 subjects with definite MS identified in the 1981 survey. Fifteen of the 31 were deceased and 3 were untraceable.

Eleven patients identified during the current survey had MS onset before January 1, 1981, but, at that time, they were not found and, as a consequence, had not been included in the previous study.

The mean age at onset was 30.75 years (range 12–55), 28.74 for men and 31.64 for women. The mean age on

the prevalence day was 43.22 years (range 15–74), 39.03 for men and 45.07 for women. The mean interval between onset of the disease and diagnosis was 4.63 years (range 1–31) for the whole cohort; it was higher in women (5.34 years) than in men (2.96 years). The average duration of MS from onset to prevalence day was 12.13 years (range 1–38), 10.03 for men and 13.08 for women. Indeed the longest intervals between onset and diagnosis have influenced these data. This is true for those patients whose onset happened before 1981, but who were diagnosed after the first survey. The mean age at onset of patients whose disease started after 1981 was 32.9 years (30.2 in men, 34.2 in women). In this cohort the mean age at diagnosis was 35.8 years (32.6 in men, 37.3 in women) and the mean interval between onset and diagnosis was 2.6 years (2.3 in men, 2.8 in women).

The overall prevalence was 165.8/100,000 population (95% confidence interval = 158.5–173.1), 107.6 for men and 218.0 for women. The age-specific prevalence was found to increase up to the age group of 35–44 years and to decrease thereafter (table 1). Seventy-seven (74.7%) patients had a relapsing-remitting form of MS; 16 (15.5%) were affected by a secondary progressive form, 9 by a primary progressive form (8.8%), and 1 (1%) was affected by a primary progressive form with relapses. As shown in table 2, the retrospective prevalence rate for the 1981 survey was 69.2/100,000 population.

Between January 1, 1993, and December 31, 2002, 56 subjects (19 men and 37 women) had their first symptoms of MS. The average annual incidence was 9.2/100,000 population (95% confidence interval = 8.4–10.0), 6.6 for men and 11.5 for women. Age- and sex-specific incidence rates of MS in Caltanissetta are shown in table 3.

The highest age-specific incidence rate was observed in the age group of 25–34 years for men and 35–44 years for women. The mean interval between the onset and the diagnosis of the disease among incident patients was 1.8 years.

Discussion

In this survey we found a prevalence of 165.8/100,000 and an incidence rate of 9.2/100,000 population. These figures (a 2.4-fold increase in prevalence and an almost 2-fold increase in incidence across 2 decades) are the highest found in the Mediterranean area including Sardinia and confirm the extremely high frequency of MS in Sicily especially in the innermost part of the island. The

Table 1. Age- and sex-specific prevalence of MS in Caltanissetta as of December 31, 2002

Age years	Men			Women			Both sexes		
	cases	population	prevalence (per 100,000)	cases	population	prevalence (per 100,000)	cases	population	prevalence (per 100,000)
0-14	0	5,170	-	0	5,014	-	0	10,184	-
15-24	3	3,948	76.0	3	3,945	76.0	6	7,893	76.0
25-34	9	4,133	217.8	7	4,380	159.8	16	8,513	187.9
35-44	9	4,311	208.8	24	4,732	507.2	33	9,043	364.9
45-54	6	3,757	159.7	22	4,220	521.3	28	7,977	351.0
55-64	3	3,041	98.6	11	3,467	317.3	14	6,508	215.1
65-74	1	2,650	37.7	3	3,365	89.2	4	6,015	66.5
≥ 75	0	1,805	-	0	2,981	-	0	4,786	-
Total	31	28,815	107.6	70	32,104	218.0	101	60,919	165.8

Table 2. Age-specific, onset-adjusted prevalence of MS in Caltanissetta on January 1, 1981

Age, years	Cases	Population	Prevalence (per 100,000)
0-14	1	14,873	6.7
15-34	24	18,663	128.6
35-54	14	14,406	97.2
55-74	3	10,505	28.6
≥ 75	0	2,266	-
Total	42	60,713	69.2

fast rising incidence rate suggests that these figures might further increase in the near future.

Increases in the frequency of MS have often been described in follow-up studies [1-4]. The reasons for such increases may include changes in the population's structure, improvement in diagnostic tools, greater awareness of the disease and longer patient survival.

During the interval between the two surveys carried out in Caltanissetta, the population structure did not change. The gender and the age distribution did not change over the three population censuses performed in 1981, 1991 and 2001. The rates of migration were also modest and the population survival has not changed during the follow-up period. Although new diagnostic modalities have become available and the physicians' awareness of MS has increased over time, we consider it unlikely that a greater than 2-fold increase in prevalence and the high and increasing incidence rate observed might be explained by these epiphenomena. Table 4 summarizes

MS figures from surveys performed in Sicily. We compared prevalences reported in the first surveys with rates recalculated at the follow-up. The increase in previous prevalence rates, corrected with new patients diagnosed in the follow-up period but who had onset before the first prevalence day, is not sufficient to justify alone the observed increase in MS at the follow-up survey.

The rates found in Caltanissetta are among the highest in Europe, but recently increasing prevalence and incidence rates have also been observed in a follow-up study conducted in Enna, a nearby Sicilian community [1]. A recent follow-up survey conducted in Catania, a coastal municipality of eastern Sicily, also reported an increased prevalence and incidence [2]. By reviewing the thorough MS epidemiological investigation some of us conducted in Monreale (northern coast of the island), an increasing prevalence was recorded between 1981 and 1991 [8], although of a lower magnitude compared to Caltanissetta and Enna. A second follow-up conducted in 2000 failed to show an additional increase in the prevalence rate, suggesting that in Sicily the increasing frequency of MS is not a homogeneous phenomenon [9].

The heterogeneous distribution of MS throughout Sicily and its main features (e.g. coastal vs. central and hilly) might not have a simple explanation. Poser's hypothesis [10] concerning the relationship between Viking invasions and MS dissemination throughout the world may be considered for the municipalities of Caltanissetta, Enna and Monreale whose population experienced an extended period of Viking domination. The high prevalence rates observed in other Sicilian communities characterized by different historical and genetic backgrounds [2, 11] are, however, not consistent with this theory.

Table 3. Age- and sex-specific average annual incidence rates of MS in Caltanissetta (January 1, 1993 to December 31, 2002)

Age years	Men				Women				Both sexes			
	cases	person-years	incidence (per 100,000)	95% CI	cases	person-years	incidence (per 100,000)	95% CI	cases	person-years	incidence (per 100,000)	95% CI
0-24	5	91,180	5.5	2.2-8.8	6	89,590	6.7	4.1-9.3	11	180,770	6.1	4.1-8.1
25-44	11	84,440	13.0	7.9-18.10	25	91,120	27.4	22.1-32.7	36	175,560	20.5	16.8-24.2
45-64	3	67,980	4.4	1.4-7.4	6	76,870	7.8	5.0-10.6	9	144,850	6.2	4.1-8.3
≥ 65	0	44,550	-	-	0	63,460	-	-	0	108,010	-	-
Total	19	288,150	6.6	4.0-10.3	37	321,040	11.5	8.1-15.9	56	609,190	9.2	6.9-11.9

Person-year counts were obtained by multiplying the corresponding population figures as of the prevalence day (December 31, 2002) by 10. CI = Confidence interval.

Table 4. Comparison of prevalence rates between previous and follow-up surveys performed in Sicily

Municipality	Study year	Prevalence at first survey	Year of follow-up	Prevalence recalculated at follow-up survey (OAPR)	Prevalence at follow-up survey
Monreale	1981	43.3 (31.3-55.3)	1991	47.2 (35.2-59.2)	72.4 (43.6-113.1)
			2000	72.4 (43.6-113.1)	71.2 (60.2-82.2)
Enna	1975	53.2 (41.8-64.6)	1995	67.4 (56.0-78.8)	120.2 (83.8-63.2)
Catania	1995	58.5 (50.7-67.5)	1999	62.1 (59.8-65.4)	92.0 (81.8-103.2)
Caltanissetta	1981	51.1 (43.4-58.8)	2002	69.2 (61.5-76.9)	165.8 (158.5-173.1)

Figures in parentheses indicate confidence intervals. OAPR = Onset-adjusted prevalence rate defined according to Poser's definition.

Moreover, even in Sicily, the rates registered in Caltanissetta and Enna represent a unique occurrence. Both towns are located in the relatively isolated inner Sicily and have a stable population with a minimal immigration for many centuries, a setting where genetic influences may have been greater. These conditions and contingencies may, in fact, have permitted a higher rate of inbreeding and consequently a more homogeneous genetic background in the inner island. A similar phenomenon had already been described in Sardinia where clusters of particularly high prevalence and incidence rates have been reported [12]. The case for MS parallels that of other complex diseases with known immunopathogenesis and definite genetic component like type I diabetes [13]. In Italy, a south-to-north increasing gradient for young-onset diabetes had been previously described [14], but unexpectedly, a high frequency of type I diabetes has recently been reported in Sicily [15]. In these semi-isolated populations,

recent environmental events may have interacted with a particular genetic background, modifying the risk for autoimmune diseases. This effect is more evident in genetically homogeneous populations with a higher probability of intracommunity inbreeding, like those located in inner Sicily and Sardinia. By contrast in coastal communities the more frequent interactions with other populations may have, over the centuries, buffered the effects of genetic influences. The evolution of MS epidemiology in central Sicily should be closely monitored in the coming years.

References

- 1 Grimaldi LMF, Salemi G, Grimaldi G, Rizzo A, Marziolo R, Lo Presti C, Maimone D, Savettieri G: High incidence and increasing prevalence of MS in Enna (Sicily), southern Italy 2001. *Neurology* 2001;57:189.
- 2 Nicoletti A, Patti F, Lo Fermo S, Corbello V, Reggio E, Maimone D, Zappia M, Reggio A: Possible increasing risk of multiple sclerosis in Catania, Sicily. *Neurology* 2005;65:1259–1263.
- 3 Pugliatti M, Riise T, Sotgiu A, Sotgiu S, Satta WM, Mannu L, Sanna G, Rosati G: Increasing incidence of multiple sclerosis in the province of Sassari, northern Sardinia. *Neuroepidemiology* 2005;25:129–134.
- 4 Granieri E, Casetta I, Govoni V, Tola MR, Marchi D, Murgia SB, Ticca A, Pugliatti M, Murgia B, Rosati G: The increasing incidence and prevalence of MS in a Sardinian province. *Neurology* 2000;55:842–848.
- 5 Savettieri G, Elian M, Giordano D, Grimaldi G, Ventura A, Dean G: A further study on the prevalence of multiple sclerosis in Sicily: Caltanissetta city. *Acta Neurol Scand* 1986;73:71–75.
- 6 Poser CM, Bendikz J, Hibberd PI: The epidemiology of multiple sclerosis: the Iceland model onset adjusted prevalence rate and other methodological considerations. *J Neurol Sci* 1992;111:143–152.
- 7 Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW: New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983;13:227–231.
- 8 Savettieri G, Salemi G, Ragonese P, Aridon P, Scola G, Randisi G: Prevalence and incidence of multiple sclerosis in Monreale city, Italy. *J Neurol* 1998;245:40–43.
- 9 Ragonese P, Salemi G, D'Amelio M, Gammino M, Aridon P, Savettieri G: Multiple sclerosis in southern Europe: Monreale City, Italy – A twenty-year follow-up incidence and prevalence study. *Neuroepidemiology* 2004;23:306–309.
- 10 Poser CM: The dissemination of multiple sclerosis: a Viking saga? A historical essay. *Ann Neurol* 1994;36(suppl 2):S231–243.
- 11 Salemi G, Ragonese P, Aridon P, Scola G, Saporito V, Conte S, Savettieri G: Incidence of multiple sclerosis in Bagheria City, Sicily, Italy. *Neurol Sci* 2000;21:361–365.
- 12 Pugliatti M, Sotgiu S, Rosati G: The world-wide prevalence of multiple sclerosis. *Clin Neurol Neurosurg* 2002;104:182–191.
- 13 Sotgiu S, Pugliatti M, Sanna A, Sotgiu A, Pastiglia P, Solinas G, Dolei A, Serra C, Sonetti B, Rosati G: Multiple sclerosis complexity in selected populations: the challenge of Sardinia, insular Italy. *Eur J Neurol* 2002;9:329–341.
- 14 Carle F, Gesuita R, Bruno G, Coppa GV, Falorni A, Lorini R, Martinucci ME, Bozzelli P, Prisco F, Sondini MT, Cherubini V, RIDI Study Group: Diabetes incidence in 0- to 14-year age group in Italy: a 10-year prospective study. *Diabetes Care* 2004 27:2790–2796.
- 15 Arpi ML, Fichera G, Mancuso M, Lucenti C, Italia S, Tomaselli L, Motta RM, Mazza A, Vigneri R, Purrello F, Squatrito S: A ten-year (1989–1998) perspective study of the incidence of Type 1 diabetes in the district of Catania (Sicily) in a 0–14 year age group. *J Endocrinol Invest* 2002;25:414–419.