A COMPLEX EPIDEMIOLOGICAL STUDY ON MULTIPLE SCLEROSIS IN THE ROSTOV REGION

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Summary

A descriptive analytical and eco-epidemiological study on multiple sclerosis in the Rostov Region was conducted with the purpose of improving medico-social support for multiple sclerosis (MS) patients. It revealed an increase in MS prevalence and its considerable variability in different areas of the region. Using the case-control method (the data about 122 pairs were analyzed), a number of external risk factors for the development of MS were determined: pneumonia at the age of 7, food allergy at the age from 7 to 15, industrial enterprises located within a distance of 5 km to residential areas, head and spine trauma at the age above 15, predominance of animal fat in the diet. Using medical-ecological cartography and correlation analysis, MS prevalence was found to be also correlated with the anthropogenic load and environmental degradation such as total air pollution index, average population density in the towns of the region.

Key words: multiple sclerosis, epidemiology, ecology, Rostov region

Introduction

Multiple Sclerosis (MS) is a chronic demyelinating disease of the central nervous system of a so far unknown etiology, and with a wide variety of clinical presentation. MS is considered to be a multifactorial disease, in the development of which virus infection, hereditary predisposition and some external factors play an important role [1-5].

MS prevalence in the world varies from region to region. The "North-South" gradient (a combination of geographic and ethnic factors) is used to identify risk factors for a region. Most of the European part of Russia, including the Ruston Region, is considered to be a moderate risk area (10 to 50 MS cases per 100 000 of the population). Whether genetic or external factors determine MS occurrence and peculiarities of its clinical manifestations, depending on the location remains a question to be answered.

Epidemiological studies are crucial in studies on "infrequent", noninfectious diseases such as MS. These studies help to identify new trends in investigating the etiology and pathogenesis of a certain pathology, to evaluate the patterns of its incidence and prevalence in different regions, as well as to optimize treatment and rehabilitation measures.

Some of the main tendencies of MS epidemiology include the increase of its prevalence in many regions, detection of MS in ethnic groups that were previously considered to be MS-free, and the increase in the number of MS cases in children as well as in persons over 45 years of age.

A complex epidemiological study was conducted and some climatic, geographical and environmental factors (as potential risk factors) and their influence on the disease development were evaluated with the purpose of improving medical-social support for MS patients.

Material and Methods

The study was conducted at the Department of Nervous Disorders and Neurosurgery of Rostov State Medical University, and started in 1995. The study included 1 275 patients (872 women and 403 men), residents of Rostov and the Rostov Region up to the check day (01.07.2011), with clinically confirmed MS diagnosis in accordance with the criteria of Poser Ch. et al. (1983) [6] and McDonald W.I. (2001) [7]. At least one examination was performed on 92 % of these patients at Rostov State Medical University. In addition, data provided by the Ministry of Public Health of the Rostov region, from the journals of the city bureau of Medical-Social Expert Commission and social organization of MS patients were used to obtain more comprehensive information.

To assess the population of the Rostov region, we used the data from annual statistical bulletins of Federal State Statistics Service (Rostovstat). The prospective epidemiological study was conducted by the method of complete statistical survey for the 15-year period. During the study, a research plan and a program were developed, and methods of primary data collection and statistical data processing were applied. The analysis and documenting the results of the study were conducted in accordance with recommendations of the Ministry of Public Health and "Epidemiological studies of multiple sclerosis (№2003/82)"(Gusev E.I. et al.) 2003) [2].

The registration document was an MS patient card, designed on the basis of a generalized form for clinical, epidemiological and social study of MS patients [2]. While the descriptive epidemiological study was being conducted, the average indices of prevalence, incidence and mortality among MS patients and the standardized prevalence index were estimated.

The analytical epidemiological study was carried out by the case-control method, using the validation form of Oslo International Think-tank on MS Epidemiology and Rostov State Medical University, (Gusev E.I. et al., 2003) [2]. The study involved examining 122 MS patients: 85 women (69.7%) and 37 men (30.3%), aged 20 to 65 years. The controls were selected by a pair method according to the patients' nationality, gender and age (±5 years).

During the ecological epidemiological study we examined climatic-geographic and socioeconomic characteristics of Rostov-on-Don and the Rostov Region. The peculiarities of MS prevalence in Rostov-on-Don and the Rostov region, subject to regionalization and environmental assessment of the territory, were also studied. The criteria used were those recommended by the Ministry of Natural Resources and Environmental Protection of the Russian Federation for identification environmental calamity and hot zones (1992). The correlation analysis of the connection between some environmental factors and MS prevalence was conducted using the method of conjugate cartography (medical-ecological mapping). The map clearly illustrated the extent of a particular negative factor, and helped to correlate it with the data on the prevalence of a certain nosologic unit.

The statistical analysis was conducted using program packages: STATISTICA 6.0 (Rebrova O.U., 2006) and Epi Info 5. The significance of MS risk factors was analyzed according to the value of **p**, the difference was considered reliable at p<0.05. Whenever necessary, we estimated the correlation index – CI (a relative risk or odds ratio) using Woolf's method, and the interval of 95% reliability - using Confield's method.

The CI reliability was estimated according to the value of χ^2. If one of the indices equaled zero, Haldane's modification was used to estimate CI.

Results

The group analyzed for MS prevalence included all the patients permanently living in Rostov and its region to the check-up day 01.07.2011 (1275 people), and included 872 women (68%) and 403 (31.6%) men. The average age of the patients was 40.7±0.4 years (age range 13-74 years). The average age of onset of MS was 28±0.4years, the earliest onset being at the age of 4 and the latest – at the age of 58. The average duration of the disease through 01.07.2011 was 12.3±0.3 years,

ranging between 3 months and 46 years.

MS prevalence in the population of the Rostov region until 01.07.2011 was 29.8 per 100 000 people (the standardized prevalence index is 26.8:100 000). Standard European Population was used for standardization (Waterhouse J. et al., 1976 [8]). According to our data, the average prevalence index in the Rostov Region for the last 5 years (from 01.01.2006 to 01.07.2011.) was 26.2 per 100 000 people. Therefore, the Rostov Region might be considered to be a medium risk zone for multiple sclerosis (from 10 to 50 MS cases per 100 000 people according to Lauer K., 1994) [10].

The prevalence was found to vary considerably, depending on age: 91% of MS patients were people aged between 20-60 years, i.e. the economically active population, which only emphasizes the socially relevant component of MS. The highest index was identified in the age groups between 30 and 59 years, and the highest prevalence was detected in the age-group between 40 and 49 years (55:100 000). Thus, the age-group between 40 and 49 years was fond to be at the highest risk for MS in the Rostov region, whereas its prevalence was half the general index.

The incidence of MS in the Rostov Region in 2010 was 0.73:100 000, and the index among women (0.8:100 000) was considerably higher than that among men (0.2:100 000). Moreover, in 2010 we registered 21 cases of a clinically isolated syndrome (CIS), which was very important for receiving full information about MS incidence. This may allow making a timely diagnosis in accordance with the McDonald criteria (2005). The average index of MS incidence for the period between 01.01.2002 to 01.01.2011 was 0.9:100 000 in the Rostov Region.

The MS mortality index was 0.07:100 000 (3 patients) in the year 2010. The average MS mortality index for the period studied (from 01.01.2002 to 01.01.2010) was 0.38:100 000. The average age of the deceased patients was 43.5±4.2, which fact further proves the social significance of MS problem.

Conducting the analytical study by using the case-control method, we identified a correlation between some external factors and the risk of MS development (Table 1).

Table1. Correlations between external factors and MS development risk in the population of the Rostov Region

Factor	Patients	Controls	Correlation index (CI) (VI)	p
Place of birth (low MS risk areas)	18	34	0.45 (0.24-0.85)	0.02
Place of birth (high and medium MS risk areas)	25	13	2.2 (1.05-4.46)	0.05
Exposure to chemical agents at age above 15	6	0	12.6 (12.49-12.64)	<0.00001
Exposure to metals at age above 15	6	0	12.6 (12.49-12.64)	<0.00001
Residence near big industrial enterprises at age above 15	23	10	2.6 (1.18-5.7)	0.03
MS cases in family history (maternal side)	6	0	12.6 (12.49-2.64)	<0.00001
Pneumonia at age under 7	12	2	6.55 (1.43-29.9)	0.01
Chronic tonsillitis at any age	104	81	1.47 (1.08-2)	0.019
Head and spine trauma at age above 15	36	20	2.13 (1.15-3.96)	0.02
Food allergy between 7 and 15 years of age.	14	4	3.82 (1.22-11.97)	0.03
Predominance of vegetable oil in the diet under age of 15;	71	91	0.47 (0.28-0.82)	0.01
Predominance of vegetable oil in the diet at age above 15 before the disease	90	117	0.12 (0.05-0.32)	<0.00001
Predominance of animal fat in the diet under age of 15	65	31	3.35 (1.95-5.75)	<0.00001
Predominance of animal fat in the diet at age above 15 before the disease	45	16	3.87 (2.04-7.35)	<0.00001

Note: The correlation index in Table 1, hereinafter referred to as CI, and 95% validity interval, hereinafter referred to as VI were calculated using Yates' correction, *p* was calculated using χ^2 Yates' correction

An analysis of birth and residence places of the MS patients and their controls was conducted. Most patients appeared to be natives of the Rostov Region or were born in areas with high MS prevalence. Among the immigrants from high and medium MS risk zones, as well as persons whose mothers were born in these zones, the risk of MS development was higher than that of the immigrants from zones with low risk for developing the disease (CI 0.45, VI 0.24-0.85, p=0.02) and the patients with mothers were natives of low MS prevalence risk areas. The results obtained agreed with the results from the study conducted by Molchanova (2002) [10] and, as we assume, it further proves the role of genetic factors in MS etiology.

We did not find differences between the phenotype of the patients and the controls. The predominance of dark-haired and dark-eyed people in both groups is likely to reflect the genetic peculiarities of the population of Northern Caucasus. The common "Scandinavian face" feature is typical of high MS prevalence risk areas, and is not characteristic for the population of our region. The 55 MS patients (45%, p<0.001)), were found to have been long exposed to harmful substances (mostly organic solvents, paints and metals) before the age of 15 before the disease development, unlike the control group (17 patients, 13.9 %). In the comparative analysis of habitation zones there was a statistically significant predominance of those MS patients, who at the age of above 15 (before the decease) were living not far (5 km) from big industrial enterprises, located in the central parts of Rostov-on-Don and Novocherkassk (e.g. "Rostselmash", "Rostvertol", "Horizont", and a permanent magnet factory). Therefore, this factor should be considered as contributing to the risk of MS development. Industrial load plays a big role in the structure of anthropogenic impact on the environment. Living near industrial enterprises as well as exposure to toxic substances for a long time can cause problems of immunoregulation and weaken natural resistance of homeostatic systems, thus increasing the risk of MS development.

The analysis of family case history showed that 6 mothers of MS patients had been also diagnosed with MS, whereas such cases were not found in the control group (p=0.04), which proves hereditary predisposition to multiple sclerosis. The MS patients were significantly more often found to have developed pneumonia at the age of 7, than those in the control group (9.8% и 1.6% respectively, p<0.05). This might be attributed to the decrease in the children's immunoreactivity along with the inflammatory process, which could trigger the autoimmune process. Significantly more often, the MS patients mentioned having had chronic tonsillitis (CI=1.47, VI=1.08-2, p=0.019, x^2=5.52). Significant differences in the frequency of viral infections in childhood were not established.

The MS patients suffered a head trauma (with a loss of consciousness) and a spine trauma at the age above 15 significantly more often than controls (29.6% and 16.4% respectively, p<0.001). Increased blood-brain barrier permeability could be a possible mechanism of involvement of trauma in MS pathogenesis, as shown by clinical, neurological and experimental data [6]. Central immunoregulatory disturbance also contributes to MS pathogenesis. In this study, we analyzed the connection between MS development and susceptibility of patients to different kinds of allergic reactions. The MS patients were found to have allergic reactions, particularly, food allergy at the age from 7 to 15 more often than those in the control group (CI=3.8; VI 1.2-12; p=0.03; x^2=4.9). Allergic reactions lead to imbalance of immune homeostasis and dysfunction of hyperphysical-adrenal system and play an important role in the pathogenesis of demyelinating diseases [11]. Predisposition to allergy in childhood might be attributed to the incapacity of the immune system and is characteristic of people at risk for autoimmune disorders.

When comparing the frequency of stressful situations recorded in the medical histories, both MS patients and those from the control group were found to have experienced stress before the age of 15 (as a rule, serious family or school problems) with comparable frequency – respectively 31.1% и 29.5%. In the age-group of above 15 years, before diagnosed with the disease, the MS patients considerably more often mentioned stressful situations (68%), as compared to persons in the control group (56.6%; p<0.001). Of the group analysed, 32% announced that their first symptoms had been preceded by a stressful situation (in the family or at work). This makes us stress does not play an important part in the MS etiology, but it can trigger the onset of the disease or lead to its exacerbation.

The respondents from the control group

significantly more often mentioned the prevalence of vegetable oil in their diet (compared to animal fat) than the MS patients: at the age of under 15-74.6 % and 52.2% (p<0.01), at the age of above 15 before the disease – 88% и 66.7% (p<0.00001), which allows to consider this factor as one diminishing the risk of developing MS. Unsaturated, fatty acids contained in vegetable oils, probably increase the antioxidant capacity, thus increasing the body`s resistance to multiple sclerosis. The prevalence of animal fat in the diet of MS patients (47.8% – at the age under 15, and 45 % – at the age above 15, and that established for the controls (25.4% and 12%; p<0.00001, respectively) may be considered the factor increasing the risk for MS development due to the proved fact of their influence linked to chronic antigenic stimulation of the immune system of genetically predisposed people [9, 12]. We believe, that the correlation between using animal fats in the diet and the risk of MS development can also be explained by the weakening of antioxidant capacity and activation of lipid peroxidation under the impact of excessive quantity of saturated acids.

We did not identify any dependence of MS prevalence on environmental peculiarities of the territory, and the regularities of MS prevalence in the Rostov Region on natural geographic features of the region. ("North-South" gradient).

The dependence of MS prevalence on anthropogenic factors (industrial, traffic, agricultural loads, air pollution) as most probable MS risk factors was also analyzed. For instance, the highest average annual MS prevalence rate in the Rostov Region was recorded in the town of Azov, which is known to experience worsening of environmental conditions. The population rate established was 69.8:100 000. Applying a systematic approach towards the authenticated data presented by Rostov Statistical Service, all the urban settlements of the region were divided into three groups, according to the presence of industrial enterprises located in the areas (coalmining, machine building, chemical and light industries) and the existing traffic network. The highest MS prevalence level was recorded in large industrial cities of the western economic part of the region (Rostov industrial agglomeration), as well as the Volgodonsk industrial agglomeration. The average MS prevalence rate in this group of urban settlements was 38.3:100 000 and was significantly different (p<0.05) from the respective rate in large mining towns (24.1:100 000) and in the group of towns situated at a greater distance from highways and large industrial enterprises (20.2:100 000). Low rates within the group of the mining towns may be explained by the shutdown of most of the mines and industrial enterprises over the last 10-15 years.

Fluctuations (from 4.5:100 000 in the population in the Azov Region to 53.6:100 000 in the Peschanokopsk region) were also elicited while analyzing the average annual MS prevalence rate in the rural areas of the regions. When we analyzed the rates in the conventional groups of rural areas, characterized by the predominance of certain branches of agriculture and by distance to industrial centers, MS prevalence in "Eastern Donbas" region was found to be almost identical to that in the South–Eastern region (20.8:100 000 and 20:100 000, respectively). The lowest rate was registered in the so-called 'eastern group' (Dubovsky, Zavetinsky, Zymovnikovsky, Remontninsky), which is known to be with the least industrial potential, inactive agriculture (sheep breeding and cultivating areas), fishery, remote from industrial centers and with low population density. The peak MS prevalence in agricultural areas was identified in the northern group (27.5:100 000), characterized by low industrial but high agricultural load, unfavorable natural factors (low eco-system sustainability, increased soil buffer capacity to high-density metals) and critical rate of soil degradation in most of the areas.

The direct dependence of the MS prevalence index on the population density index was identified during the study. In the towns of the Rostov Region with MS prevalence below average (less than 31.2 per 100 000 of the population), the average density of the population per 1 sq. km was found to be 944.4, which was significantly lower than in the towns with MS prevalence above 31.2 per 100 000 of the population (2183 people per one sq.km, p<0.05). Moreover, the group of large industrial cities in the region with high and medium MS prevalence (38.3:100 000) was found to have an overall air pollution index that is considered critical and intensive. However, excessive air pollution was considered satisfactory in the group of towns with the least average MS prevalence (such towns as Salsk, Millerovo, Kamensk-Shahtinsky, Krasny Sulin). The fact that the overall air pollution index in the mining

towns of Shahti, Zverevo, Gukovo was found as satisfactory can be explained by a considerable decline in coal mining for the past 20 years. The average MS density in this group was 24.4%, which was below the average index for the region.

Discussion

We have identified a considerable increase in MS prevalence with a stable incidence rate and a decrease in mortality. In our opinion, it happens due to both true increase in prevalence rate and the change in research methodology (the analysis of not only hospital, but ambulatory cases, the creation of the population patients' registry). It can as well be explained by the improved diagnostics, broad implementation of MRI methods and the opening of MS Centre. Mortality decrease is connected with the rise in life expectancy of the given category of patients, which is the result of the improved quality of medical services and a wide range of pathogenetic and symptomatic therapies.

The findings of the analytical epidemiological study show some associations with a number of exogenous factors in the development of multiple sclerosis in genetically predisposed individuals. In other words, this is the multifactorial nature of the disease which proves the significance of both external and genetic factors involved in predisposition to MS [13, 14].

The eco-epidemiological study has identified a clear link between MS and the ecological situation (high population density as the indicator of anthropogenic load on the environment, residence in environmentally unfavorable areas in the region with high industrial potential), which once again proves the multifactorial nature of multiple sclerosis and lets us think of MS as a "marker" disease. Unfavorable ecological conditions of some populated areas in the Rostov region may be considered potentially dangerous in terms of MS development risk.

It is of vital importance to attract attention of healthcare authorities to the rise of MS prevalence, as a multifactorial, "marker" disease, in the Rostov Region, particularly in environmentally unfavorable areas. Xenogenic intoxication of the population, aggravated by general social and economic transformations, reduces the overall human resistance and leads to the rise in incidence of multifactorial diseases. In order to develop the efficient methods of MS prevention, it is necessary to take into account the environmental factors of occurrence of such diseases. In accordance with the results of our study such preventive measures may consist of the improvement of environmental conditions in residential areas, timely treatment and sanitation of various nidi of infection, prophylaxis of traumatism, dietary correction for people predisposed to MS. Thus, for instance, the use of antioxidants (unsaturated fatty acids, in particular), which have properties protecting against MS development, will enable to reduce the chances of developing the disease in the risk-group (patients with clinically isolated syndrome, especially with hereditary aggravation). Taking environmental recovery measures will considerably help to reduce MS incidence.

Conclusions

On the basis of our epidemiological study on multiple sclerosis in the Rostov Region we made the following conclusions:

- The Rostov Region is in the medium MS development risk zone, and the disease prevalence tends to increase.
- The most significant prognostic factors of the MS development risk in the population of the Rostov Region are industrial enterprises located in the living area (within 5 km), age above 15 (before the disease development), family history on the maternal side, history of pneumonia before the age of 7, history of chronic tonsillitis before onset of MS, head and spine trauma at the age above 15, food allergy at the age 7-15 years, predominance of animal fat in the diet. Probably, the predominance of vegetable oil in the diet is a factor decreasing the risk for MS development.
- The MS prevalence index fluctuated within broad limits in the urban and rural areas of the region, which might be attributed to environmental inhomogenity (ecological characteristics of a certain area). Environmental factors have a complex impact on the MS development risk, and the anthropogenic load and environmental degradation have greater influence as compared to natural environmental characteristics.
- The highest MS prevalence rate was found in large industrial cities of the Rostov region, in rural areas of the northern group with a heavy agricultural load (high-tech agriculture) and in the rural areas of the south-western group

and the eastern Donbass, characterized by the proximity to big industrial centers and transport highways.

- The MS prevalence rate in the areas with high or medium density of the population significantly exceeds the one in areas with low and medium population density.

Thus, there is an obvious correlation between multiple sclerosis and environmental situation (high population density as an indicator of anthropogenic load on the environment, residence in environmentally unfavourable zones of the region with high industrial potential and a high air pollution rate), which is in support of our assumption that multiple sclerosis is a multifactorial disease.

It is of crucial importance to attract the attention of health authorities to the increasing MS prevalence as a multifactorial disease in the region, especially in environmentally disadvantaged areas. Xenogenic intoxication of the population, aggravated by general social and economic changes weakens the general resistance of the human organism and leads to increased incidence of multifactorial diseases. The ecological factors of the incidence of these diseases need to be taken into account when developing efficient preventive measures.

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