

THE PREVALENCE OF MULTIPLE SCLEROSIS IN MURES COUNTY, CENTRAL ROMANIA

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INTRODUCTION AND OBJECTIVES

For over a century, since the early clinical and pathological descriptions of multiple sclerosis (MS), investigators have struggled to determine the etiology of this illness. For several decades now a variety of epidemiological studies have been conducted in order to provide clues to causation.

Descriptive epidemiological studies in MS are plagued by some key diagnostic issues. First of all, any successful investigation of the occurrence of a disease requires accuracy of diagnosis. MS remains a clinical diagnosis, with no simple laboratory investigation available that reliably certifies a case. The likelihood is greater that patients are underrecognized than overrecognized in most surveys. The availability of MRI techniques are already helping to improve the reliability of case ascertainment. Many investigators have examined the occurrence of MS in a variety of geographic locations. The prevalence refers to the number of cases present (alive) at any particular time (referred to as „prevalence day“) within a defined population.

To obtain reliable data of MS, we evaluated the prevalence of the disease in Mures county.

MATERIAL AND METHODS

We made an epidemiological study of prevalence of MS in Mureș county. Patients with MS were identified

from all the available sources. We gathered the number of defined MS mostly from general practitioners, hospital database MS Society and very few from nursing homes and MS society (figure 1).

The study was carried out over a 4 month period, from september 2006 to january 2007. The day of 1st. october 2006 was chosen as the prevalence day, when all the patients began to be checked to confirm that were still alive and living in the area. The onset of MS was determined by interviewing patients and reviewing their medical records. In parallel was interviewed directly or by phone every general practitioner from Mures county, a total of 387 general practitioners.

We took into account only patients with definite MS according to McDonald criteria. All the MS patients diagnosed by Poser criteria have been revised by McDonald criteria.

Cerebral and spinal magnetic resonance imaging (MRI) was performed in 112 patients (13.7%) and all the examinations were positive for definite MS. We also excluded patients with clinically isolated syndromes.

Distribution of the disease course consisted of the three categories: relapsing remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS).

The following age classification was chosen for age-specific prevalence rates: ≤ 20; 21-30; 31-40; 41-50; 51-60; 61 ≤.

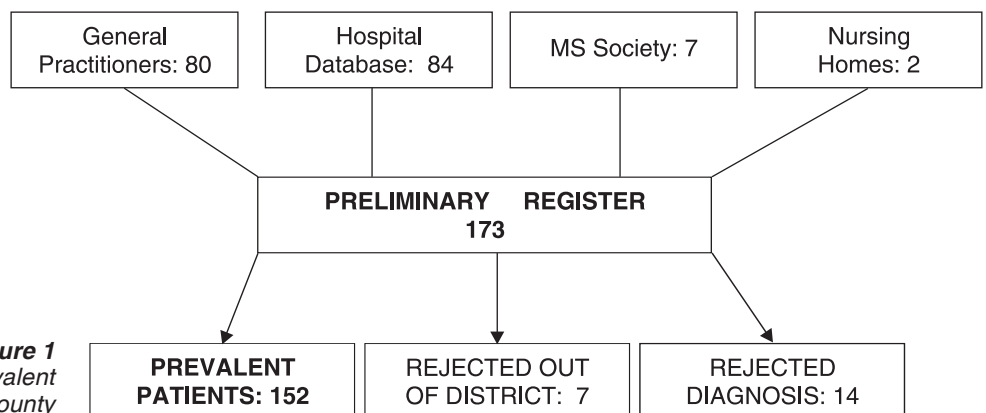


Figure 1
Sources available for prevalent MS patients from Mures county

The disability was measured with Kurtzke Expanded Disability Status Scale (EDSS) and patients were divided into mild disability (EDSS 0-3.5), moderately disabled (4-6.5) and severe affected (7-9.5).

The demographic data and the informations regarding Mures county population, were obtained from the National Institute of Statistics.

Data regarding the weather conditions in Mures county were from the National Institute of Meteorology.

Mures county is located in the center of Romania, between latitudes 46°09'-47°00'N, longitude 23°55'-25°14'E and covers an area of 6714 m² (figure 2).

It has 6 towns and has wide availability of health care services and easy access to hospitals. At 1st. july 2006, the total population was 583,383 inhabitants divided in 397,645 women and 285,738 men. The number of inhabitants per square kilometre is 88,1. The ethnical distribution of the population was: 53.3% romanians, 39.3% hungarians, 7% gypsies, 0.4 % others. Since the majority of MS epidemiological studies found a low prevalence among the gipsy population, we divided the population of our county in: caucasians (93%) and gypsies (7%).

Migration is very rare in or out of Mures county, so this phenomenon was left out, being without importance in our region. 31% of the county surface is afforested. A percentage of 67% of the population resides in rural area.

The weather in the region is specific for temperate zone with mean daily temperature of 8.9°C (16.9°C in winter to 32.7°C in summer), the mean annual rainfall is approximately 625 mm.

RESULTS

A total of 152 MS patients resided in Mures county in 1st. october 2006. Fifty two patients (34.2%) were



Figure 2
Mures county (dark map)

identified by more then one source so we classified them in the place where the patient was first registered as having MS (e.g.: regional hospital prior to general practitioner). Approximately equal number of patients were found in general practitioner's archives and in the medical records from 10 years interval of our hospital (figure 1).

The overall prevalence was 26.1/10⁵, 27.8/10⁵ in women and 24.8/10⁵ in men. Age and sex specific prevalence are reported in table 1.

Eightyone patients were women and seventy one were men (F/M ratio: 1.14:1). Mean age was 47.7 years (range from 17 to 74 years) without any significant difference between women (47.4) and men (47.9) (figure 3).

Mean age at onset of MS patients was 27.4 year (range from 16 to 55 years), without any significant difference between sexes (27.6 years in women and 27.3 years in men).

The overall mean duration of the disease was 11.5 year (3 months-46 years). In figure 4 are represented the mean duration of the disease. The following duration classification was chosen: 0-5 years; 5.1-10 years; 11-15 years; 15.1 + years.

From an MS patients, 3 (2%) were gipsy. The prevalence of MS in the gipsy population was 7.4/10⁵. This represents a prevalence 3 folds less than the prevalence found in the caucasian population of our county.

Two cases (1.3%) had a first degree relative with MS. The prevalence of „familial“ MS was 0.3/10⁵.

Table 1
Age and sex prevalence rate of MS in Mures county on prevalence day

	Total		Women	Men
Age (y)	No	Rate/10 ⁵	No	No
0-20	1	0.71	1	–
21-30	12	13.3	9	4
31-40	27	29.3	15	12
41-50	50	68.2	29	19
51-60	48	66.3	20	28
61 ≤	14	12.1	5	8

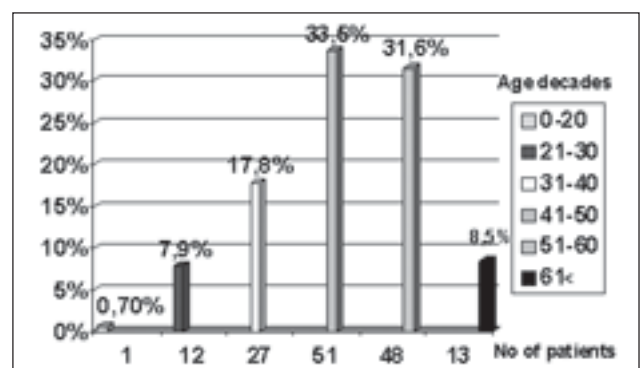


Figure 3
Repartition of MS patients regarding age decades

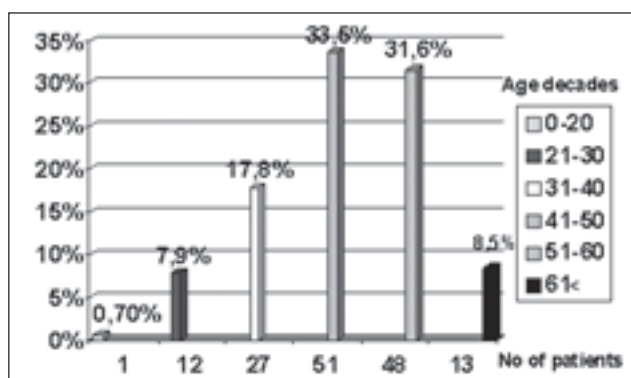


Figure 4

Number and percentage of MS patients in evolution interval

The clinical course of the disease was: RRMS in 65 patients (42.8%), SPMS in 58 (38.2%) and PPMS in 29 (19%).

Mean age at onset was 25.8 years in patients with RR course, 26.9 years in patients with SP course and 35.3 years in patients with PP course.

Symptoms at the onset of the disease were fully recalled and reported from 128 patients (84.2%). In 72 patient (56.3%) more than one symptom was reported.

The other 56 patient had a monosymptomatic onset: motor symptoms were present in 17 patient (30.3%); sensory in 16 (28.6%); optic neuritis in 13 (23.2%) and brainstem in 10 (17.9%).

Median EDSS disability score was 4.4 (range 0-9,5). In figure no 5 are the number and percentage of MS patients in EDSS value-interval: 0-3.5 (mild); 4-6.5 (moderately); 7< (severe disabled).

A number of 67 patients (44.1%) were mild, 38 (25%) were moderately and 47 (30.9%) severely disabled patients.

Regarding the treatment, approximately a half of MS patients, respective 68 (44.7%) did not take any medication, 56 (36.8%) were under symptomatic therapy, 24 patients (15.9%) were treated with immunomodulatory therapy and 4 patients (2.6%) were under Mitoxantrone treatment.

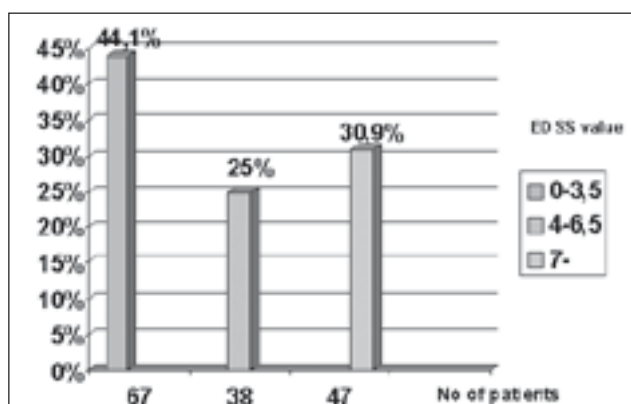


Figure 5

Number and percentage of MS patients in EDSS interval

DISCUSSION

Our prevalence ($26.1/10^5$) is comparable with the datas found by our colleagues Becus and Popoviciu in 1994. They made a study concerning the same region and they found a prevalence of $21/10^5$. Our data from 2006 indicates a slight increase in prevalence compared with that gathered in 1994, due to better case ascertainment, improved survival, more complex diagnostic methods, a trend toward increasing awareness of population and general practitioners regarding MS and better neurology services in the last years. In Bucuresti, Petrescu and Verdes (2) estimated a mean prevalence rate of $26/10^5$ for România, with a female: male ratio of 1.14. Prevalence of MS in Mures county is lower than in other european counties at comparable latitudes. Despite the data from systematic epidemiological studies on MS conducted over the past three decades, the reliable informations are incomplete in nearly two-thirds of european countries (3).

The attempt to redefine the geographical pattern of MS in Europe is a hard task because:

- the variability of the surveyed populations with respect to size, age structure, ethnicity;
- the capability to detect benign, early cases or clinically isolated syndromes;
- the different access to medical care, number of neurologists, availability of new diagnostic procedures, public awareness about MS (3).

Countries that surrounds Romania have a higher MS prevalence. The MS prevalence rates found in Hungary in the years between 1992 and 1996 ranged from 32 to $79/10^5$. Recent data obtained from Csongrad county showed a total prevalence of $62/10^5$ (4;5). The most recent prevalence data from Serbia were assessed for the region of Belgrade in 1996, showing a prevalence rate of 51 per 10^5 (6). In Bulgaria, most recent epidemiological assessments on MS showed a prevalence of $39/10^5$ (7). In Russia prevalence of MS was found between 31 in Ufa to $60/10^5$ in Novosibirsk and in Ukraine was $41/10^5$ (3;8). Other european countries or regions lying at the same latitude have much higher prevalence rates. For example the north of Italy has a prevalence rate that varies from $81/10^5$ in the province of Padova, $69/10^5$ in Ferrera to $53/10^5$ in district of L'Aquila (9-11).

In Switzerland, the prevalence rate was $110/10^5$ for the Canton of Berne in 1986 (12). MS prevalence in France is lower than in other european countries. A total mean prevalence rate of about $50/10^5$ was reported in 1986 (13). Confavreux et al reported (14) in 1992 a prevalence of $>100/10^5$ in France, as recorded in EDMUS data base. Valladolid is a region situated in the north part of Spain with a $58.3/10^5$

prevalence of MS (15). In Japan the rates of prevalence is $6\text{--}9/10^5$ (16).

To comment this low prevalence in Mures County comparing with other counties situated at the same latitude is a difficult task. The existence of a latitudinal gradient, with incidence and prevalence rates increasing as one moves further from the equator is evident, although there has been discussion of the responsibility of genetics for at least part of this trend. One must not forget that we included only patients with definite MS while the majority of epidemiological studies had a much larger MS population for analyze and prevalence rate estimation.

We must notice the very low rate of familial MS in this survey: $2(1.3/10^5)$, which differs from 4.5%, the rate found by Bernet- Bernady et al (17).

The low prevalence for gipsy population ($7.4/10^5$) was found also in hungarian gipsies ($4.5/10^5$). The number of gipsy MS patients was too low to conclude about the evolution of MS. The fact that in an ethnic group MS has a low prevalence does not imply that MS evolution is benign. For example, in France, north africans have a more severe disability than europeans with MS (34). Prevalence of MS in gipsies from Bulgaria was $18.4/10^5$ (35).

Epidemiologic data for MS in Olmsted county, Minnesota, have been recorded for almost 100 years and the prevalence of MS determined was $177/10^5$ in 2002. This county, situated at 44° latitude has a high prevalence partially because of demographic characteristics, the authors confirming the link between scandinavian ancestry (specific for Minnesota) and the risk of MS (18, 19).

Studies of frequency trends in sites around the world try to provide clues to the cause of MS. The geografic distribution pattern, together with data from migrant studies, indicate that environmental factors are of etiologic importance. There is a marked genetic susceptibility to MS, which is associated primarily with certain HLA class II antigens (20).

As the literature presents, the climate influences MS prevalence. For example, the scandinavian population from More and Romsdal county, Norway, which has a proved genetic predisposition towards MS, has also an exposure to a humid-temperate climate with a mean daily temperature of 6.3°C and a mean annual rainfall approximately 1355 mm. The prevalence for MS of this norwegian population is $75.4/10^5$ (20).

One of the highest prevalence rates that have been estimated for a large community in southern Europe is in Sardinia province, where the prevalence found was $151.9/10^5$. This finding strengthens the hypothesis of the environmental role and genetic

factors among Sardinians in determining the notable difference in MS frequency between Sardinians and other Mediterraneans (27).

The same very high prevalence ($101.4/10^5$) in MS was found in the Turkish population living in a district of Istanbul (28). In Germany, the prevalence rate reported was $127/10^5$ which is also high (29).

Even higher rates of nearly $200/10^5$ were found for Scotland offshore islands (Shetlands and Orkneys) but they were based on the small population (30). Clusters of MS, a so called epidemic MS was described most comprehensively by Kurtzke (cited by Comston and Confavreux 18). Prevalence fell in Feroe Islands from $309/10^5$ in 1974 to $240/10^5$ in 1983.

Further studies may help to map the prevalence of MS in Romania and might disclose future changes in prevalence. The wide range of the latency between onset of symptoms and diagnosis might have limited the inclusion of patients who were still undiagnosed on the prevalence day. The continuous monitoring of all the available sources thereafter helps to reduce this bias. It is a need to continuously neighbouring county hospitals as patients from Mures county might be followed by other medical services.

The essential conclusions to be drawn from the geography and prevalence of MS are:

- a north-south (as well as west-east in the United States) gradient exists independent from genetic/racial factors;
- major differences in prevalence occur in the absence of difference in latitude;
- individuals from the same ethnic derivation have either the similar prevalence or have very different prevalence rates in widely separated geographical areas;
- specific resistance isolates are shown to exist regardless of latitude.

Existing prevalence information leads to the almost inescapable conclusion that the geography of MS cannot be explained by any single known environmental or genetic factor in isolation. A combination of a heterogeneous distribution of both genetic and environmental factors appears to be required to explain the available data on MS and geography (21, 26).

Our women to men ratio of 1.14:1 confirmed the well known higher occurrence of the disease in women. Our colleagues, in 1994 found this ratio being higher regarding women 1.34 (1). The ratio in other studies varies from 1.9:1 to 3.6:1 (24, 25, 27). For example, in sardinian province, the women/man ratio is 2.2:1 (27).

Multiple sclerosis is more prevalent in the age group 41-50 and the mean age of our MS patients

was 47.7. These results corresponds to those found in same studies (17), our patients are older with one decade than those found in Italy by Giranieri et al. and are younger with one decade than those found by Rothwell in Great Britain (11,32).

The age at onset of MS was 27.4 years in Mures county, value found again in other studies (11, 25, 27, 33). Our patients are younger than those from France, where a mean age of 34.5 years was found (17).

Our population of MS patients has a long disease duration of 11.5 years and 36.8% of cases had MS for more than 15 years. This duration is longer than the mean duration of the disease of 9.4 years found in Italy (11). Regarding the clinical course, the majority of patients (42.8%) had a relapsing remitting evolution, 38.2% a secondary progressive and 19% a primary

progressive course. These data is different from those found in Italy (74.7% RRSM; 18.3% SPSM; 7% PPSM) or in France (73.4% RRSM; 65% SPSM; 20% PPSM) (11, 17). The predominance of motor signs followed by sensory, optic and brainstem syndrome at the onset can be found in other studies too (11,17,19).

The neurological disability for our MS patients was moderate, mean EDSS was 4.4. This value is concordant with that found in other european counties (11,15,17) and USA (36,37).

CONCLUSION

Mures County is a medium risk area for definite MS, but further genetic and environment studies are required.

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