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Epilepsy and Multiple Sclerosis in Sicily: A Population-based Study

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Summary: *Purpose:* To evaluate the association between epilepsy and multiple sclerosis (MS), we analyzed the incidence of epilepsy in a population-based incidence cohort of MS in Catania, Sicily.

Methods: According to Poser's diagnostic criteria, 170 incident cases of MS have been identified from 1975 to 1994 in the city of Catania. All these subjects underwent a complete neurological examination to confirm the diagnosis of MS and to identify those patients with a history of seizures. Diagnosis of epilepsy was based on the criteria proposed by the International League Against Epilepsy (ILAE) in 1993, and seizures were classified according to the classification of the ILAE, 1981.

Results: From 1975 to 1994, 170 subjects with MS had the clinical onset of the disease. The mean annual incidence of MS was 2.3/100,000 (95% CI, 2.0–2.6). Of the 170 defined MS patients, four developed epilepsy after the onset and also diagnosis of MS, giving an incidence rate of epilepsy of 285/100,000 person years at risk (95% CI, 119–684) and 147.8/100,000 when age adjusted to the world standard population. The cumulative risk of developing epilepsy after the onset of MS, evaluated by using the life-table methods, was zero at 1 year and 1.76% at 5 years. Of these four patients, three were classified as having partial seizures with secondary generalization and one with tonic–clonic seizures.

Conclusions: Our data are consistent with those reported in literature suggesting that the risk of developing epilepsy is threefold higher among MS patients than in the general population.
Key Words: Epilepsy—Multiple sclerosis—Epidemiology.

The prevalence of epilepsy in industrialized countries ranges from 3 to 9 per 1,000, whereas age-adjusted incidence ranges from 28.9 to 53.1 per 100,000 (1). Multiple sclerosis (MS) is a chronic neurologic disease with a wide spectrum of symptoms and signs. According to previous reports, the prevalence of seizures in MS patients seems substantially higher than that in the general population. In most publications, the prevalence of epilepsy varies from 1 to 4%, but figures $\leq$10% have been presented (2). Unfortunately these data may not be accurate because they are based on series of clinical patients, and the majority of published studies do not mention the diagnostic criteria used to classify the patients. A prevalence of 3.5% was reported in a survey carried out in Finland in which the authors studied a prevalent cohort of MS patients.

To our knowledge, the only data available concerning the risk of epilepsy among MS patients are those reported by Olafsson et al. in 1999 (3). The authors studied a population-based incidence cohort of MS patients, reporting a threefold increase in risk for developing epilepsy compared with the general population.

In an attempt to add further evidence of a causal relation between MS and epilepsy, we evaluated the risk of epilepsy in a population-based incidence cohort of MS identified in the city of Catania from 1975 to 1994.

MATERIALS AND METHODS

At the end of the 1990s, we carried out an epidemiologic survey to determine prevalence and incidence of MS in the city of Catania (4). Catania is the capital of the province in the eastern Sicily that covers some 181 km^2 at a mean altitude of $\sim$30 m above sea level. Its official population in 1991, the date of the last census, is 333,075 inhabitants with 174,267 women and 158,808 men (5). Considering the overall study period, according to census data, the population decreased from 400,048 in 1971 to 382,692 in 1981 and 333,075 in 1991, remaining stable from 1991 to 1995 (337,332 inhabitants). During the study period, 1975–1994, no significant changes were seen in sex and age structure of the population. In particular during the study period, an internal migration flow from the city of Catania to the surrounding areas was found, but

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always in the province of Catania. The province of Catania covers 3,552 km^2 and, although the whole population of the province was stable over the period, ~1,000,000 inhabitants, considering only the surrounding areas, <15 km from the city, there was an increase from 84,200 inhabitants in 1971 to 146,882 in 1981 and to 185,140 in 1991.

Immigration flow from other countries was low and stable over the period and in particular in the last census of 1991, there were only 4,036 foreign residents, 1.2% of the population, the most coming from Africa and Europe. On the basis of these data, the population could be considered ethnically stable in the city.

The primary sources for the MS case ascertainment were the neurologic and motor-rehabilitation departments, the Multiple Sclerosis Center, the Italian Multiple Sclerosis Association, private neurologists, and family doctors. All surviving potential MS patients identified from these sources, except the MS patients followed up in our neurological department and MS center, were called to undergo neurologic examination performed by trained neurologists of our team to confirm the diagnosis. For deceased patients or in case of cognitive impairment, information was collected by trained physicians from close relatives (4).

We considered as prevalent and incident cases all patients who satisfied the Poser's criteria for clinically definite multiple sclerosis (CDMS), laboratory-supported definite multiple sclerosis (LSDMS), clinically probable multiple sclerosis (CPMS), and laboratory-supported probable multiple sclerosis (LSPMS) (6).

We calculated the prevalence rate of MS as point prevalence at January 1, 1995, and incidence during 1975–1994, considering all patients who had the onset of disease during this study period. All patients were followed up at least at 5 years after the onset of disease.

We also determined prevalence and incidence of epilepsy in our cohort of MS patients identified during the study period. All patients with a suspected history of seizures underwent an extensive evaluation performed by an expert epileptologist and also a standard electroencephalographic (EEG) recording by using 20-channel equipment. For deceased patients or in case of cognitive impairment, information about seizures was collected by trained physicians from close relatives; when possible also clinical papers were revised. We accepted the definition of epilepsy proposed by ILAE 1993: "Epilepsy is a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause. Multiple seizures occurring in a 24-h period are considered a single event" (7). Seizures at the time of an MS exacerbation were considered acute symptomatic seizures and then excluded from the analysis. Seizure types were identified on the basis of the classification proposed by ILAE 1981 (8).

The prevalence of epilepsy was determined as a point prevalence defined as the proportion of patients with epilepsy in the MS population at a specified time [prevalence day (P.D.), January 1, 1995]. We compared the prevalence of epilepsy among the MS patients with the prevalence of epilepsy found in Sicily in a door-to-door survey carried out in 1987 (9). To allow comparison, both crude rates were age adjusted to the World Standard population, using the direct method of standardization (10).

Cumulative risk of epilepsy at 1 and 5 years was obtained by using the life-table methods. We evaluated the incidence rate of epilepsy, estimating the total person time at risk; 95% confidence interval (CI) of rates also was calculated.

Few population-based studies have been carried out in Italy to determine the incidence of epilepsy. To compare the incidence of epilepsy among the MS population with that in the general population, we used the population-based study carried out in Copparo by Granieri et al., published in 1983 (11), in which the authors used similar diagnostic criteria for epilepsy (Hauser and Kurland, 1975) (12). To allow comparison, both rates were age adjusted to the World Standard population, by using the direct method of standardization. Analysis was carried out by using the EPI-INFO 6 (13).

RESULTS

We detected 195 patients with MS who had had the onset of disease on prevalent day, at January 1, 1995 (PD), in a population of 333,075 inhabitants. The prevalence of MS (onset-adjusted prevalence rate) in the city of Catania was 58.5/100,000 (95% CI, 50.7–67.5). The age-specific prevalence showed a peak in the group aged 35–44 years (145.1/100,000). From 1975 to 1994, 170 subjects with MS had the clinical onset of the disease. The mean annual incidence was 2.3/100,000 (95% CI, 2.0–2.6). Age-specific incidence shows a peak in the group aged 25–34 years (6.32/100,000) (4).

Totally we identified five patients (four men and one woman) who had a diagnosis of epilepsy fulfilling the ILAE diagnostic criteria. In one patient (number 1 in Table 1) with partial seizures with secondary generalization, the onset and diagnosis of epilepsy was before the onset of MS, but this patient had also other predisposing

TABLE 1. *Clinical features of defined epileptic patients identified among the incidence cohort of MS patients*

Patient	Age at onset of MS (yr)	Age at diagnosis of MS (yr)	Age at onset of epilepsy (yr)	Type of seizure
1	19	21	11	PSSG
2	18	32	34	PSSG
3	40	41	44	TC
4	27	27	30	PSSG
5	31	33	33	PSSG

PSSG, partial seizures with secondary generalization; TC, tonic–clonic seizures.

factors for epilepsy (dystocic delivery and perinatal asphyxia). For the other four patients, the onset of epilepsy was subsequent to the onset and also diagnosis of MS. Concerning the type of seizures, three of them had partial seizures with secondary generalization, and one case was classified as tonic–clonic seizures (Table 1). None of these patients had other known risk factors for epilepsy other than MS. No patients had single unprovoked seizures. All patients were classified with active epilepsy according to the definition of ILAE 1993 (7) and were treated with antiepileptic drugs (AEDs).

To estimate the point prevalence of epilepsy among the MS patients (195 prevalent cases at the PD), we excluded two patients who had the onset of MS during the incidence study period (1975–1994), but died before the PD. The crude prevalence of defined epilepsy, at January 1, 1995, among the MS patients, was 15,4/1,000 (95% CI, 3.9–41.2) when we included also the patient who had the onset of epilepsy before the onset of MS, and 10.2/1,000 (95%CI, 1.7–33.5) when this patient was excluded from the analysis. To compare the prevalence of epilepsy found in our cohort of MS patients with the prevalence found in a previous survey carried out in Sicily (3.3/1.000) (9), we age adjusted both rates to the World Standard population by using the direct method of standardization. The age-adjusted prevalence of epilepsy in Sicily was (3.7/1.000), whereas the age-adjusted prevalence rate among the MS population was 7.7/1,000, when the case that had the onset of epilepsy before the onset of MS was included, and 5.1/1.000 when this case was excluded from the analysis.

To evaluate the incidence of epilepsy, we considered only the 170 MS incident cases identified who had the onset on MS during 1975–1994. All five epilepsy patients identified were incident cases of MS. To estimate the risk of epilepsy after the onset of MS, the patient who had the onset of seizures before the onset of MS was excluded from this analysis, whereas we included the other four cases for whom the diagnosis of epilepsy was subsequent to the onset and also diagnosis of MS. Regarding the time from the onset of MS to the first seizure, these patients developed seizures 2, 3, 4, and 16 years after the first manifestation of MS. The cumulative risk for developing epilepsy in this cohort of MS patients was zero at 1 year and 1.76% (95% CI, 0–4.72%) at 5 years.

To calculate the incidence rate over the 20-year follow-up, we estimated the total person-years at risk from the clinical onset of MS. The total person-time at risk was 1,402.45 years, and the incidence rate over the 20-year period was 285 per 100,000 person-year at risk (95% CI, 119–684). Age-specific incidence rate is shown in Table 2. Age-adjusted incidence risk directly standardized to the World Standard population was 147.8/100,000. The crude incidence risk of epilepsy found in Copparo in 1983 was 33.1 per 100,000 per year (11). To allow comparison, we age-adjusted the incidence risk found in Copparo to the same World Standard population, obtaining an age-adjusted incidence risk of 44.7 per 100,000; the relative risk was 3.29 (95% CI, 2.36–4.59).

TABLE 2. *Age-specific incidence rate of epilepsy in the incidence cohort of MS patients*

Age at onset (MS) (yr)	Number of cases (epilepsy)	Total person-years at risk	Rate per 1,000 person-year
0–14	—	66.61	—
15–24	—	535.19	—
25–34	3	486.07	6.17
35–44	1	194.11	5.15
45–54	—	102.08	—
55+	—	18.39	—
Total	4	1,402.45	2.85

On the basis of these data, we can conclude that the risk of epilepsy after the onset of MS is threefold higher when compared with the risk in the general population.

DISCUSSION

Several articles concerning the relation between epilepsy and MS have suggested an increased risk of epilepsy among MS patients. Unfortunately the majority of these data come from clinical series and are consequently prone to selection bias (14). Often studies do not use a standard definition of epilepsy, do not take into account the distinction between epilepsy starting before and after the onset of MS, or the occurrence of symptomatic or single seizure. For all these reasons, interpretation and comparison of results is often difficult.

Epilepsy is a common condition, and coincidental association can occur, so a causative link is difficult to establish, even if magnetic resonance imaging studies have suggested the possible correlation between seizures and the presence of corticosubcortical MS lesions (15). Our data on the prevalence and incidence of epilepsy among the MS patients come from a well-defined cohort of MS patients and are based on well-defined diagnostic criteria for both disorders. For these reasons, an appropriate comparison is possible only with other population-based surveys with similar design and diagnostic criteria adopted.

The crude prevalence of epilepsy (15.4/1,000) found in our cohort of MS patients is lower than the crude rate reported in the prevalence cohort of MS patients in Finland (35/1,000), but it is close to the rate for active epilepsy (20/1,000) reported in the same survey (2). Nevertheless, both crude and age-adjusted prevalence rates are significantly higher when compared with the crude and age-adjusted prevalence rate of epilepsy found in the Sicilian population (9).

It is important to underline that several factors (age and sex distribution of our MS prevalent population, life expectancy, and disease duration, etc.) should affect the comparison of these prevalence data, and they should be

taken into consideration in interpreting these results. We are also aware that the prevalence of epilepsy found in the Sicilian population (3.3/1,000), which we used for comparison, is lower than rates reported from other Italian surveys; in any case, the prevalence rate found in our MS population is close to those reported from other MS cohorts (2) and is generally higher than crude rates reported from industrialized countries.

The incidence of epilepsy is significantly higher in our cohort of incidence cases of MS than in general population, confirming a threefold higher risk of epilepsy after the onset of MS, as reported also in Iceland (3), where a very similar study design and diagnostic criteria were adopted.

Even if several factors can affect our data (the small denominators of our MS cohort with a total follow-up time of 1,402 person-years at risk, the use of age-adjusted rates for comparison, the retrospective nature of the survey), our results are close to those reported from other population-based surveys.

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