

Epidemiologic Data of Multiple Sclerosis in Northern Greece during the Last Thirty Years (1979-2008)

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Received December 03, 2012; Revised April 26, 2013; Accepted April 27, 2013

Abstract The epidemiologic profile of multiple sclerosis (MS), one of the most common diseases of the central nervous system, is not well defined in northern Greece. We analyzed retrospectively the records of the MS patients admitted in our Neurology Department, between the years 1979-2008. We studied a total of 1180 MS patients, with an average annual rate of 39 ± 11.8 MS patients, demonstrating a female to male ratio of 1.6:1. The estimated prevalence of MS in Thessaloniki, the largest city in northern Greece, on December 31 2008, was 57:100,000 placing the area in the high-risk zone while it was 6,8:100,000 on December 31, 1981, in the medium-risk zone. The mean age during the exacerbation of the disease was 28 ± 9 years for females and 31 ± 8 years for males, with significant difference between means ($t = 5.8, p < 0.001$). The average annual rate of attacks was 1.6 ± 0.7 per 100,000 population. Patients' admissions was significantly less in winter with comparison to the other seasons ($t = 3, p = 0.002$). As far as monthly distribution, the maximum number of admissions was noted in May (121 patients, 10.25%) and September (118 patients, 10%) and the minimum in December (58 patients, 4.9%). Our study indicates an increase of the incidence of MS in northern Greece, central Macedonia prefecture and mainly in the city of Thessaloniki, during the last 30 years.

Keywords: multiple sclerosis, epidemiologic data, northern Greece, Central Macedonia, Thessaloniki

1. Introduction

The first description of MS was made by Jean Gruveilhier and Robert Caruswell in 1835; the former described the neuropathology of the disease [1]. Thirty three years later Charcot introduced the term "Scleroses en plaque" referring to this new disease [2]. The aetiopathogenesis of multiple sclerosis remains unclear in spite of the continuous investigations.

1.1. Diagnostic Criteria

There are no pathognomonic tests for the diagnosis of MS, which remains clinical despite the many paraclinical tests. Diagnostic criteria require evidence of dissemination of neurologic signs and symptoms in space and time, based on anamnestic, clinical and paraclinical evidences. The first classification was made from Allison and Millar (1954) [3] among others, while Schumacher and Rose followed in 1965 [4]. Early diagnostic criteria, such as those of Schumacher and colleagues, depended entirely on history and physical examination. In 1983, Poser et al. [5] established new criteria that was uniformly accepted by the majority of neurologists and was most widely used in MS epidemiological research over the past two decades. The criteria made use of paraclinical data, including MRI and CSF examination and patients were assigned to the following categories by using them: (i) clinically definite MS (CDMS), (ii) laboratory-supported definite MS (LSD-MS), (iii) clinically probable MS (CPMS) and (iv) laboratory-supported probable MS (LSPMS). According

to these indications, patients could receive a diagnosis of MS or possible MS. The most recently developed diagnostic criteria are the McDonald criteria [6,7,8], which allow earlier diagnosis in some patients in comparison to previous criteria, making use of advances in MRI techniques. They propose the terms MS, possible MS or not MS instead of the former terms used by Poser criteria.

1.2. MS Variants

Differential diagnosis of MS should be addressed between a wide array of vascular, metabolic or infectious diseases before concluding to the diagnosis, but it is also important to distinguish MS from its variants or other demyelinating disorders. Clinically isolated syndromes are episodes of acute or subacute demyelination that may involve the spinal cord, brainstem, or optic nerves, and which may or may not lead to the subsequent development of MS [6]. Also, acute disseminated encephalomyelitis (ADEM) is a monophasic syndrome with clinical and radiological image similar to MS [9]. Neuromyelitis optica (Devic's disease) is a monophasic or relapsing-remitting inflammatory demyelinating disorder clinically characterised by episodes of optic neuritis and transverse myelitis with differing underlying pathology from that of classical MS. Other variants include Schilder's disease and Balo's concentric sclerosis. Existence of this wide range of differentials diagnosis and variants makes case definition a critical aspect of any study of MS epidemiology.

1.3. Former Studies in the Balkan Peninsula

Studies on population and geographical patterns have been very common in MS, and have led to the proposal of different etiological theories. We will present some relevant data from neighboring countries, as well as from Greece.

In western Herzegovina, in 2003 the annual incidence of MS was 1.6/100,000, with a female/male ratio of 1.5. Crude prevalence of MS was 27/100,000 [10], placing the area in a medium frequency zone. Previous study, in 1996, regarding Belgrade had reported a higher age-adjusted prevalence value of 41.5/100,000 with female/male ratio 1.9. According to this data, Belgrade is an area with high prevalence of multiple sclerosis [11]. For Bulgaria, there are several epidemiological assessments on MS reported in literature. In 1995, population-based studies conducted in two small communities adding up to nearly 55,000 population showed a mean prevalence rate of 39 per 100 000 and a female/ male ratio of 2.0 [12]. In the urban area of Sofia and the rural town of Somokov, the prevalence of MS was lower in Gypsies [13], similarly to that reported for the Hungarian Baranya County [14]. The first survey of MS prevalence in Albania was carried out for the year 1988, but it was based on the criteria of Rose et al. [15] for definite and probable MS. A prevalence rate of 10 per 100 000 with a female/male ratio of 1.1 with a mean annual incidence rate was 0.5 per 100 000 for the period 1968-1987, places the country in the medium frequency zone. No data for the distribution of disease course and severity were available [16].

In *Greece*, the prevalence rates, for the *western* part, were higher than expected in comparison to previous studies conducted in Greece, but closer to the results of studies reported recently in Sicily and Istanbul. The crude prevalence rate of definite MS cases increased significantly in 23 years from 10.1/100,000 recorded in north-eastern Greece in 1984 to 119.61/100,000 on December 31, 2006 in western Greece for the 780 cases still alive. The mean annual incidence rate increased from 2.71/100,000 recorded during the period 1984-1989 to 10.73/100,000 in the 5-year period of 2002-2006. These findings place the western Greece in the high-risk zone [17,18].

The prevalence rate of the definite MS cases, in the province of Evros in *north-eastern* Greece on December 31, 1999, was 38.9/100,000 and places the area in the high-risk zone. The mean annual incidence measured in 5-year intervals increased from 0.66/100,000 in 1974-1978 to 2.36/100,000 in 1994-1999. The increase in prevalence can be attributed to many causes and not only etiological changes since prevalence is known to depend on survival rate and migrations of affected people, but the increase in the annual incidence rate indicates the possibility of an alteration in risk factors of the disease [18,19].

There have been none recent epidemiologic study in northern Greece and especially in Thessaloniki, on the prevalence and characteristics of MS in this area. The purpose of the present investigation is to analyze some of the epidemiologic data on MS patients from the northern part of Greece and especially from Thessaloniki, and examine how these have been changed during the last thirty years.

2. Materials and Methods

2.1. Regional Characteristics

Thessaloniki is situated at 40°38' north and 22°56' east [20] and is the capital of Central Macedonia prefecture. Central Macedonia prefecture is one of the thirteen regions of Greece, consisting of the central part of the geographical and historical region of Macedonia. It is the biggest prefecture of Greece in size with surface of 18,881 km², representing 14,3% of the total country surface, and second in population after Attika with 1,880,058 residents from the 2001 census, representing 17,77% of the total population [21]. The region was established in the 1987 administrative reform. It is bordered to the north by Former Yugoslav Republic of Macedonia (since 1991) and Bulgaria.

Our Department is located in AHEPA University Hospital, one of the biggest hospitals in northern Greece located in Thessaloniki. AHEPA Hospital is associated closely with the Aristotelian University of Thessaloniki and is located within the extended area of the University. It is a major teaching hospital and part of the National Healthcare System of Greece. AHEPA University Hospital was founded in 1947 with the economic support of the AHEPA; a Greek Organization of the United States of America. Practically though, the hospital started its normal operation in March 1953. Nowadays there are two Neurology Departments in AHEPA Hospital, the 1st & 2nd, from the total of six that are placed in the Public Hospitals in the city of Thessaloniki. During these 30 year period many changes have happened in the health care of the city of Thessaloniki. Historically, the two above mentioned clinics, the 1st & 2nd Neurology Departments were the first and only two in operation in the period 1979-1983. In 1983 a third neurology clinic began its operation and in 1988 a fourth one. From 1999 a fifth neurology clinic opens for the public, so for the period 1999-2008 there are five public clinics working consecutively, one being responsible for the whole prefecture every day. All of the clinics have about the same number of staff, the same in-patient potential and regular MS outpatient clinics once a week.

2.2. Study Design

We analyzed retrospectively the records of the MS patients admitted in the 1st Department of Neurology of Aristotelian University, Thessaloniki, Greece, between the years of 1979 and 2008. We selected those patients with a definite MS diagnosis according to the criteria of Poser [5]; retrospective application of the McDonald's criteria was included [6,7]. Patients with multiple hospitalizations were discharged, as well as patients with concordance with other diseases, patients with MS variants or questionable diagnosis. Attempt was made to collect data regarding sex, age, place of residence, season of admittance, first symptoms of the disease, age of disease onset, family and personal history and precipitating factors of MS onset. The study was approved by Aristotelian University (Thessaloniki) and AHEPA Hospital ethics committee.

Statistical analyses were made with SPSS 17.0 (Statistical Package for Social Sciences) after anonymous registration. Normality check was made using

Kolmogorov-Smirnov test, and depending on the type of our variables parametric or non parametric tests were used.

3. Results

We studied the cases of 1180 MS patients admitted in our department during the last 30 years, with an average annual rate of 39 ± 11.8 MS patients, 725 of them female (61.4%) and 455 male (38.6%), demonstrating a female to male ratio of 1.6:1 (Figure 1, Figure 2). The sex ratio/year diagram shows the predominance of the female sex in the most recent years with the highest value of 2.64:1 in the year 2006 (Figure 3). The chi-square test for the gender variable (females and males) for the 30-year period showed significant difference between them ($\chi^2 = 61, p < 0,001$) with female predominance in our area of study. Mean age of the group of MS patients was 37 ± 11 years for females and $39,5 \pm 13$ years for males, presenting a significant difference between men and women ($t = 3,5, p < 0,001$). The mean age during the exacerbation of the disease was 28 ± 9 years for females and 31 ± 8 years for males, with significant difference between means ($t = 5,8, p < 0,001$) and women showing a younger age of MS onset.

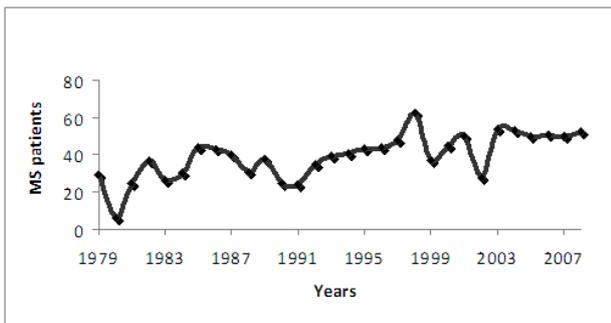


Figure 1. Patients with MS admitted in our department per year

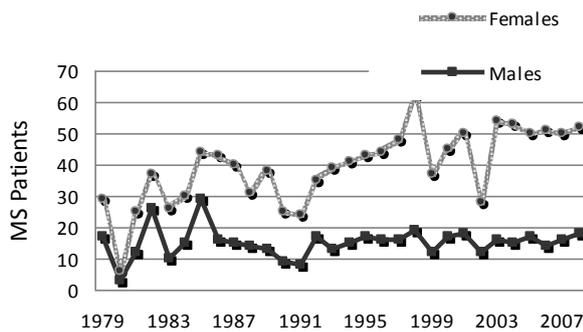


Figure 2. Patients with MS admitted in our department per year by sex

In the present study, the most frequent symptom during the onset of the disease was sensory disturbances (32%) followed by diplopia (24%), optic neuritis (17%) and weakness (16%) (Figure 4). In a lot of cases two or more symptoms were considered as initial. Many risk factors, referring in the literature, are conducted with the onset and the deterioration of MS [1,22,23]. Risk factors, reported by our patients upon examiner's question, were the following: stress (35%), puerperium (5%), surgical anaesthesia (4.4%), CNS-acting drugs (3.4%), viral infections (4%), craniocerebral trauma (4.4%) and very high temperature (12%), unknown (31,8%) (Figure 5). We

found five families with more than one MS member: i) a mother and her 2 daughters, ii) two sisters iii) a mother, her two daughters and her mother, iv) a mother and her daughter and v) a father and his daughter. The familial form of MS in our sample inflicted N=13 patients, 1, 1% of our sample, mostly women. One of our patients had a twin brother who didn't suffer from any neurological disorder or disease.

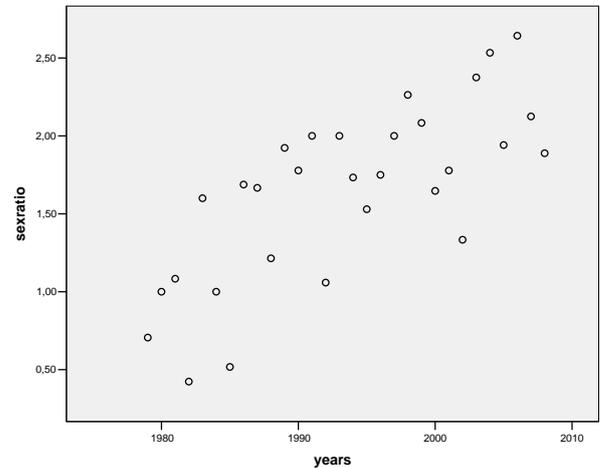


Figure 3. Sex ratio per year

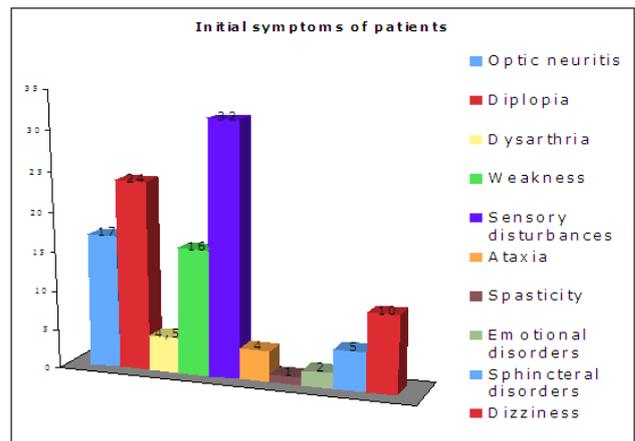


Figure 4. Initial symptoms of patients

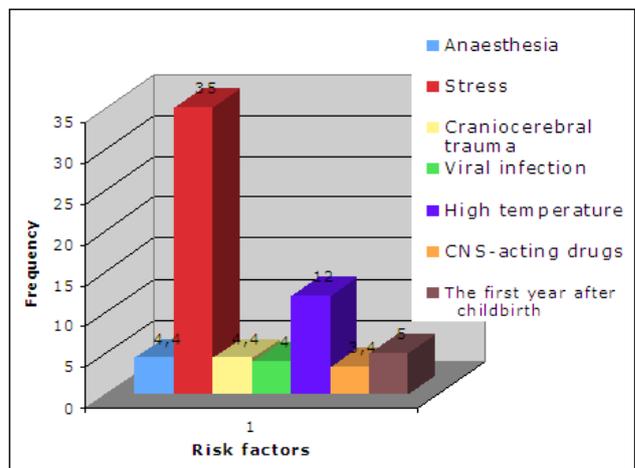


Figure 5. Precipitating factors of MS onset

Our study shows that patients' admissions during spring were 26.6%, during summer 26.9%, during winter 20,7%

and during autumn 25,8% of the total number of admissions, showing significant less admissions in winter with comparison to the other seasons ($t = 3, p = 0,002$). As far as monthly distribution, the maximum number of admissions was noted in May (121 patients, 10,25%) and September (118 patients, 10%) and the minimum in December (58 patients, 4,9%). December has significantly lower admissions in comparison to all other months ($p < 0,001$ to $p = 0,01$), while May has significantly more admissions in comparison to February ($p = 0,02$), April ($p = 0,03$) and October ($p = 0,04$). This is maybe due to the increasing sunlight exposure and temperature or to seasonal viruses or allergens [24,25] (Figure 6, Figure 7).

Most of the patients of the present study were living in northern Greece and especially in Central Macedonia (83%). Examining our data a difference was noted in the admissions of MS patients coming from urban and rural areas between the periods 1979-1992 and 1993-2008. During 1979-1992 there was no difference in the percentages between the group living in the Municipality of Thessaloniki (first group - 37%) and the one living in the rest of Central Macedonia (second group - 38,2%). However, during 1993-2008 there was a significant increase of urban population of MS patients (68,5%) in comparison to a decrease in rural population living in the rest of Central Macedonia (22%) ($p < 0,001$) (Figure 8). The year 1993 was selected as it produced the most notable results.

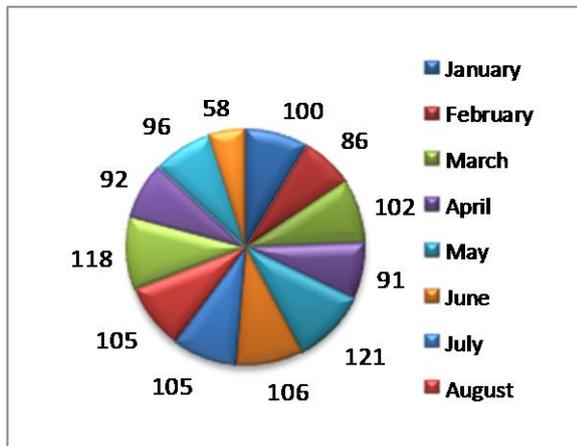


Figure 6. Monthly distribution of patients' admissions

In our study the average annual rate of attacks or average incidence rate for our department was 0.39 ± 0.11 per 100.000 population. The annual incidence rates are shown in Figure 9. We calculated the annual average incidence rates for Central Macedonia prefecture and the results are shown in Figure 10. The calculation of incidence was based on the year of disease onset. The mean annual incidence rate was 1.6 ± 0.7 for the 30-year period. There is a gradual rise of the incidence rate from 1.5 to 2.5 from years 1993 to 2001 and then constant values of about 2.6 from years 2003-2008. The incidence rate rose from 0,77 per 100.000 population for the period 1979-1984 to 2,58 per 100.000 population for the period 2003-2008.

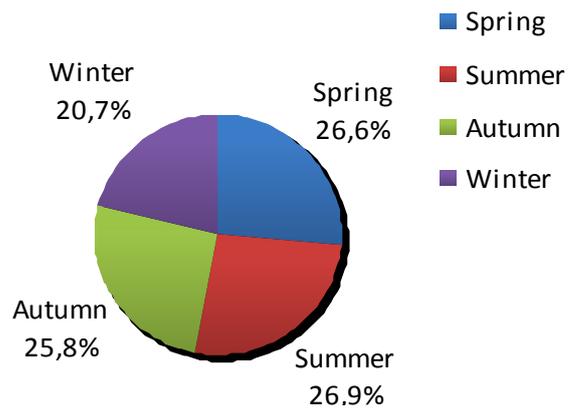


Figure 7. seasonal distribution of patients' admissions

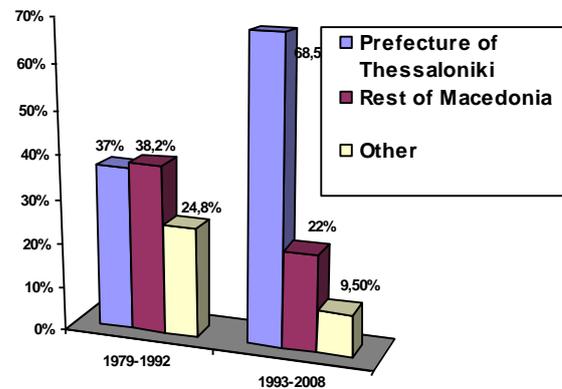


Figure 8. Geographical distribution between urban and rural areas before and after 1993

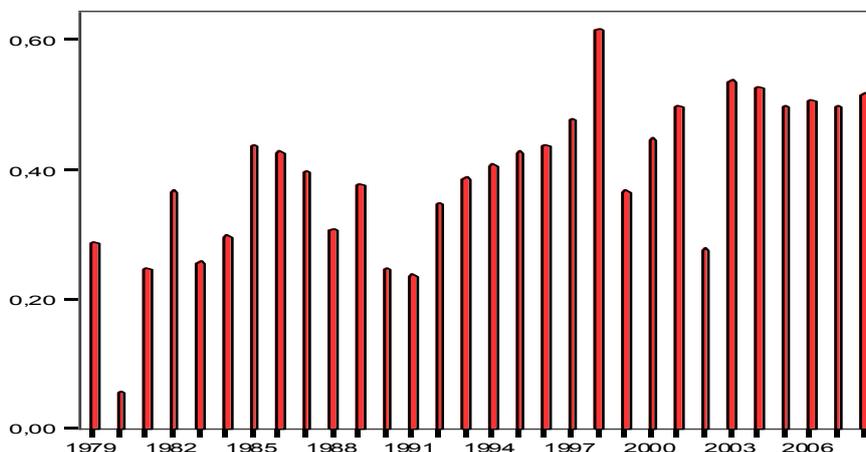


Figure 9. Annual incidence rates per 100.000 population for clinical MS in AHEPA hospital (1st Department) 1979-2008

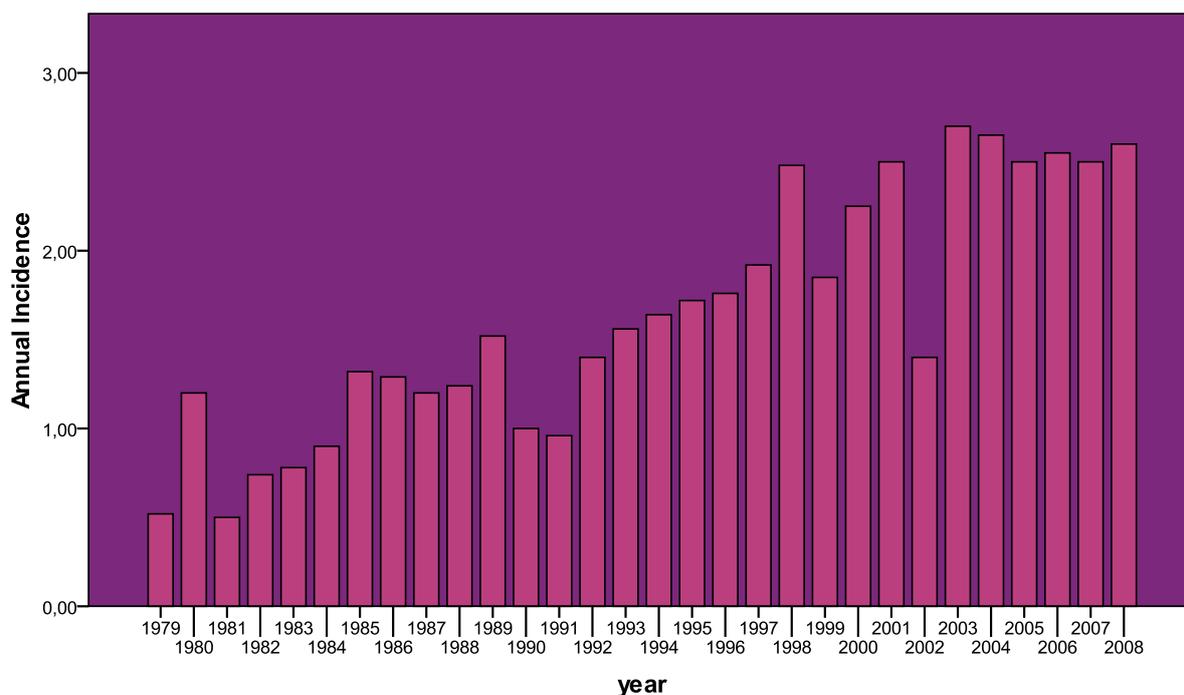


Figure 10. Annual incidence rates per 100,000 population for clinical MS in 1979-2008 (Central Macedonia)

According to the 2001 census and the 2008 population calculation [26] the total population of Central Macedonia Prefecture in 2008 was estimated to 1,880,058 inhabitants. The prevalence of multiple sclerosis on *December 31 2008* in the central Macedonia Prefecture was approximately *57:100,000*, placing the area in the high-risk zone. According to the 1981 census the total population of Central Macedonia Prefecture was 1,600,000 inhabitants. An estimated prevalence of MS on *December 31 1981*, was *6,8:100,000*.

4. Discussion

The geographic and temporal variations in the incidence and prevalence of MS have been intensively studied. However, it is important to note that several difficulties may arise when comparing incidence and prevalence studies from different areas or time intervals. Firstly, the populations studied may vary with respect to their size, age distribution, and ethnicity; Secondly, there may be differences between studies in the completeness of case ascertainment (affected by access to medical care, availability of diagnostic procedures such as MRI, public awareness of MS, number of neurologists, resources available to investigators). For example, mean rates tend to be higher in countries where the degree of disease investigation is also higher, where there is better accuracy in survey methodology and nationwide registry systems are in use like northern countries [27]. Thirdly, there may be differences in the diagnostic criteria used and variability in their application. It has been stated that when comparing all categories of Poser Committee diagnostic criteria with McDonald's criteria, MS rates appear to be overestimated when the latter are used [28]. And on the other hand, the lack of attacks and of recurrent episodes in primary progressive forms may lead to an underestimation of such forms when the Poser Committee criteria are used [29]. In our study, we have a generally genetically

homogeneous population, with a relatively slow influx of residents from the neighbor countries, mainly Albania. Due to the vast national population of the study, the changes in incidence during the 30 year period from 0,77 per 100,000 population (1979-1984) to 2,58 per 100,000 population (2003-2008) reflect changes in environmental factors rather than change in population national percentage.

The sex ratio results are similar with the ones presented in earlier studies in northern Greece [25,30,31,32,33], as well as the latest data from the World Health Organization for the particular disease [34]. Furthermore, from the statistical analyses the mean age of women patients was significantly lower from men patients and the mean age of disease onset was significantly lower in women, too. So, our results are in concordance with the worldwide conclusion that women have MS onset in a younger age than men [34].

The prevalence of multiple sclerosis in central Macedonia was approximately *57:100,000* in 2008, placing the area in the high-risk zone and it was *6,8:100,000* in 1981. It is higher than the values noted on Evros in 1996 [19] (*38,9:100,000*) but lower than the values of the western part of Greece noted in 1981 and 2006 in comparison to our two measurements respectively [17]. In comparison to Albania [15], we have similar values, and higher than the values counted in western Herzegovina [10] (*27:100,000*) in 2006, Belgrade in 1996 (*41,5:100,000*) [11] and Bulgaria in 1995 (*39:100,000*) [12]. Our study indicates an increase in the prevalence of MS, probably due to improved diagnostic approaches or to changes in the way of living.

The relation between the initial symptoms of the disease and the long term prognosis is well established by many authors indicating that the prognosis is better when the initial symptom is optic neuritis and worse when the initial symptoms include cerebellar or motor disorders [35,36,37].

As far as MS genetics are concerned, family members of affected individuals have a greater risk of disease than the general population [38,39]. Half-siblings of affected persons have about half the risk of full siblings of developing MS, while adopted siblings have no greater risk than the general population [39]. This indicates that genetic factors do contribute to an individual's risk of MS but cannot explain development of the disease since monozygotic twins have only 30% concordance and not 100% [40]. The daughters of MS mothers have the greatest risk of demonstrating MS; this conclusion is reached by many investigators [41,42,43].

There are many data referring to the geographic distribution of MS and differences between urban and rural population, maybe due to various factors like occupational, nutritional, environmental and other exogenous parameters. [22,23,44,45,46,47]. Such observational studies were used to show associations, but association and causation in MS are not equivalent. The most important aspect is the establishment of temporality between the induction time- time from the action of any causal factor and disease initiation- and the latent period -time between disease initiation and detection of clinical onset. In MS the causes are unknown, and thus we cannot distinguish between the induction and latent periods.

5. Conclusion

Although more people are being diagnosed with MS today than in the past, the reasons for this are not clear. Likely contributors, however, include greater awareness of the disease, better access to medical care, and improved diagnostic capabilities.

Studying the natural course of disease through epidemiological studies and trying to realise the role of contributors to the disease is one way to try to understand this complicated disease. What we have come to know so far from studies is that any given environmental agent may cause MS in a genetically susceptible individual, though the interaction needed is not known. Due to the unknown latent period between exposure and symptom onset and the rarity of the disease, large scale studies with precise methodological guidelines should be organised.

Competing Interests

The authors have no competing interests.

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