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COMPREHENSIVE EPIDEMIOLOGY OF MULTIPLE SCLEROSIS IN EUROPE AND ARMENIA: HIDDEN PANDEMICS ?

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Abstract

Multiple sclerosis (MS) is a chronic demyelinating disease affecting the central nervous system, known since the 18th century. MS is both the most common non-traumatic neurological disease and cause of early disablement in young adults. By latest estimations, it may affect approximately two million people worldwide, and over half million persons in Europe have MS. The social burden and costs associated with MS are very high because of its long duration, the early loss of productivity, the need for assistance in daily activities and the use of high-cost treatments and multidisciplinary health care. Despite the high incidence and prevalence of MS in European countries, the general standards of both evaluation and treatment are lacking. Moreover, improved diagnostic criteria reveal more profound and serious situation then it was acknowledged in recent decade. MS shows threatening growth rates in South and East European countries, including Armenia. This article is the first epidemiological study of MS in Armenia aiming to increase public and medical professionals' awareness and appreciation of the problem in the country.

Keywords: multiple sclerosis, epidemiology, Europe, Armenia.

The geographic distribution of MS had very specific nature around the world. A significantly higher incidence of the disease was found in the most northern latitudes of the northern and the southern hemispheres compared to most southern latitudes. Those observations were based on the incidence of the disease in Scandinavia, northern United States and Canada, as well as Australia and New Zealand. Another data from migration studies showed that if the exposure to a higher risk environment occurs during adolescence (before 15 years of age), the migrant assumes the higher risk of the environment [*Compston A., 1998*]. "Epidemics" of MS have been reported and these provide further evidence of importance of environmental factors in MS. The most notable "epidemic" was described on the Faeroe Islands after they were occupied by British troops during World War II. Occasionally, similar increases in incidence of athe disease were observed in other European islands, including Shetland, Orkney, Iceland, and Sardinia. A specific reason (a virus? genetics? an environment?) for these "epidemics" has not been identified yet.

Serious investigations were done toward understanding of MS. Total number of descriptive studies on MS completed during the past 50 years is over 150; many of them had cohort or retrospective nature. The most recent descriptive studies based on more appropriate methods contradicted the accepted belief that the distribution of MS in Europe is related to latitude [*Granieri E., 1997*]. Until 1980, European countries from 36° to 46° north latitude were regarded as having a much lower prevalence rate of MS, about 5 to 25 cases

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per 100000, compared to countries of Central and Northern Europe. This view was mainly based on old comparison surveys done in Italy and Sweden between 1959 and 1975. More recent studies performed in Southern Europe found that MS prevalence is, in fact, much higher than it had been previously believed [*Rosati G., 1994*]. Therefore, the MS distribution in Europe appears to be more complicated than supposed in the past, with great variations not only between areas at the same latitude but also within the countries. There are highly significant deviations from homogeneity, and the high-rate areas tend to be contiguous, forming clusters or foci of MS. For instance, in Europe MS is common in southern Scandinavian but not the north, in the Orkney and Shetland Islands but not the Faroes or Iceland, in Sardinia but not in neighboring Corsica or Spain, in Sicily but not in neighboring Malta.

The distribution of MS in Scandinavian countries primarily observed as initial foci for MS, was studied over several years by Kurtzke [*Kurtzke J., 1967; 1974; 1975*]. The high-frequency areas in the north appeared to describe a "Fennoscandian focus", in the southern inland lake region of Sweden. This probably is where MS originated in the early 18th century and diffused across the Baltic States, Northern Europe, and other countries [*Kurtzke J., 1974*]. It was found that frequency of this disease becomes variable, and in some areas incidences of MS have fallen; this is probably caused by a saturation or migration effect in those places that have been subjected to intense epidemiological scrutiny.

In Denmark, a superb survey of Koch-Herriksen's team between 1948 and 1986, shows lowering of incidence and prevalence rates compared with rates of early periods [*Koch-Henrichsen N. et al., 1994*]. Incidence rates for the three decades from 1950 to 1980 were 5.1, 3.8, and 4.3, respectively. Interestingly, the fall of incidence rate between 1950 and 1960 depended on a reduced rate in people under the age of 35 because of war. After making a correction for the impact of laboratory investigations on the timing of diagnosis, they concluded that a change in environmental factors determined the frequency of MS in the middle decade [*Koch-Henrichsen N. et al., 1994*].

In western areas of Norway, the incidence for definite or probable MS seems to be unstable. It has gradually changed from 1.1 per 100 000 observed between 1953 and 1957 to 4.9 per 100000 between 1978 and 1982 and to 3.4 per 100000 between 1983 and 1987 [*Larsen J. et al., 1984; Gronning M. et al., 1991; Gronning M., 1994*]. A recent study shows that incidence of MS in the two northernmost counties of Norway, Troms and Finnmark, has been increasing over the past 10 years, but it is still lower than on the western coast and in the eastern part of Norway [*Gronlie S. et al., 2000*].

Other regional variations between the western and the southern parts of Finland were found in MS occurrence from 1964 to 1979 [*Lauer K., 1994*]. A recent incidence study of definite cases from 1979 to 1993 demonstrated a persisting gradient: incidence was 5.1 per 100000 in southern Uusimaa, 11.6 in western Seinäjoki, and 5.2 in neighboring Vaasa [*Sumelahti M.-L. et al., 2000*]. The overall regional differences in Finland are because of high MS occurrence in Seinäjoki, where also an exceptionally high familial clustering of the disease had been found earlier [*Lauer K., 1994; Sumelahti M.-L. et al., 2001*].

A comprehensive analysis done in Gothenburg, Sweden, shows that incidence for definite and probable MS dropped progressively from a stable rate of 4.2 per 100000 between 1950 and 1964 over successive 5-year periods between 1974 and 1988 to 2.0 per 100000. Meanwhile, in the same years, the prevalence was stable [*Svenningsson A. et al., 1990*]. The most recent study in Vastebottern County (northern Sweden) indicates an onset adjusted crude prevalence of MS of 125 per 100000. Finally, the prevalence of MS is higher than previous reports from other major areas in Scandinavia [*Sundstrom P. et al., 2001*].

The number of people with MS in the United Kingdom is an estimate based on a number of studies of local areas. When the prevalence rates from these studies are applied to the national population, it suggests the figure of 85000 people

with MS in the UK, although this is increasingly believed to be lower than the actual figure. Similarly, there is no accurate record of the number of new cases of MS being diagnosed each year. Serial estimates of point prevalence in England and Wales in 1985 and 1988 were 117 per 100,000 and 120 per 100,000, respectively, and about 168 in Northern Ireland and as high as 190 in Scotland [*Hennessey A. et al., 1989*]. Individual studies in Orkney have recorded rates of over 200 [*Swingler R., Compston D., 1986*].

Recent epidemiological studies confirm the high overall frequency of MS in the UK and, with notable exceptions, continue to show a temporal trend of increasing prevalence in each newly surveyed district. An increase in MS prevalence in Wales over 50 years was shown, reflecting the dissemination of the disease over time in practically every region where serial studies had been performed [*Swingler R., Compston D., 1986*]. Further surveys show a national difference in MS frequency, with 137 percent more MS in Scotland than in England and Wales [*Allison R., Millard J., 1954; Compston A., 1998*]. A recent study in the Tayside Health Board area (Scotland) shows a prevalence similar to that found in revised figures from the Grampian region in Scotland, but significantly higher than recent estimates from England and Wales [*Forbes R. et al., 1999*].

If the results of local area studies are applied nationwide, it suggests that about 2 500 people in the UK are diagnosed with MS each year, or about 50 a week [*Swingler R., Compston D., 1986; Compston A., 1998*]. Methodological differences may account for most of the reported differences between the north and south, although evidence still suggests that MS is more prevalent in northern Great Britain and Northern Ireland than in England and Wales.

Most of continental Europe appears to be a complicated puzzle of distinct ethnic groups, mixed by centuries of population movement, with different frequency rates. This genetic heterogeneity makes interpreting the epidemiological data difficult.

In western Poland, MS prevalence transiently decreased from 51 to 43 per 100000 between 1965 and 1981 [*Wender M. et al., 1985*]. Other contemporary surveys include the estimate of prevalence for native Estonians, Russians, and other nationalities of 55, 29, and 42 per 100000, respectively, in southern Estonia [*Gross K. et al., 1993*].

In Germany, particularly southern Lower Saxony, mean annual incidence increased from 2.6 per 100000 to 4.6 per 100000 and prevalence increased from 51 to 118 per 100000, between 1969 and 1989 [*Poser S. et al., 1989*]. In a recent study from southern Hesse, in Germany, the prevalence among Germans was four times of that found in other ethnic groups residing in the study area. It is likely that Germanic ancestry carries a higher risk of MS compared to other populations of continental Europe [*Lauer K., Firhaber W., 1994*].

France may emerge in time as a region that has prevalence for MS, which is genuinely lower than would be expected from its geographical position within Europe, if social and ethnic factors are unimportant in determining of the distribution [*Compston A., 1998*]. According to different studies, the prevalence rate ranges from 38 per 100000 to 58 per 100000.

A recent survey done in Valladolid, northern Spain indicates the country as a high-risk area for MS with prevalence rates over 50 per 100.000 [*Tola M. et al., 1999*]. This has been confirmed by another study performed in the Balearic Islands (Minorca), showing a prevalence rate of 68.6 per 100.000 and the incidence rate of 3.4 per 100000 a year [*Casquero P. et al., 2001*].

Occasionally, reports show the low prevalence of MS among Gypsies compared to other ethnic groups in Bulgaria and Romania, which according to the literature make a low prevalence area. These reports have found that the prevalence of MS in Gypsies is 19.1 per 100000 in the first region and 18.4 in the second. This result suggests that MS is less common in Gypsies than in other whites living in the same areas [*Milanov I. et al., 1999*].

In Italy, previous epidemiological studies showed a low prevalence of MS, ranging between 4 and 21 cases per 100000, whereas studies that

are more recent found values between 39 and 102 cases per 100000 in different areas, supporting the consideration of an increase in prevalence of MS in past decades. These data might be due to true changes or only reflect improved case identification. A study on prevalence of MS in central Italy showed a rate of 53 per 100000, supporting the consideration of Italy as an area, in which MS has a high prevalence [*Totaro R. et al., 2000*]. The incidence of MS found in a recent study done in Bagheria confirms the high frequency of MS in Sicily and indicates that MS is homogeneously distributed (at least in the northwestern and central parts of Sicily) independently from the altitude and from the presence of evident features of Norman domination [*Salemi G. et al., 2000*]. According to these data, in an epidemiologic survey conducted in the city of Catania, the prevalence rate was found to be 58.5 per 100000 and the mean annual 2.3 per 100000 [*Nicoletti A. et al., 2001*]. There is no gradient between continental Italy and Sicily, with the exception of Sardinia. All descriptive studies conducted on this island during the last two decades show a twice prevalence and incidence of MS compared with continental Italy.

The Sardinian study done on a sample, representing a fifth of the entire Sardinian population [*Granieri E. et al., 2000*], confirmed that the MS risk is much higher than in the rest of Italy and indeed is identical to the risk actually found in most of the UK and the other parts of northern Europe. Interestingly, the Sardinians represent a distinct homogeneous population from early split in the Caucasoid group, whose prehistoric area of origin is not known. The most recent survey performed in northwestern Sardinia, Sassari, indicates a prevalence of 144.4 per 100000 population and a notable increase in MS incidence over time [*Pugliatti M. et al., 2001*]. This particular finding disproves the hypothesis that this disease distribution follows a latitude-related gradient, prompting the assumption that the frequency of MS in Sardinia is one of the highest in the world and prompting the hypothesis of an MS "Sardinian focus".

Table.

Prevalence of MS in European Countries

COUNTRY	Absolute Number	Prevalence per 100000
Austria	8000	100
Belarus	4700	47
Belgium	9093	88
Bosnia and Herzegovina	1300	80
Bulgaria	4000	44.5
Croatia	3500	87.5
Czech Republic	13000	130
Denmark	7500	122
Estonia	1500	102
Finland	6000	110
France	80000	80
Germany	122000	152
Greece	9000	78
Hungary	20000	176
Iceland	320	110
Ireland	10000	100
Italy	54000	90
Latvia	2500	50
Luxembourg	450	105
Netherlands	16000	100
Norway	6000	125
Poland	50000	120
Portugal	5000	50
Romania	8000	31
Serbia and Montenegro	4500	50
Slovakia	8400	175
Slovenia	3000	155
Spain	40000	59
Sweden	13000	100
Switzerland	9000	110
FYR Macedonia	675	32
Turkey	25000	34
United Kingdom	85000	110

Figure 1. *MS prevalence map (per 100000) in Europe.*

The precise data from East European countries in 1970-80s is lacking. With the collapse of the Soviet system, the appreciation of the problem of MS and integration into main European studies gave an excessive statistical data. The last studies suggest the prevalence of MS in countries with more homogeneous population, as with Slavonic origin (Czech Republic, Poland, and Slovenia), 120-150 per 100000 population, respectively, or in Hungary, where the prevalence is one of the highest in Europe, 176 per 100000.

Most recently available data on MS distribution in Europe was retrieved from web-based multinational team with contribution from many countries http://www.europeanmapofms.org. With their permission, we analyzed provided information to combine the statistical data (presented in Table), counted in absolute numbers and prevalence, based on last census studies in every country.

Based on these epidemiological data of prevalence per 100000, we also created the map of MS distribution in Europe (Figure 1). As clearly seen from the map, during the last decades MS has major growth rates and spread to south and east of the Europe; moreover, the prevalence in Central and Eastern Europe overcomes the North-Scandinavian countries, initially acknowledged as MS foci. As it was assumed by many researchers, this situation is connected neither with population migration, nor with improvement of diagnostic methods or newly adopted criteria for MS [*Compston A., 1998; Freedman M. et al., 2002; McDonald W. et al., 2001*].

The first empirical evaluation of MS in our country, Armenia, was done in 1981 [*Darbinyan V., 1981*]. The prevalence at that time was estimated as 3.75 per 100000, which was entirely comparable with other countries of the same latitude worldwide. The highest incidence of MS was found in regions of Armenia with less homogeneous Armenian population and higher inclusions of clusters of Slavonic origin (i.e., villages of Molokans in Lori region).

This situation has dramatic development starting in early 1990s, with massive emigration and immigration to and out of Armenia, when both

density and structure of population changed. Since many neurologists were unaware of the typical course of MS and diagnostic criteria, the real number of patients was hidden behind diagnoses of "chronic encephalomyelitis", "optic neuritis-encephalitis", "idiopathic encephalitis or myelitis", etc.

Indeed, annual increase of the total number of patients with MS becomes a driving force for us to start creation of the MS Armenian National Database. Throughout work was done in main three neurological departments of the city of Yerevan, and each suspicious case was re-evaluated and revisited, the diagnosis of MS was confirmed or denied.

Our current database includes 366 patients with MS, with complete data on 135 in-hospital patients and 231 persons with MS whose diagnose was established and further evaluation and treatment was done in outpatient departments (OPD). Gender distribution reflects coincidences with worldwide data: 53% women (195) and 47% men (171); mean age of the onset of disease was 24 ± 3.2 years.

The annual distribution of MS in Armenia during the last 10 years is presented as Figure 2. This figure illustrates only the total number of primarily admitted patients whether they had the first attack or relapse of MS.

Since we operate only with precise data of in-patients departments, and in order to exclude probable obstacles and mistakes because of incomplete data of OPD patients, we decided to analyze data of geographical distribution only for 135 patients (Figure 3).

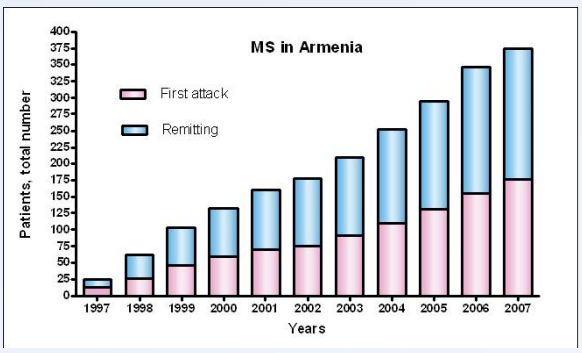

Figure 2. *The growth of annual distribution of MS in Armenia.*

Figure 3. *Geographical distribution of MS (total number of patients) in Armenia during the last decade.*

Thus, our data confirm the threatening growth of the number of patients with MS in Armenia. Although we consider that we passed through substantial improvement of diagnostic techniques, and instead of one low-resolution MRI machine (in 1997) now we are equipped with two high-sensitive MRI machines, moreover, the educational work with neurologists-in-trainings, residents and family doctors gave wider implementation of modern criteria for detection of MS, the main reason of this recorded growth still remains veiled. If we record only the growth of the annual number of relapses of MS, it will primarily point an improvement in detection and diagnostics, meaning that we finally confirm the diagnosis of MS. However, we have firm records of annual increase of the total number of the first attack of MS that prove the growth during the observed decade.

This is our first report on MS in Armenia, and the work towards completing the database, unveiling the main features and diagnostic obstacles of the disease is still on. Our aim is to increase public awareness on both medical needs and social problems of MS patients.

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