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# NEUROLOGY

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*Neurology* 2001;57;1891-1893

**This information is current as of October 3, 2007**

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AMERICAN ACADEMY OF  
NEUROLOGY

# High incidence and increasing prevalence of MS in Enna (Sicily), southern Italy

**Article abstract**—Twenty years after a first survey, a follow-up study was performed on the prevalence of MS in Enna (Sicily), southern Italy. The prevalence of definite MS rose from 53 to 120.2 per 100,000 population. The incidence of definite MS for the period 1986 to 1995 was 5.7 per 100,000 per year. The innermost part of Sicily shows an elevated prevalence of MS, second only to Sardinia in the Mediterranean area.

NEUROLOGY 2001;57:1891–1893

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Epidemiologic studies performed in the past decades indicate that the latitude-related model proposed to interpret the distribution of MS<sup>1</sup> does not apply to many regions of the Mediterranean area. Sicily and Sardinia, the two major Mediterranean islands, show an elevated frequency of MS and a recent increase in disease frequency.<sup>2–8</sup> The prevalence of MS in rural areas of Sardinia reaches the rate of 151.9 per 100,000 population.<sup>2</sup> The highest prevalence reported in Sicily so far has been in the town of Monreale (72.4 per 100,000 population).<sup>7</sup> The most recent incidence rates range from 3.3 (Sicily) to 4.2 (Sardinia).<sup>2,7</sup>

The first survey demonstrating an unexpectedly high prevalence of MS in Sicily was performed in Enna 25 years ago.<sup>3</sup> To confirm the rise of MS prevalence in the Mediterranean area we assessed the prevalence and incidence of MS in a follow-up study based on the town of Enna.

**Materials and methods.** *Area of investigation.* The city of Enna is located in central Sicily, at the top of a mountain (mean altitude, 931 m above the sea). The population, on prevalence day December 31, 1995, was 28,273 inhabitants. The population on December 31, 1975 (i.e., prevalence day of the previous study) was 28,189 inhabitants, indicating a substantial stability of this community. The size and the structure of the population did not change over 20 years. We asked the Regional Epidemiologic Office for particular events occurring in Enna during the past 25 years (epidemics, changes in daily living, migrational flows, diet).

The national health care system was established in this area in 1946. The level of public medical care is relatively high: Enna hosts a general hospital with a neurology unit; other neurologic outpatient services and rehabilitation facilities are available in the area.

*Case collection and ascertainment.* We employed various strategies to identify people suspected of having MS in the town of Enna. The prevalence survey performed in 1975 constituted the basis for the present survey. We made a formal diagnostic reappraisal of all living patients considered in the original study. Personal contacts were undertaken with all general practitioners and neurologists practicing in Enna. The population was also informed through local TV. The local chapter of the Italian MS Association was involved in the study and contributed to the identification of patients. Archives of the Neurologic Unit of the Enna Hospital, of all major MS centers of Italy, and of all centers of rehabilitation located in Enna were searched. Patients were classified according to the criteria of Poser et al.<sup>9</sup>

*Data analysis.* To calculate prevalence ratios, we searched for patients with MS who were living and resident in the study area on December 31, 1995. Crude as well as age- and sex-specific prevalence ratios were calculated. Clinical features were also recorded.

Crude as well as age- and sex-specific incidence ratios were computed for the period January 1, 1986 to December 31, 1995.

**Results.** On December 31, 1995, 34 patients with clinically definite MS (15 men, 19 women) were resident in the study area. Five of them were the survivors of the 15 subjects with definite MS identified during the 1975 survey. In four subjects, MS began before January 1, 1975, but at that time they were not found and, as a consequence, not included in the previous study.

The mean age at onset was 24.3 years (range, 9 to 41 years), 25.3 years for men and 23.5 years for women. The mean age on prevalence day was 37.6 years (range, 19 to 67 years), 38.1 years for men and 35.4 years for women. The mean interval between onset of the disease and diagnosis was 4.2 years (range, 1 to 15 years); it was higher in men (5.7 years) than in women (3.0 years). The average duration of MS from onset to prevalence day was 12.7 years (range, 1 to 32 years), 13.0 years for men and 12.4 years for women.

The overall prevalence was 120.2 per 100,000 population (95% CI, 83.8 to 167.2), 110.5 for men and 129.2 for women. Age-specific prevalence was higher between 25 and 54 years and decreased thereafter (table 1).

Twenty-three patients have a relapsing-remitting course of disease; 10 patients were affected by a secondary progressive form, and one patient had a primary disease progressive course.

Onset-adjusted prevalence calculated for the 1975 study

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Received April 16, 2001. Accepted in final form August 7, 2001.

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**Table 1** Age- and sex-specific prevalence of MS in Enna as of December 31, 1995

Age, y	Men			Women			Both sexes		
	Cases, n	Population	Prevalence (per 100,000)	Cases, n	Population	Prevalence (per 100,000)	Cases, n	Population	Prevalence (per 100,000)
0-14	0	2,757	—	0	2,604	—	0	5,361	—
15-24	2	2,230	89.7	3	2,202	136.2	5	4,432	112.8
25-34	5	1,985	251.9	6	2,149	279.2	11	4,134	266.1
35-44	3	1,947	154.1	5	2,103	237.8	8	4,050	197.5
45-54	3	1,558	192.5	5	1,741	287.2	8	3,299	242.5
55-64	1	1,412	70.8	0	1,722	—	1	3,134	31.9
65-74	1	1,013	98.8	0	1,264	—	1	2,277	43.9
75+	0	667	—	0	919	—	0	1,586	—
Total	15	13,569	110.5	19	14,704	129.2	34	28,273	120.2

was 67.4 per 100,000 population. Table 2 shows the age-specific, onset-adjusted prevalence on January 1, 1975.

Between January 1, 1986 and December 31, 1995, 16 subjects (seven men and nine women) living in the study area had their first symptoms of MS. The average annual incidence was 5.7 per 100,000 population (95% CI, 2.0 to 10.5), 5.1 for men and 6.1 for women. Sex- and age-specific incidence ratios of MS in Enna are shown in table 3. The highest ratio was observed in the age group 15 to 24 years.

The mean period between the onset and the diagnosis of the disease among incident patients was 3.0 years; it was higher in women (4.0 years) than in men (1.7 years). No HLA characterization of the population of Enna is avail-

able at present. No epidemics, changes of daily living, or variation of migrational flows or diet have been recorded.

**Discussion.** We found a prevalence of 120.2 per 100,000 and an incidence ratio of 5.7 per 100,000 population in Enna City. These are among the highest ratios found in the Mediterranean area (second only to Sardinia and at the level of northern European countries) and confirm the high frequency of MS in Sicily. Nonetheless, we might have even underestimated the ratios of MS in this area: assuming the common male:female ratio of about 1:2, the expected number of women with MS should have been higher than the observed. This discrepancy could be related to a selective underreporting.

As in Sardinia<sup>2</sup> and in Monreale,<sup>7</sup> the city of Enna shows an increase in MS prevalence. It is unknown whether this increase depends on a true change in MS frequency, related to environmental or socioeconomic changes, or reflects an improved case ascertainment depending on greater awareness and on new and more sophisticated diagnostic procedures. Incidence remained stable along the incidence period studied (1986 to 1995). Although the interval between the onset and the diagnosis of MS was 3.9

**Table 2** Age-specific, onset-adjusted prevalence of MS in Enna at January 1, 1975

Age, y	Cases, n	Population	Prevalence (per 100,000)
0-14	0	7,403	—
15-34	12	8,266	145.2
35-54	5	6,630	75.4
55-74	2	4,869	41.1
75+	0	1,021	—
Total	19	28,189	67.4

**Table 3** Age- and sex-specific average annual incidence rates of MS in Enna (January 1, 1986-December 31, 1995)

Age, y	Men			Women			Both sexes		
	Cases, n	Person-years*	Incidence (100,000)	Cases, n	Person-years*	Incidence (100,000)	Cases, n	Person-years*	Incidence (100,000)
0-14	0	27,570	—	1	26,040	3.8	1	53,610	1.9
15-24	4	22,300	17.9	5	22,020	22.7	9	44,320	20.3
25-34	3	19,850	15.1	2	21,490	9.3	5	41,340	12.1
35-44	0	19,470	—	1	21,030	4.7	1	40,500	2.5
45+	0	46,500	—	0	56,460	—	0	102,960	—
Total	7	135,690	5.1	9	147,040	6.1	16	282,730	5.7

\* Person-year counts were obtained by multiplying the corresponding population figures as of the prevalence day (December 31, 1995) by 10.

years in the period 1986 to 1990 and 2.1 years in the period 1991 to 1995 (indicating an improvement in diagnostic efficiency), the twofold increase in prevalence observed over 20 years strongly suggests a real increase in the disease frequency. Unfortunately, the lack of previous data on the incidence of MS in Enna or the changes in lag time between the onset and the diagnosis, precludes comparison with the previous study.

The incidence found in Enna, together with that reported in two other Sicilian cities (Monreale<sup>7</sup> and Bagheria<sup>8</sup>), is comparable to that reported either in Sardinia<sup>2</sup> or in Northern European countries; this further supports the high frequency of MS in this Mediterranean island. The Regional Epidemiologic Office has not detected particular events occurring in Enna during the past 20 years. Genetic predisposition might, indeed, play a role in the recorded elevated frequency of MS. Because Enna was one of the major centers of the Viking domination in Sicily, our data support Poser's<sup>10</sup> hypothesis on the contribution of Viking migrations to the dissemination of MS.

#### Acknowledgment

The authors thank the local branch of the Italian MS Association, and especially its former president, Dr. Angelo Campanile. They also thank all the people, practitioners, and institutions that helped them during this study.

#### References

1. Kurtzke JF. Epidemiology of multiple sclerosis. In: Vinken PJ, Bruyn GW, Klawans HL, eds. Handbook of clinical neurology. Amsterdam: Elsevier, 1985:259–287.
2. Granieri E, Casetta I, Govoni V, et al. The increasing incidence and prevalence of MS in a Sardinian province. *Neurology* 2000;55:842–848.
3. Dean G, Grimaldi G, Kelly R, Karhausen L. Multiple sclerosis in southern Europe: I: prevalence in Sicily in 1975. *J Epidemiol Community Health* 1979;33:107–110.
4. Dean G, Savettieri G, Giordano D, et al. The prevalence of multiple sclerosis in Sicily: II: Agrigento city. *J Epidemiol Community Health* 1981;35:118–122.
5. Savettieri G, Daricello B, Giordano D, Karhausen L, Dean G. The prevalence of multiple sclerosis in Sicily: I: Monreale city. *J Epidemiol Community Health* 1981;35:114–117.
6. Savettieri G, Elia 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.
7. 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.
8. Salemi G, Ragonese P, Aridon P, et al. Incidence of multiple sclerosis in Bagheria City, Sicily, Italy. *Neurol Sci* 2000;21:361–365.
9. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983;13:227–231.
10. Poser CM. The dissemination of multiple sclerosis: a Viking saga? A historical essay. *Ann Neurol* 1994;36(suppl 2):S231–S243.

## Polymorphisms in the vicinity of the hypocretin/orexin are not associated with human narcolepsy

**Article abstract**—Human narcolepsy/cataplexy is associated with reduced hypocretin (orexin) transmission. A common preprohypocretin (HCRT) polymorphism (–909C/T) was identified and tested in 502 subjects (105 trio families, 80 Caucasian narcolepsy cases, and 107 Caucasian control subjects). This polymorphism was not associated with the disease. The promoter and 5' untranslated (5'UTR) regions of the HCRT gene (–320 to +21 from ATG) were also sequenced in 281 subjects. None of the subjects carried –22T, a rare 5'UTR polymorphism previously reported to be associated with narcolepsy. The HCRT locus is not a major narcolepsy susceptibility locus.

NEUROLOGY 2001;57:1893–1895

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Narcolepsy is characterized by excessive daytime sleepiness, cataplexy (a pathognomonic symptom), hypnagogic hallucinations, and sleep paralysis. Narcolepsy/cataplexy affects 1/2,000 and usually begins during adolescence.<sup>4</sup> The disorder is tightly associated with HLA, suggesting an autoimmune mediation.<sup>5</sup>

Most human cases have no family history, and monozygotic twins are frequently discordant, suggesting complex genetic inheritance and environmental effects.<sup>4</sup>

Recent studies have demonstrated a major role for hypocretins in the pathophysiology of narcolepsy.<sup>2</sup> A genetically determined canine model is associated with hypocretin receptor-2 mutations.<sup>3</sup> In humans, hypocretin-1 is undetectable in the CSF of most cases.<sup>2</sup> Most strikingly, recent neuropathologic studies indicate an almost complete loss of hypocretin (HCRT) mRNA and peptides in human narcoleptic brains.<sup>6</sup>

In humans, hypocretin abnormalities are rarely due to HCRT gene alterations.<sup>6</sup> An extensive mutation screening study in 74 selected cases identified a single mutation in the signal sequence of the HCRT

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Supported by NIH (NS23724, NS33797, and HL59601) (E.M.) and Deutsche Forschungsgemeinschaft (DFG-HU 827/2-1) (M.H.).

Received May 1, 2001. Accepted in final form August 1, 2001.

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