RISK FACTORS FOR MULTIPLE SCLEROSIS IN VOLYN REGION (UKRAINE)

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Abstract

The prevalence rate of multiple sclerosis (MS) in Volyn Region (101.0 per 100000) is the highest in Ukraine. To study MS risk factors in Volyn Region, special questionnaires were distributed among all MS patients residing in Volyn region. Results were obtained from 227 respondents including 154 women and 73 men of mean age 43±10.6 years. The control group included 105 healthy respondents inhabiting Volyn region.

We found associated risk factors for MS to be: mother of Volyn origin, maternal age after 27 years old and paternal age after 29 years old at birth of respondent, subject's born as a third child, brestfeeding for less than one year, living in the zone of industrial pollution, near mobile, TV- and radio re-translators, full traffic automobile roads, time spending outdoors less than one hour in winter and less than eight hours in summer, consumption of fruit and vegetables less than 5 times a week, of beef less than 3 times a week, poultry meet less than 3, berries less than 3, cereals less than 4 times a week, chronic stressful situations in life.

Patients with MS more frequently reported AVRI, hepatitis and herpes simplex virus. Among patients with MS there were fewer respondents with history of chickenpox, rubella and DPT (diphtheria, pertussis, tetanus), BCG immunizations.

Here, we introduced a novel study of MS risk factors within Volyn Region. The Registry established in 2012 is being constantly updated and can be a database for a long-term retrospective study involving a large number of patients.

Keywords: multiple sclerosis, risk factors, Volyn Region.

1. Introduction

Multiple sclerosis (MS) is an organ-specific autoimmune disorder which develops in genetically susceptible individuals as a result of the influence of environmental factors [1]. The results of studies of MS familial cases show evidence for a significant maternal genome effect on MS occurrence. Risk of MS increases if the maternal origin is a zone of the high prevalence of the disease [1, 2]. Environmental factors impacting the genetic susceptibility to MS are unknown. Numerous epidemiological studies are being conducted to determine the causes and mechanisms of MS development.

Environmental factors influencing and causing the susceptibility to MS occur both in the pre- and postnatal periods. The parents' age at their child birth, number of older sibs, birth in the urban or rural areas, duration of breastfeeding and related insufficiency of serum vitamin D are the possible causes of MS described in the medical literature [3].

Frequent childhood infections reduce susceptibility to MS [4]. According to the so-called 'hygiene hypothesis' modern living conditions in the industrialized countries isolate infants and children from many infectious challenges and are required for the development of appropriate immunoregulatory networks. An altered sequence of infections may generate and maintain a deficit within the immunological network preceding the onset of MS for years or decades [5]. The frequency of allergic reactions in patients suffering from MS is lower than in other respondents [6, 3]. The meta-analysis of effects of various immunizations on MS risk in adults (BCG, chickenpox, diphtheria, haemophilus influenza B (Hib), hepatitis A, B, influenza, Japanese encephalitis, measles, mumps, pertussis, polio, rabies rotavirus, rubella, tetanus, typhoid fever, yellow fever) shows that

none of them is associated with higher risk. In fact, diphtheria and tetanus immunizations may be associated with a lower risk of MS. [7].

The WHO (World Health Organization) report 2008 clearly indicates that MS has a geographical distribution corresponding to countries with hyper caloric, high-fat/high carbohydrate diets and reduced exposure to the ultraviolet sunlight. Accordingly, a study by the North American Research Committee on Multiple Sclerosis (NARCOMS) has recently found that a quarter of the patients were obese and 31.3 % were overweight [8].

Adverse ecological conditions of living may be an exogenous causative factor realizing the genetic susceptibility to MS. It was the deterioration of the ecological environment that had caused the high rate of MS in Sardinia, Norway, Canada and the USA in the 60s and 90s of the previous century. Scientific publications of the 90s mentioned the MS prevalence growth in Europe associated with opening of factories [9–11].

Epidemiological studies are highly informative to understand the nature, contribution and interaction of genetic and environmental factors in MS [1].

2. Aim

The aim of investigation is evaluating of potential risk factors of multiple sclerosis, described in the others international scientific sources, for inhabitants of Volyn region

3. Materials and Methods

Volyn Region is situated in the northwestern part of Ukraine. It borders with the Poland Republic in the West. The length of the border is 135 km. Volyn Region is genetically homogeneous. Ukrainians are estimated at 96.9 % of the whole population of the region. There were insignificant waves of migration.

The Volyn Registry of Patients with MS was established in Volyn Regional Clinical Hospital in 2012. At the beginning of 2014 the Register included 810 patients with MS (101.0 per 100 000). This rate was the highest among other regions of Ukraine. In 2013 the prevalence of MS in Ukraine was 53.3 per 100 000.

To study MS risk factors in Volyn Region, special questionnaires were designed and distributed among all MS patients residing in Volyn Region. Patients were asked to indicate their sex, date and place of birth, height and weight, childhood infections and vaccinations, frequency of respiratory diseases before and after 18 years old, living conditions, distance to and duration of living near environmentally hazardous facilities, events of stress situations, diet preferences, time spend outdoor in summer and in winter, parental dates of birth and place of origin (Volyn region, south or eastern part of Ukraine or other countries), number of sisters and brothers. Results were obtained from 227 respondents including 154 women and 73 men of mean age 43±10.6 years.

The control group included 105 healthy respondents (students, donors, workers and employees of the hospital) inhabiting Volyn Region. Study groups were matched by age and gender. The exclusion criteria for the control group were the demyelinating diseases, optic neuritis, dementia of different genesis, and incomplete questionnaires. The filling of questionnaires was voluntary. All patients and healthy controls gave their written consents prior to answering the questions under the requirements of the Helsinki Declaration.

The research protocol was approved by the Ethical Committee of O. O. Bogomolets National Medical University. The analytical epidemiological study was conducted to determine the most significant MS risk factors for patients in Volyn region.

Pearson's χ^2 tests were performed to compare groups with and without MS. A two-tail p value of <0.05 was considered statistically significant for the study. 95 % confidence intervals were calculated for each rate or ratio. The software Excel and Stata12 were used in the statistical calculations.

4. Results

Among MS patients, there was statistically significant greater number of individuals whose mothers had Volyn origin. The difference between groups of healthy controls and MS patients as to the paternal origin was non-significant.

46

The average age of parents at the respondent's birth was considerably senior in patients with MS. The average age of mothers in this group was 27.2±5.2 whilst the father's age was 29.9±5.9 years old; the mother's age of healthy controls was 24.7±4.8 years old whereas the father's age was 26.9±5.3. The number of respondents who was born as a third child or more in the family was also higher in the MS group. As to the urban or rural origins, a statistically significant difference between the groups was not found. MS group included fewer subjects breastfed after the 1 year of age than the control group.

Patients with MS more often indicated the adverse environmental circumstances in anamnesis like the residence in the industrially contaminated areas (near industrial warehouses or factories, closed military areas and landfills) comparing to healthy controls. Most respondents with MS mentioned the presence of mobile- or TV- or radio re-translators and heavy traffic on roads near their houses. The duration of residence in such adverse conditions was longer among the patients with MS. It was 17.1±12.7 years in comparison with 11.5±9.2 years in healthy controls (p=0.033). The difference between the groups concerning the distance from home to the ecologically dangerous objects was not statistically significant.

Patients with MS spend less time outdoors than healthy controls (less than 1 hour in winter and 8 hours in summer), include fewer fruits and vegetables in the diet (less than5 times a week), beef and poultry meat (less than 3times a week), berries (less than 3 times a week during the season), cereals (less than 4 times a week). As to pork, the significant difference among the groups was not found.

Chronic stressful situations in life were mostly reported by the patients with MS.

As to the other MS risk factors, namely, source of drinking water, passive smoking, overweight, there were no statistically significant differences between the study groups.

All answers received from questionaires of 227 patients with MS and 105 healthy controls were calculated in absolute numbers and percentage. The results of this investigation are summarized in the **Table 1** and shown on the **Fig. 1**.
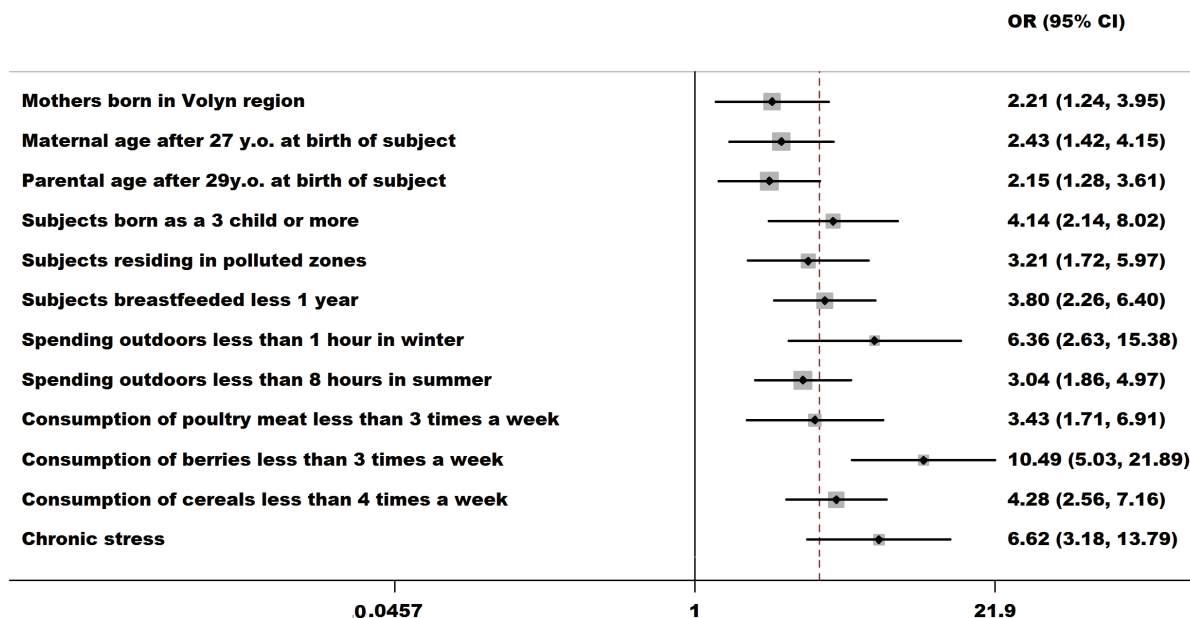
OR (95% CI)

	OR (95% CI)
Mothers born in Volyn region	2.21 (1.24, 3.95)
Maternal age after 27 y.o. at birth of subject	2.43 (1.42, 4.15)
Parental age after 29y.o. at birth of subject	2.15 (1.28, 3.61)
Subjects born as a 3 child or more	4.14 (2.14, 8.02)
Subjects residing in polluted zones	3.21 (1.72, 5.97)
Subjects breastfeeded less 1 year	3.80 (2.26, 6.40)
Spending outdoors less than 1 hour in winter	6.36 (2.63, 15.38)
Spending outdoors less than 8 hours in summer	3.04 (1.86, 4.97)
Consumption of poultry meat less than 3 times a week	3.43 (1.71, 6.91)
Consumption of berries less than 3 times a week	10.49 (5.03, 21.89)
Consumption of cereals less than 4 times a week	4.28 (2.56, 7.16)
Chronic stress	6.62 (3.18, 13.79)

0.0457   1   21.9

Fig. 1. Risk Factors for Multiple Sclerosis in the Volyn Population

Patients with MS more frequently reported diseases like hepatitis, tonsillitis, chlamydiosis, acute respiratory viral infections (ARVI) for more than three times annually after 18 years old, and symptoms caused by herpes simplex virus. Statistically significant results were obtained only for AVRI, hepatitis and herpes simplex virus.

Table 1

Risk Factors for multiple sclerosis in the Volyn population

Risk Factors	Group of Patients with MS (n=227)		Affirmative Answers in the Healthy Controls Group (n=105)	Odds Ratio and Confidence Interval (95 %)	χ^2	
	total number of obtained answers	quantity and percentage rate of affirmative answers				
Mother of the Volyn origin	124	97 (78.2 %)	65 (61.9 %)	2.2 [1.2–4.0]	7.3	p=0.007
Father of the Volyn origin	124	81 (65.3 %)	65 (61.9 %)	1.2 [0.68–2.0]	0.3	p=0.592
Maternal age (after 27 years old) at birth of the respondent	144	71 (49.3 %)	30 (28.6 %)	2.4 [1.42–4.2]	10.8	p=0.001
Paternal age (after 29 years old) at birth of the respondent	141	76 (54.3 %)	37 (35.2 %)	2.1 [1.28–3.6]	8.4	p=0.004
Respondents born as the third child or more	224	78 (34.8 %)	12 (11.4 %)	4.1 [2.14–8.0]	19.7	p=0.000
Respondents born in the urban areas	207	59 (28.5 %)	41 (39.0 %)	0.6 [0.38–1.0]	3.6	p=0.059
Respondents residing in zones industrially polluted and contaminated	78	42 (53.8 %)	28 (26.7 %)	3.2 [1.72–6.0]	14.0	p=0.000
Living near mobile, TV and radio retranslators	78	28 (35.9 %)	2 (1.9 %)	28.8 [6.61–125.9]	37.7	p=0.000
Domiciling near heavy traffic roads	78	7 (9.0 %)	1 (1 %)	10.3 [1.23–85.2]	6.9	p=0.009
Breastfeeding for less than one year	158	112 (70.9 %)	41 (39 %)	3.8 [2.26–6.4]	26.3	p=0.000
Time spending outdoors less than one hour in winter	187	52 (27.8 %)	6 (5.7 %)	6.4 [2.63–15.4]	20.6	P=0.000
Time spending outdoors less than eight hours in summer	196	124 (63.3 %)	38 (36.2 %)	3.0 [1.86–5.0]	20.2	p=0.000
Consumption of fruit and vegetables less than 5 times a week	178	84 (47.2 %)	33 (31.4 %)	1.9 [1.18–3.2]	6.8	p=0.009
Consumption of pork 4 and more times a week	166	67 (40.4 %)	42 (42.4 %)	0.9 [0.55–1.5]	0.1	p=0.741
Consumption of beef less than 3 times a week	70	66 (94.3 %)	30 (28.6 %)	41.3 [13.8–123.2]	73.2	p=0.000
Consumption of poultry meat less than 3 times a week	140	126 (90.0 %)	76 (72.4 %)	3.4 [1.71–6.9]	12.9	p=0.000
Consumption of berries less than 3 times a week	101	90 (89.1 %)	46 (43.8 %)	10.5 [5.03–21.9]	47.1	p=0.000
Consumption of cereals less than 4 times a week	180	121 (67.2 %)	34 (32.4 %)	4.3 [2.56–7.2]	32.5	p=0.000
Well is a source of drinking water	222	82 (36.9 %)	34 (32.4 %)	1.2 [0.75–2.0]	0.6	p=0.421
Centralized water supply	222	109 (49.1 %)	48 (45.7 %)	1.1 [0.72–1.8]	0.3	p=0.567
Borehole is a source of drinking water	222	31 (14.0 %)	23 (21.9 %)	0.6 [0.32–1.1]	3.3	p=0.071
Allergic reactions in the respondent's anamnesis	164	84 (51.2 %)	47 (44.8 %)	1.3 [0.79–2.1]	1.1	p=0.301
Chronic stress	112	101 (90.2 %)	61 (58.1 %)	6.6 [3.18–13.8]	29.5	p=0.000
Passive smoking in the respondent's anamnesis	197	75 (38.1 %)	31 (29.5 %)	1.5 [0.88–2.4]	2.2	p=0.138
Obesity	207	79 (38.2 %)	51 (48.6 %)	0.7 [0.41–1.1]	3.1	p=0.078

Among patients with MS there were fewer respondents with history of viral infections specific to childhood (measles, mumps, rubella, chickenpox, pertussis). However, statistically significant differences between the groups were reached only concerning chickenpox and rubella.

The group of patients with MS is characterized by a statistically significant smaller number of subjects having been immunized with DPT (diphtheria, pertussis, tetanus) vaccine and BCG. As to other vaccines, any difference was not statistically proved.

All answers about the history of childhood disease and immunization received from questionaires were summarized in the **Table 2.**

Table 2

History of Childhood Infectious Diseases and Immunization of Patients with MS and Healthy Respondents under Control

| Infectious Disease | Group of Patients with MS (n=227) | | Group of Healthy Controls (n=105) | Odds Ratio and Confidential Interval (95 %) | χ^2 | |
	total number of obtained answers	quantity and percentage rate of affirmative answers				
ARVI in respondents until 18 more than 3 times per year	147	21 (14.3 %)	8 (7.6 %)	2.0 [0.86-4.8]	2.7	p=0.102
ARVI in respondents after 18 more than 3 times per year	157	89 (56.7 %)	5 (4.8 %)	26.2 [10.1-67.8]	73.7	p=0.000
Measles	196	69 (35.2 %)	40 (38.1 %)	0.9 [0.54-1.4]	0.2	p=0.619
Herpes simplex	196	21 (10.7 %)	4 (3.8 %)	3.0 [1.01-9.1]	4.3	p=0.039
Infectious mononucleosis	196	2 (1.0 %)	2 (1.9 %)	0.5 [0.07-3.8]	0.4	p=0.523
Mumps	196	54 (27.6 %)	30 (28.6 %)	1.0 [0.56-1.6]	0.0	p=0.851
Scarlet fever	196	10 (5.1 %)	4 (3.8 %)	1.4 [0.42-4.4]	0.3	p=0.612
Rubella	196	16 (8.2 %)	20 (19 %)	0.4 [0.19-0.8]	7.7	p=0.006
Chickenpox	196	86 (43.9 %)	67 (63.8 %)	0.4 [0.27-0.7]	10.9	p=0.001
Pertussis	196	17 (8.7 %)	15 (14.3 %)	0.6 [0.27-1.2]	2.3	p=0.132
Hepatitis	195	48 (24.6 %)	7 (6.7 %)	4.6 [1.99-10.5]	14.7	p=0.000
Rheumatism	196	11 (5.6 %)	6 (5.7 %)	1.0 [0.35-2.7]	0.0	p=0.971
Tonsillitis	194	59 (30.4 %)	24 (22.9 %)	1.5 [0.85-2.6]	1.9	p=0.164
Chlamydiosis	196	13 (6.6 %)	2 (1.9 %)	3.7 [0.81-16.5]	3.2	p=0.072
Immunization (Vaccination) against						
Diphtheria, pertussis, tetanus (DPT)	201	145 (72.1 %)	87 (82.9 %)	0.5 [0.3-1.0]	4.3	p=0.038
BCG	187	132 (70.6 %)	91 (86.7 %)	0.4 [0.19-0.7]	9.6	p=0.002
Measles, mumps, rubella	187	105 (56.1 %)	48 (45.7 %)	1.5 [0.94-2.5]	2.9	p=0.087
Hepatitis	187	60 (32.1 %)	45 (42.9 %)	0.6 [0.38-1.0]	3.4	p=0.066

4. Discussion

Volyn region is a zone of high risk of MS. But prevalence rate differs (sometimes twofold) between districts of region [12]. This heterogeneity does not clearly follows a latitudinal or other geographic basis. The high prevalence of MS on the territory of Volyn Region may be caused by some genetic characteristics of its population. Based on results of our survey, this phenomenon is explained by a maternal genome effect on the risk of MS. These results are similar with conclusions of others interracial observations of parent-of-origin effect in multiple sclerosis in Canada [13, 14] and effects of immigration [15].

Otherwise, recent studies, showing lack of genetic differences between monozygotic twins discordant for MS, highlighted the importance of environment [16]. Among the most investigated non-genetic MS risk factors are vitamin D levels, smoke influence, exposure to childhood infections, residing in polluted zones, nutritional habits, psycological stress etc [17].

The senior age of parents at the subjects'birth, presence of two or more older sibs, breast-feeding for less than 1 year give reasons to consider all these factors to be MS risk factors for Volyn population during the prenatal and an early childhood period in genetically susceptible individuals. The increased risk of MS may be associated with insufficient supplement of vitamin D3 in prenatal period. 25-hydroxyvitamin D through immunomodulatory effects increases the immunological self-tolerance and atttenuates initiation and progression of MS [18].

Our data demonstrates the protective role of sun exposure to the risk of MS. The ultraviolet radiation converts cutaneous 7-dehydrocholesterol to vitamin D3. Others studies also confirmed a link between sunlight and decreased MS risk [17, 19]. But insufficient outdoor time (particularly in the fresh air) for patients with MS may be evaluated as a risk factor of MS and simultaneously a result of patients' limited physical activities.

Any long-time exposure to environmentally adverse conditions is meaningful for the increased risk of MS development. This survey confirms our previous study results published in 2014 in Ukrainian Neurological Journal showing twofold prevalence of MS in the anthropogenically polluted areas of the region [20] and others studies in Canada, Japan, Australia, Europe which reveal the association between increased prevalence of MS and process of «Westernization», industry growth [6, 15, 17, 21].

The importance of the hyper caloric diet rich in fats, peculiar to the Volyn inhabitants, is an additional risk factor for MS and is confirmed in our survey. Anne Cross, M. D., of Washington University in St. Louis presented follow-up mechanistic data to Piccio et al. (2008) at the 2014 ACTRIMS-ECTRIMS meeting in Boston. Calorie restriction appears to reduce pro-inflammatory leptin and interleukin-6, while increasing adiponectin, an anti-inflammatory molecule. Thus, hypocaloric diet reduces the susceptibility to and severity of autoimmune encephalomyelitis in mice [22]. Otherwise, Rotstein and her colleagues, including Kassandra Munger, catalogued the diets of 480 people with MS. This was the first large, prospective, population-based study to investigate whether overall diet quality may contribute to the development of MS, and no evidence for such an association was found [23]. Until then, the general advice is: take in more vitamin D; avoid salty, fatty foods; eat more fruits and vegetables, and keep a balanced intake of nutrients [24]. Based on results of our survey, these advices are actual for Volyn patients too.

We cannot state that the chronic stress is a risk factor of MS as the increased anxiety and uneasiness occur in the pre-morbid period of MS.

Our survey does not reveal any association between MS risk and factors which were described as significant by other authors. The source of drinking water, passive smoking and over-weight are not significant factors for MS patients residing Volyn region.

The higher incidence of ARVI (more than 3 times a year) and any herpes symptoms in the patients' group may be the result of reduced body resistance of patients with MS. The childhood diseases like chickenpox and rubella as well as DPT vaccination and BCG may have protective immune-regulating effects on the risk of MS development. These result are similar with another studies [7, 25]. The mechanizm through which these two vaccines may exert effect remains unclear. Today, none of the immunazations are associated with higher risk of developing of MS [7].

5. Conclusions

– Volyn region is one of 25 regions of Ukraine with the highest prevalence of MS in Ukraine. But heterogenity of epidemiologic ratios of MS within one region puts a lot of questions to neurologist concerning factors of development of disease and mechanizm through which they may exert.

– Our survey defined risk and protective factors for MS which are special for Volyn inhabitants. Despite our study involved a small number of respondents, the influence of some factors on the development of MS, as previously described in the world medical research sources, was confirmed. We introduced a novel study of MS risk factors within Volyn Region. The Registry established in 2012 is being constantly updated and can be a database for a long-term retrospective study involving a large number of patients.

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