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The Town of Čabar, Croatia, Familiar Pseudocluster for Multiple Sclerosis – Descriptive Epidemiological Study

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A B S T R A C T

Previous descriptive surveys in the town of Čabar, Croatia carried out by our own epidemiological research group, have established that this area is at high risk for MS. To confirm the above assumption and to update MS frequency in this area we conducted a community-based intensive prevalence and incidence study. On December 31st 2001, the average prevalence was 205.7 per 100,000 with prevailing age-specific prevalence in the group of patients between 30 and 49 years of age. The average incidence (1948.–2004.) was 5.52/100.000 population per year (95% CI=3.27–8.72), average mortality in the year was 2.76/100 000 inhabitants (95% CI=1.26–5.24). Sexual index stood at 1:11, starting time was 10:04±28.53 in the year, and the average duration of the disease to the prevalence 11:11±27.26 years.

Key words: *epidemiology; incidence; multiple sclerosis; prevalence; familiar pseudocluster, Croatia*

Introduction

The epidemiological studies in Gorski Kotar, Croatia have been intensively conducted for half a century[1–7]. Previous descriptive studies carried out in the Gorski Kotar, Croatia confirmed increased prevalence of multiple sclerosis (MS) in this area. The MS incidence and prevalence rates seem uneven, with noticeable variations between very limited areas: high in the west (Town of Čabar), low in the east (Town of Vrbovsko)[1–7].

We undertook the present study in order to estimate the trends in MS prevalence and incidence in Town of Cabar (TC), the area of greatest risk for this disease in Croatia.

Patients and Methods

The geographic, climatic, and socio-economic characteristics have been described in detail in a previous epidemiologic investigation[1–5].

Case ascertainment and diagnostic criteria

MS patients were drawn from the following sources: files of Neurological Unit of Clinical Hospital Centre Rijeka, and other hospitals in Croatia and Abroad, archives of the Motor Rehabilitation Unit; files from the neuroradiological services, and neurophysiological centers. All patients with diagnoses of MS, demyelinating disease, optic neuritis, encephalomyelitis, myelitis, and ataxia were reviewed by trained neurologists of our team. For deceased patients, available clinical files were examined. The senior neurologists of our team reviewed all information collected for each patient to verify the validity of diagnosis and to establish the clinical onset, defined as the time of the first symptoms of MS. Information on whether patients were alive and resident in the study area at the prevalence day was obtained from the register offices. To allow comparison with previous surveys and literature data, case definition for the incidence and prevalence estimates was based on Poser's diagnostic criteria for diagnosis of definite and probable MS[8].

Medical ethics

The recommendations of World medical association declaration of Helsinki[9] were followed in the research. All the subjects were acknowledged with the aims of the

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research and they signified their agreements for the questioning.

Statistical analysis

Statistical analysis was performed by use of the chi test and *t*-test. The degree of statistical significance was chosen as a value $p<0.05$. Statistical analyses were performed with the statistical software.

Results

On the prevalence of 29 potential MS patients were identified during the past 58 years (January 1st 1943 to December 31st 2001). As the total population on the prevalence day was 4387 (2187 women and 2200 men), the prevalence rate was 205.7 per 100 000 population[10–12].

The age-specific prevalence rates reached a maximum in the age group 45–49 years, and 30–34 years. The prevalence rapidly declined after fifty years of age due to the death of the patients (Figure 1). The male/female ratio was 1.11.

The mean age of MS patients was 45.06±12.75 years, 46.83±15.20 years for men, and 43.15±10.68 years for women. The course of the disease was relapsing–remitting in 71%, primary progressive in 14% of cases, progressive relapsing in 6% and secondary progressive in 9%. The age at onset was 28.39±8.03 years, 25.92±10.61 years for men, and 30.69±8.69 years for women. The duration of illness to the prevalence day was 27.18±10.67; 22.9±10.9 years for men, and 30.54±11.6 years for women. The mean duration of illness from onset of symptoms until diagnosis was 4.52±5.3 years, 3.94±5.2 for men, and 5.00±4.5 years for women.

The average annual incidence for MS in the TC for the entire period was 5.52 cases per 100 000 population (95% CI=3.27–8.72) (Figure 2). The incidence of MS was particularly high in the period 1984–1988. All the MS patients were born within the borders of the TC (Figure 3). In 16 (84.21%) patients the disease has occurred in the place of birth and residence until 18 years of age. In other

Fig. 1. The geographical position of the Town of Čabar, Croatia.

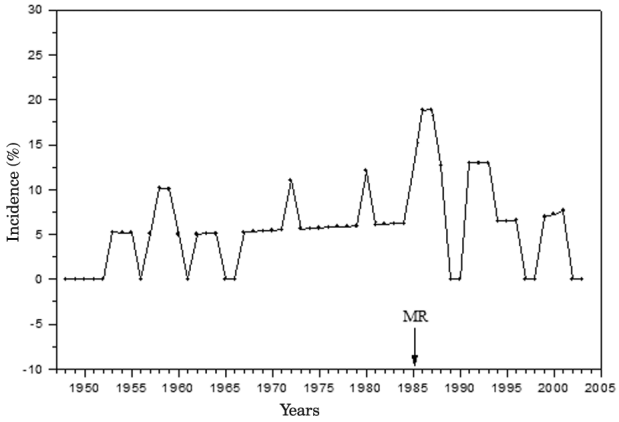

Fig. 2. The incidence of multiple sclerosis in the Town of Čabar, Croatia (1948–2004).

3 patients, the disease has occurred outside of Gorski Kotar, in Croatia (Rijeka) or abroad (in Udine, Rome).

The average annual mortality of patients was 2.76/100 000 inhabitants (95% CI=1.26–5.24) (Figure 4). MS patients in the TC lived an average of 52.64±12,33 years, men 46.60±1.24 years, women 57.07±15.66 years. MS patients often died due to causes associated with MS. The most common causes of death were sepsis, either because of ulcers, whether as a result of Gram-negative urinary tract infections, followed by inflammation of the respiratory tract. One patient committed suicide.

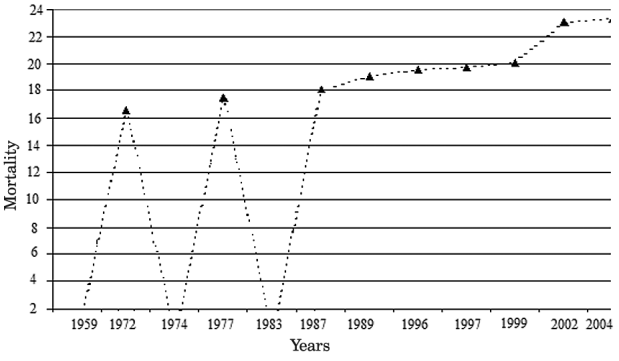

Fig. 3. Mortality from multiple sclerosis in the Town of Čabar Croatia (1959.–2004.) (per 100,000 inhabitants)

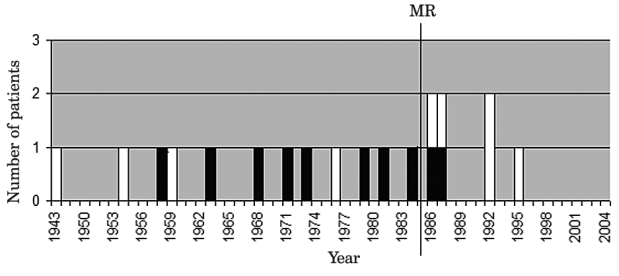

Fig. 4. Familial (■) and sporadic cases (□) of multiple sclerosis in the Town of Čabar, Croatia (1943.–2004.)

Familial multiple sclerosis

Ten (52.63%) of 19 MS patients recognized in the TC were familiar cases of the disease. These cases were observed only in the thirty years period, 1958–1988, later they are no longer recorded. MS has prevailed between the cousins and cousins (p=0.0046), less frequently between the brothers, mother and child. On the day of prevalence in the TC lived another 6 (66.6%) of these cases. therefore, The TC in epidemiological sense, represents real familiar pseudo-cluster for MS.

Discussion and Conclusion

Historical, demographic, and linguistic particularities in the TC are very well known, which is easier and simultaneously enrich the research[1,3,4,7]. In year 1972, J. Sepčić proves that in the Rijeka region the distribution of MS is inhomogeneous. In mountain Communities of Čabar and Delnice higher value of MS prevalence was detected in comparison to the coastal area. Repeated survey conducted in the period from 1985. to 1986. confirms a high prevalence of MS in the TC: 179.9/100.000 inhabitants. The prevalence of disease in the TC was three times higher than the rate registered in the neighboring area of the eastern Istria (40.6/100.000 inhabitants), City of Rijeka (59.6/100.000 inhabitants), the province of Veneto, Italy (30/100.000 inhabitants), the Town of Vrbovsko (66.3/100.000 inhabitants)[1,4,5].

High-risk areas in central Europe that are located in northern Bohemia (Czech Republic)[13] and Hungary[14] are associated with the environmental pollution due to industrialization (Bohemia) and viral infections of the upper respiratory system (Hungary). In the TC, place of birth has higher prevalence than the place of domicile (residence), which indicates genetic and hereditary factors in etiopathogenesis of the disease. Our study, like some other studies (Finland)[15], confirms that the place of birth of MS patients and their parents is located in areas that were built around major villages (towns), or are connected to local roads. The high prevalence of MS in the TC shows certain stability in time. The prevalence is higher in women, and that may be due to hormonal and immunological characteristics of generative phase of their lives. MS is always pronounced when the incidence is estimated by the place of birth: 16 patients were born and raised in the same village to the 18 years of age.

MS mortality rate in the TC is high and almost equal to the standardized mortality index of MS in the Danish registry of the MS disease (2.89%, 95% CI 2.82–2.98 for the 1949–1999), the basis of all the studies on the survival of MS patients[16] and it shows no inclination in time. Permanently increased incidence of MS in the TC, and the occurrence of familial cases of the disease, 10 of them, proves importance of genetic factors in the tendency of getting MS in this area.

The period from the onset of the symptoms and signs to the clinical diagnosis of MS is gradually shortened due to the help of new procedures and techniques. Materljan E. et al. reported that for a period 1949–1958 it was 9.1±8.6 years and 1.3±1.7 years for the interval 1971–1991[1]. Rosati et al. Italy (Sardinia) confirmed the same values: 8 years for the period 1962 to 1971, and 1.8 years from the 1982 to 1991[17].

Occurrence of the MS in the TC was lower than in other areas (counties) in Croatia[4]. Interestingly, the same was reported in Macomer, Sardinia[18] and in Scandinavia[19]. It can be interpreted as the genetic influence on MS: low age at onset is often associated with familial MS[20]. In autochthonous population of Gorski Kotar, Croatia, the familiar forms of MS more often are observed than in other Croatian areasd[4].

High prevalence and almost permanent high incidence of familial cases of MS in the TC, is a consequence of the so-called »founder effect«. All MS patients in the investigated area today belong to Croatian ethnic group, but they are of the German genetic background. Their ancestors migrated from the north of the Europe across Slovenia to the Gorski Kotar, in the TC. They originate from areas in which, even today the high prevalence of MS persists: in Saxony 118/100,000 population (299 MS patients to 252,271) and Turingiji (Germany) 111.28/100,000 population[21–23]. The appearance of MS in the TC is, therefore, mainly conditioned by genetic factors.

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GRAD ČABAR, HRVATSKA, FAMILIJARNI PSEUDOCLUSTER MULTIPLE SKLEROZE – DESKRIPTIVNO EPIDEMIOLOŠKA STUDIJA

S A Ž E T A K

Prijašnja epidemiološka istraživanja multiple skleroze (MS) u Gorskome kotaru, Hrvatska, dokazala su da je to područje, posebice Grad Čabar na zapadu, visokog rizika za tu bolest. Brižljiva deskriptivno-epidemiološka reanaliza MS u Gradu Čabru potvrdila je 31. prosinca 2001. visoku sirovu prevalenciju od 205.7/100 000 stanovnika. Dobno specifična prevalencija prevladavala je u skupini bolesnika između 30. i 49. godine života. Prosječna incidencija (1948.–2004.) bila je 5.52/100.000 stanovnika na godinu (95% CI=3.27–8.72); prosječna smrtnost u godini dana (1959.–2004.) iznosila je 2.76/100 000 stanovnika (95% CI=1.26–5.24). Spolni indeks iznosio je 1.11; početno doba bilo je u 28.53±10.04 godini; a prosječno trajanje bolesti do dana prevalencije 27.26±11.11 godina. Od 1958. do 1988. bilo je deset familijarnih slučajeva MS; prevladavali su parovi bratića-sestrična, braće i majka-sin/kći. Svi su MS bolesnici u Gradu Čabru bili potomci kroatiziranih Nijemaca. Visoki postotak familijarnih slučajeva MS, njih 52.63%, rođenih i nastanjenih do početka bolesti u području relativno prometno izoliranom i izloženom depopulaciji, određuju Grad Čabar kao familijarni pseudocluster MS. U Gradu Čabru genetski čimbenik – utjecaj osnivača – i danas je u velikoj mjeri odgovoran za održavanje većeg rizika za MS.