Parity and age at childbirth are correlated to the sex ratio and survival in multiple sclerosis

Dzietność i wiek rodzących korelują ze wskaźnikiem płci oraz przeżyciem w stwardnieniu rozsianym

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Wprowadzenie. Relacja pomiędzy reprodukcją i ryzykiem stwardnienia rozsianego (MS) jest przedmiotem bieżących badań.

Cel badania. Stwierdzenie czy dzietność w populacji Polski wykazuje asocjację ze wskaźnikiem płci i przeżyciem w zbiorowości MS.

Materiał i metoda. Badanie objęło 9 705 chorych (M – 4131, K – 5 574), którzy zmarli w latach 1981-1990, 2001-2010 w Polsce. Liczba żywourodzonych dzieci (LBC), współczynnik dzietności (PR), mediana wieku rodzących kobiet w ogólnej populacji skorelowano ze wskaźnikiem płci i przeżyciem w MS. Wszystkie dane demograficzne uzyskano z Głównego Urzędu Statystycznego w Warszawie.

Wyniki. Wskaźnik K:M w MS wzrósł w latach 1981-2010 wykazując rosnące występowanie choroby u kobiet; p<0,00001. Przeciętne przeżycie mężczyzn i kobiet z MS istotnie wzrosło w latach 1981-2010; p<0,0001. Stwierdzono mocną odwróconą asocjację między liczbą LBC, PR w ogólnej populacji i wskaźnikiem K:M w MS: r=-0,775, r=-0,785, p<0,00001. Mediana wieku pierwiastek pozytywnie korelowała z wskaźnikiem K:M w MS: r=+0,778, p<0,0001. Stwierdzono odwróconą korelację między liczbą LBC i przeciętną długością życia kobiet i mężczyzn z MS: r=-0,870, r=-0,735, p<0,0001.

Wnioski. Niższa liczba żywourodzonych dzieci, zmniejszony współczynnik dzietności i wyższy wiek pierwiastek w populacji Polski wykazały asocjację ze wzrastającym występowaniem MS u kobiet. Mniejsza liczba LBC cechowała się odwróconą korelacją z dłuższym przeżyciem kobiet i mężczyzn chorych na MS.

Słowa kluczowe: *stwardnienie rozsiane, dzietność, wskaźnik płci, przeżycie*

Introduction. Relation between reproduction and risk of multiple sclerosis (MS) is the topic of current investigations.

Aim. The aim of this study was to ascertain whether parity in the Polish population was associated with the sex ratio and survival in MS assemblage.

Material & Method. The study included 9705 MS individuals (M – 4131, F – 5574), who died in the years 1981-1990, 2001-2010 in Poland. The number of liveborn children (LBC), parity rate (PR), median age at childbirth in the general population were correlated to the sex ratio and survival in MS. All demographic data were obtained from the Central Statistical Office in Warsaw.

Results. The F:M ratio in MS increased between 1981-2010 showing a rising occurrence of the disease in women; p<0.00001. Average life duration of men and women with MS increased between 1981-2010; p<0.0001. Strong inverse association was found between the number of LBC, PR in the general population and the F:M ratio in MS: r=-0.775, r=-0.785, p<0.00001. Median age of primiparae was positively correlated to the F:M ratio in MS: r=+0.778, p<0.0001. Inverse correlation was ascertained between the number of LBC and average life duration in MS women and men: r=-0.870, r=-0.735, p<0.0001.

Conclusions. The lower number of liverborn children, decreased parity rate and increased age of primiparae in the Polish population were associated with the rising occurrence of MS in women. Less numerous LBC was inversely correlated to longer survival in women and men with MS.

Key words: *multiple sclerosis, parity, sex ratio, survival*

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Abbreviations

F – females
FMR – females to males ratio
LBC – liveborn children
M – males
MS – multiple sclerosis
OR – odds ratio
PR – parity rate
RR – relative risk

Introduction

Multiple sclerosis (MS) is a multifactorial disease originating from interaction of environmental, immunologic and genetic factors [1-3]. Studies on MS aetiology are devoted to solar radiation exposure, age at the past viral infection, smoking, diet, level of vitamin D_3 and to the function of T regulatory cells [2-5]. Reproduction (parity) before MS onset is also considered as factor which may influence risk of the

disease [7, 8]. Previous studies on the association of parity and MS risk have given conflicting results [7-10]. Part of the findings documented no association between antecedent pregnancy, the number of liveborn children, age of primiparae and MS risk [9, 10]. Other studies either proved protective effect of parity on MS initiation or described an increased risk of the disease after pregnancy and puerperium [7, 8, 11].

The topic of the present study was to ascertain whether the number of liveborn children (LBC), parity rate (PR), age of women at childbirth in the Polish population are correlated to the sex ratio and survival in MS assemblage. The results of this investigation may help to explain a possible relation between the long-term, nationwide parity rate and the occurrence of MS in females as well as the duration of life in MS individuals. The partial explanation of the rising occurrence of MS in women may be sought in the decreased parity within the general population.

Material and method

The study aimed to determine the relation between the past number of liveborn children (LBC), parity rate (PR), age of women at childbirth in the general population and the long-term sex ratio as well as survival in MS assemblage. Two large cohorts included 9 705 (M – 4 131, F – 5 574). MS individuals, who died in Poland between 1981-1990 and 2001-2010. The MS diagnosis was established using code 6/7-10, 340, 345, G35 according to the International Classification of the Diseases. On the basis of 2 cohorts the F:M ratio and average life duration in deceased MS patients were ascertained. Demographic data of MS individuals who died between 1981-1990 were compared with data of patients who died between 2001-2010 using t Student test. The annual number of LBC, annual PR and annual median age of primiparae (at the reproductive age of 15-49 years) in the Polish female population were correlated to the sex ratio in MS assemblage over two decades. A correlation was carried out between the number of LBC, median age of all mothers at lifetime childbearings in the general population and annual average life duration of the Polish MS individuals. The correlations were performed using the Pearson test and the linear regression analysis. Demographic information pertaining to cohorts of deceased MS individuals and the Polish general population was obtained from the Central Statistical Office in Warsaw.

Results

The proportion of women prevailed over men in two cohorts of 9 705 MS individuals (57.4% vs. 42.6%). The ratio of women to men was 1.37:1.0. The average F:M ratio over the period of 2001-2010 ranged 1.52 (SD 0.14) and was higher than in the period of 1981-1990 with the ratio 1.21 (SD 0.10); the difference between two ratios was highly significant; t-Student test: $p<0.00001$, Table I.

The increasing F:M ratio in MS assemblage showed an inverse association with an average, annual number of liveborn children (LBC) in the general population in the periods of 1981-90 and 2001-10. The number of LBC and parity rate (PR) gradually decreased over time. The decrease of both variables was statistically significant; t Student test: $p<0.0001$, Tab. I. The correlation coefficient of LBC to the F:M ratio in MS was strong: $r=-0.775$, $p<0.00001$. By using the same test the increasing F:M ratio in MS showed an inverse association with the decreasing parity rate (PR) in the Polish population over two decades: $r=-0.785$, $p<0.0001$. The results demonstrated that the lower the number of LBC and PR the higher the proportion of women with MS who died between 1981-90 and 2001-10 in Poland. The relationship between the number of LBC and the F:M ratio in MS is presented by Fig. 1.

Table I. Annual number of deceased individuals and F:M ratio in multiple sclerosis with regard to number of liveborn children, parity and age of primiparae in Polish population

Year	Annual number of deceased MS patients		Female to male ratio in MS per year	Number of liveborn children in general population (in thousands)*	Average annual parity rate in general population	Median age of primiparae in general population
	men	women				
1981	267	290	1.08	681.7	2.23	22.9
1982	243	273	1.12	705.4	2.33	23.0
1983	284	319	1.12	723.6	2.41	23.1
1984	229	308	1.34	701.7	2.37	23.2
1985	251	291	1.15	680.1	2.32	23.3
1986	238	304	1.27	637.2	2.21	23.2
1987	201	283	1.40	607.8	2.15	23.2
1988	232	293	1.26	589.9	2.12	23.2
1989	243	273	1.12	564.4	2.06	23.1
1990	235	302	1.28	547.7	1.99	23.0
1981-1990	2423	2936	1.21 (SD 0.10)	643.95 (SD 63.25)	2.22 (SD 0.13)	23.12 (SD 0.12)
2001	186	271	1.45	368.2	1.31	24.0
2002	183	264	1.44	353.8	1.24	24.3
2003	156	270	1.73	351.1	1.22	24.7
2004	158	218	1.37	356.1	1.22	25.0
2005	184	267	1.45	364.4	1.24	25.4
2006	169	272	1.60	374.2	1.26	25.6
2007	171	265	1.55	387.9	1.30	25.8
2008	174	268	1.37	414.5	1.39	25.9
2009	162	290	1.79	417.6	1.39	26.3
2010	165	253	1.53	413.3	1.37	26.6
2001-2010	1708	2638	1.52 (SD 0.14)	380.11 (SD 26.42)	1.29 (SD 0.06)	25.4 (SD 0.85)

* Population of women at reproductive age of 15-49 years

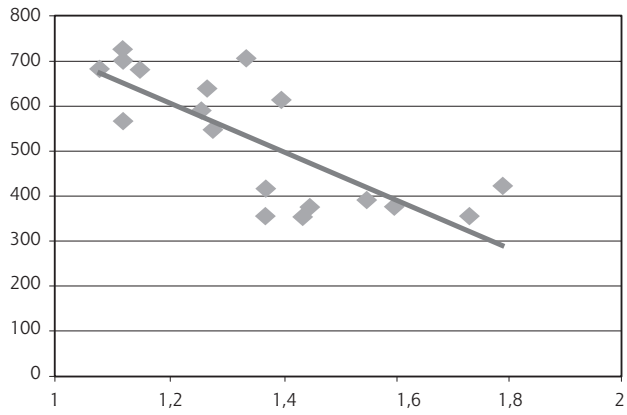

Fig. 1. Graphic presentation of linear regression between number of liveborn children (LBC, y axis) in general population and F:M ratio in MS assemblage (x axis) through years 1981-90, 2001-2009 in Poland. Inverse correlation coefficient between variables was r=-0.775, p<0.0001

The outcome of analysis supports the hypothesis that the past low parity rate was an additional factor triggering the MS development. The relation between median age of primiparae in the general population and the F:M ratio in MS assemblage was further investigated. Median age of primiparae was rising from 22.9 years to 25.4 years; p<0.0001. The age of women at the first childbirth in the general population correlated to the F:M ratio in MS:r=+0.778, p<0.0001. One may consider that the growing age of primiparae, including those with MS, reduced the chance of subsequent childbearings and thereby increased the risk of the disease. Older age of primiparae may have also other unknown effect on MS pathogenesis.

The second part of the study aimed at the determination of the relation of the past number of LBC and median age of women at lifetime childbirths to an average survival in MS individuals. The average life duration of MS patients evidently increased between 1981-2010 (with the ten-year interval). The life span of men extended from 49.4 yrs. to 57.2 yrs. and in women from 49.4 yrs. to 57.9 yrs., Table II.

The length of life over 2 decades was examined by t Student test. There was a significant increase by 7.8 yrs. in MS men and by 8.7 yrs. in MS women; p<0.00001. The analysis of relation between annual number of LBC in the general population and annual, average duration of life in MS individuals exhibited a significant inverse correlation. The r coefficient of survival correlation in men and women with MS was -0.735 and -0.870, p<0.0001. That inverse relationship of the number of childbirths in the general population with survival in MS assemblage implicates the role not only of biological factors but also the character of social and economic factors which lengthen the life in MS individuals. The correlation of the lower number of LBC to longer survival in men with MS indicates that this relation was not sex-specific.

Table II shows an increase of median, maternal age at lifetime childbearings in the general population over two decades. The average age increased in the range of 24.3-28.6 years; the age difference was statistically significant: p<0.0001. The growing age of women at lifetime childbirths correlated with longer survival in females and males with MS: p<0.0001. The finding suggests that increasing maternal age is related with social, lifestyle and occupational factors which contribute to longer survival of MS individuals.

Table II. Annual average life duration in multiple sclerosis assemblage related to number of liveborn children and maternal age at lifetime childbirth in general population

Year	Annual average life duration of MS women	Annual average life duration of MS men	Annual number of liveborn children in general population*	Median age of mothers at all births in general population
1981	49.2	49.4	681.7	25.3
1982	49.6	52.0	705.4	25.5
1983	50.0	50.8	723.6	25.7
1984	49.9	50.0	701.7	26.0
1985	51.5	51.1	680.1	26.0
1986	54.0	52.2	637.2	26.2
1987	52.0	53.2	607.8	26.2
1988	51.1	51.3	589.9	26.2
1989	52.5	52.6	564.4	26.1
1990	53.8	53.9	547.7	26.0
1981-1990	51.4 (SD 1.71)	51.6 (SD 1.40)	643.9 (SD 63.2)	25.9 (SD 0.31)
2001	56.1	55.3	368.2	26.4
2002	56.0	53.7	353.8	26.6
2003	56.2	54.7	351.1	26.9
2004	55.0	54.7	356.1	27.1
2005	55.2	55.2	364.4	27.4
2006	55.2	56.4	374.2	27.6
2007	56.4	55.8	387.9	27.9
2008	58.2	56.7	414.5	28.1
2009	59.2	57.0	417.6	28.3
2010	57.9	57.2	413.3	28.6
2001-2010	56.5 (SD 1.42)	55.6 (SD 1.15)	380.1 (SD 26.4)	27.4 (SD 0.70)

* Population of women at reproductive age of 15-49 years

Discussion

In several studies attention was paid to the relation between the number of LBC and MS in parents [7-10]. A part of comparative, case-control or population-based studies did not discover the association of the offspring number with parental risk of MS [9, 10, 12, 13]. The Nurses Health Study demonstrated that four years before the MS onset the disease risk among parous women was almost identical to that of childless females in the USA [10]. White, married women from the U.K. showed a lower relative risk (RR) of MS after giving birth to 3 children then the childless women (0.4 vs.

1.0), but the difference was not statistically significant [14]. Yet The AusImmune Study considered that the greater number of offspring evidently decreased MS risk in mothers [8]. One childbirth reduced the odds ratio (OR) of first demyelinating event in mothers to 0.49, birth of 5 or more children decreased OR to 0.06; $p<0.001$ [8]. In contrast, more numerous childbirths before the MS onset in married mothers did not influence the risk of MS in fathers (OR=0.71, p=0.71), [8]. The results of investigation based on the Danish MS population confirmed that birth of 4 or more offspring reduced RR to 0.62; $p<0.001$ [15]. Interestingly, the parity of married couples also lowered RR of the disease onset in fathers (0.89, $p<0.001$), [15]. The authors considered that the MS risk increased in both parents with time since the birth of the most recent child. After the birth of last child $\geqslant$20 years, RR of MS was 1.11. However, more recent childbirth 2-4 years prior to onset reduced RR to 0.71, $p<0.001$ [15]. A highly significant effect of 1+ childbirth on MS risk in women was found in a case-control study: if only 0-5 years lapse between the latest childbirth and onset of MS: RR 0.68, $p=0.1^{-3}$ [16]. That protective effect vanished during 10 years [16]. One ought to emphasize that the past childbirth did not decrease MS risk in males [8, 16]. By and large parous women were more protected against developing the disease than childless women, although that protection was not lifelong [7, 15-17].

Holmquist et al. [17]. found a significant correlation between the number of LBC before the MS onset and age of mothers at the first symptom of the disease. Parous women had the MS onset at an average age of 31 years, but childless women showed the onset of the disease already at the age of 23 years. Birth of one child delayed the age at onset to 24.6 years, birth of 3 children approximately retarded the onset to 27 years [17]. Nulliparous women had higher MS risk than multiparous females. The number of observed nulliparous MS women (74/153) was much greater than the number of expected MS women (50/153) in Sweden ($p=0.09^{-3}$), [7]. It is noteworthy that the percentage of nulliparous women with MS increased if time of the onset clearly drew nearer (83% vs. 64%) [16].

The relationship between the age of primiparae and MS risk was investigated in four studies [8, 15-17]. Maternal and paternal age at the first childbirth did not differ in the Danish MS patients as compared to age of controls [16]. The effect of age on MS risk was contradictory [8, 16, 17]. In two studies older mothers at the age $\geqslant$30 years have been more protected against MS than younger ones [15, 17]. In other investigations older age was not protective [8, 16]. The present study showed a positive correlation between growing age of primiparae in the general population and higher occurrence of MS in women. Divergent outcomes in the literature suggest rather a social than a biological effect of reproductive age on MS incidence.

MS women particularly in large towns had less children than controls and the parity rate in MS assemblage was lower as compared to the general population [15]. This study showed an inverse correlation between the smaller number of LBC or lower PR and longer survival of women and men with MS. That correlation between parity in the Polish population and duration of life in MS assemblage may be interpreted as a rather widespread social, economic and cultural event occurring in most European countries.

The analysis of association between reproductive or environmental factors and a higher occurrence of MS in women is more complex than it seemingly appears. The risk of MS in women may be related to age, race, geographic latitude, month of birth, exposure to ultraviolet B radiation, vitamin D level and HLA-DRB1, HLA-DRQB2 genes [1, 3, 18-20]. The relation of the disease risk is also considered to the level of hygiene and education, viral infections in late childhood or adolescence, migration and urbanization [1, 4, 18, 21, 22]. Further relations include a change of lifestyle, smoking, sedentary indoor occupation, dietary habits and obesity [18, 23, 24]. On the other hand such factors as early age at menarche, breastfeeding, use of contraceptives rather do not increase the risk of the disease [12, 14, 17].

Hormonal, immunologic and metabolic factors are capable to reduce MS risk during pregnancy. The women's response to antigens is more strongly modulated by the vitamin D_3 level [26]. During pregnancy the levels of estrogens, progesterone and prostaglandins gradually increase [13, 25, 26]. Hormonal changes are accompanied by a higher activity of T_H2 lymphocytes producing anti-inflammatory cytokines, activity of TCD4+CD25+ regulatory cells and possibly by the reduced activity of T autoreactive lymphocytes [26, 27]. A higher level of vitamin D_3 promotes production of IL-4, IL-10 cytokines as well as pregnancy-associated proteins [12, 13, 26]. Maternal, placental and fetal factors induce shift toward accreting immunosuppression and immunotolerance [23].

Summing up, the present study shows evidence supporting the protective role of parity in MS women. It has, however, at least two shortcomings. Firstly, there was no information on the number of offspring born by MS women prior to the disease diagnosis. Secondly, no data pertaining to age of MS women at childbirth was taken into consideration. Limited information makes the analysis only partially relevant to the process of reasoning. Nevertheless, the population-based, long-term, statistical outcomes favour the hypothesis that decreased parity was associated with the rising occurrence of MS in the Polish women.

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