Medical and Biological Sciences, 2012, 26/3, 39-44

ORIGINAL ARTICLE / PRACA ORYGINALNA

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DISTORTION OF BIRTH DISTRIBUTION IN MULTIPLE SCLEROSIS: RELATION TO SEASON, GENDER AND RESIDENTIAL PROVINCE

DYSTORSJA ROZMIESZCZENIA URODZEŃ W STWARDNIENIU ROZSIANYM: RELACJA DO PORY ROKU, PŁCI I ZAMIESZKANEGO WOJEWÓDZTWA

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Summary

Introduction. Season of birth may influence risk of multiple sclerosis (MS) in higher geographic latitudes.

Aim of the study is to determine if seasonal birth distribution of MS people is associated with risk of the disease in Poland.

Material and method. This study included 436 MS patients (M – 171, F – 265) who were born in the years 1918–1995 and died in the year 2007 in Poland. Data on month of birth, gender, diagnosis and place of the last residence were obtained from the Central Statistical Office. Monthly birth distribution in registered MS cohort was compared to month of birth in expected MS people from collected group and from the general population. Analysis was carried out using chi square test and Fisher's exact test.

Results. The greatest number of birth in observed MS cohort was found in April as compared to the number of expected MS group (59 vs. 36.3; p=0.001) or to expected MS assemblage from the general population (59 vs. 40.2; p=0.003). Observed monthly birth distribution was different from the expected monthly birth pattern in MS cohort (p=0.008), but not from the expected distribution in MS assemblage from the general population (p=0.223). April/November birth ratio (59:28) significantly increased; p=0.001. Seasonal birth distribution was significantly different in MS females (p=0.019), but not in MS males (p=0.476). The greater number of provinces was resided by April born than by November born MS patients (p=0.037 for M and p=0.025 for F).

Conclusions. Higher MS risk was associated with birth in April. Difference in seasonal birth distribution of MS patients indicates association of spring born women with development of the disease.

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Streszczenie

Wstęp. Pora roku urodzenia może wpływać na ryzyko stwardnienia rozsianego (SM) w wyższych szerokościach geograficznych.

Celem pracy jest określenie, czy sezonowe rozmieszczenie urodzeń chorych na SM wykazuje asocjację z ryzykiem choroby w Polsce.

Materiał i metoda. Badanie objęło 436 pacjentów z SM (M – 171, K – 265), którzy urodzili się w latach 1918-1995 i zmarli w 2007 r. w Polsce. Dane o miesiącu urodzenia, płci, rozpoznaniu i miejscu ostatniego zamieszkania uzyskano z GUS. Miesięczne rozmieszczenie urodzeń w zarejestrowanej kohorcie SM porównano z miesięcznym rozmieszczeniem urodzeń oczekiwanych chorych z zebranej grupy SM i z populacji ogólnej. Analizę przeprowadzono testem chi kwadrat oraz dokładnym testem wg Fishera.

Wyniki. Największą liczbę urodzeń w obserwowanej kohorcie SM stwierdzono w kwietniu w porównaniu z liczbą urodzeń w grupie oczekiwanych chorych na SM (59 vs. 36.3; p=0.001) lub do oczekiwanych chorych w populacji generalnej (59 vs. 40.2; p=0.003). Miesięczne rozmieszczenie obserwowanych urodzeń różniło się od tego u ocze-

kiwanych chorych na SM (p=0.008), lecz nie od rozmieszczenia urodzeń osób z SM w populacji ogólnej (p=0.223). Wskaźnik urodzeń kwiecień/listopad był istotnie podwyższony; p=001. Sezonowe rozmieszczenie urodzeń w SM znamiennie różniło się wśród kobiet (p=0.019), lecz nie wśród mężczyzn (p=0.476). Większa liczba województw była zamieszkana przez chorych na SM urodzonych w kwietniu niż przez urodzonych w listopadzie (p=0.037 pośród M, p=0.026 pośród K).

W n i o s k i . Wyższe ryzyko SM kojarzyło się z urodzeniem w kwietniu. Różnica w sezonowym rozmieszczeniu urodzeń chorych ze SM wskazuje na asocjację kobiet urodzonych wiosną z rozwojem choroby.

Key words: multiple sclerosis, month of birth, gender, residence

Słowa kluczowe: stwardnienie rozsiane, miesiąc urodzenia, płeć, miejsce zamieszkania

INTRODUCTION

Growing evidence proves that climate, infection, chemo-physical factors, imbalance of T helper cells and dendritic cells as well as HLA and non-HLA genes shape susceptibility to multiple sclerosis (MS), [1, 2, 3]. Recent reports have shown that more MS patients were born in spring and fewer in autumn [4, 8]. Spring born children with insufficient exposure to sunlight may have less T regulatory cells, greater activity of T 17 cell subset and predisposition to autoimmune reactions [9, 10]. Autumn born children show possibly greater subset of T regulatory cells, balanced T_H1: T_H2 cell ratio and are less prone to autoimmune reactions [9, 10]. Therefore current studies have been focused on association between spring birth and MS onset, frequency of relapses, early clinical progression and the number of active brain lesions [4, 5, 11, 12, 13]. Distortion of birth distribution in MS was clearly divergent in different countries [14, 15, 16]. These conflicting results are apparently due to latitude, environmental factors, ethnic origin of patients, unequal samples and different methods of analysis [4, 14].

The aim of this study is to find out if birth distribution in MS is related particularly to a month, a season or to a gender and a place of the last residence in Poland. Present investigation on seasonality of birth may shed additional light on aetiology of the disease.

MATERIAL AND METHOD

The study included 436 MS patients who were born between the years of 1918–1995 and died in Poland in the year 2007. All demographic data concerning MS group and the general population derived from the Central Statistical Office in Warsaw. The diagnosis of MS was ascertained on death certificates issued by neurologists and other physicians. Death certificates of people with MS were registered under ICD code G35 (2007). Mean age of 171 MS males at the time of death was 55.8 years and of 265 MS females it was 56.4 years. Although place of birth and place of MS onset was not available, it is most likely that entire cohort of patients was born within boundaries of Poland (1918–1995) and acquired the disease above northern latitude of 49^{o}N. Birth distribution of MS people was assessed according to a month, a season, a gender and a place of the last residence in the year 2007. A monthly woman to men birth ratio was calculated and monthly values of the ratio were compared. The numbers of residential and non-residential provinces for MS people born in the selected spring month and one autumn month were analysed. Monthly birth distribution in the observed MS cohort was controlled in twofold way. Firstly, monthly birth variation in MS group was compared to the expected monthly birth values. Secondly, monthly birth distribution of observed MS people was compared to the monthly birth variation of expected MS assemblage in the general population born in the year 1960. The comparison was carried out as if the observed MS birth pattern came from that in the general population. Statistical analysis was performed using chi square test and exact Fisher's test.

RESULTS

The greatest number of people with MS was born in April (59, CI 45.8–74.6) and the smallest - in November or September (28, CI 18.7–39.7). Percentages of born in these months were 13.5 and 6.4. The number of the observed births in April was significantly higher as compared to the number of expected April births (59 vs. 36.3); p=0.001. The cohort of observed MS patients born in April was also significantly higher in comparison to the number of the expected April born MS people in the general population (59 vs. 40.2); p=0.003.

Table 1 shows that in the analysed birth pattern peak of MS patients occurred in April (59/436), whereas nadir appeared in November or September

Table 1. *Monthly number of observed and expected birth in multiple sclerosis cohort and monthly number of observed live birth in the general population in Poland. All MS patients died in the year 2007*

Tabela 1. *Miesięczna liczba obserwowanych i oczekiwanych urodzeń w kohorcie stwardnienia rozsianego (SR) oraz miesięczna liczba żywych urodzeń w populacji ogólnej w Polsce. Wszyscy chorzy na SR zmarli w 2007 roku*

Miesiąc urodzenia Month of birth	Liczba miesięcznych urodzeń w kohorcie stwardnienia rozsianego (1918-1995) The number of monthly birth in MS cohort (1918-1995)			Miesięczny wskaźnik liczby urodzeń kobiet do mężczyzn ze SR Monthly women to men birth ratio in MS	Średnia miesięczna liczba oczekiwanych urodzeń w kohorcie SR Mean monthly number of expected birth in MS cohort	Miesięczna liczba oczekiwanych urodzeń chorych na SR w populacji ogólnej (1960) Monthly number of expected MS birth in the general population (1960)	Miesięczna liczba żywych urodzeń w ogólnej populacji (1960) Monthly number of live birth in the general population (1960)
	ogółem total	mężczyźni men	kobiety women				
Jan	46	20	26	1.30	36.3	40.7	61 626
Feb	30	13	17	1.30	36.3	39.1	59 344
Mar	42	10	32	3.20	36.3	42.8	64 833
Apr	59	23	36	1.56	36.3	40.2	60 966
May	33	14	19	1.35	36.3	39.8	60 327
Jun	37	13	24	1.84	36.3	36.8	55 783
Jul	37	18	19	1.05	36.3	37.1	56 269
Aug	37	15	22	1.46	36.3	34.6	52 519
Sept	28	14	14	1.00	36.3	33.6	50 983
Oct	30	10	20	2.00	36.3	32.3	48 996
Nov	28	10	18	1.80	36.3	30.0	45 455
Dec	29	11	18	1.63	36.3	29.0	43 839
Ogółem Total	436	171	265	1.54	436	436	660 940*

* Liczba żywych urodzeń w 1960 roku nie zawiera 8544 osób zarejestrowanych po tym roku
* Live birth in the year 1960 do not include 8544 people registered after that year

(28/436). Monthly birth variation between the observed and expected MS people was significantly different; p=0.008. However, monthly observed birth distribution in MS cohort did not differ (with exception of April) from the expected MS birth distribution in the general population; p=0.223, figure 1.

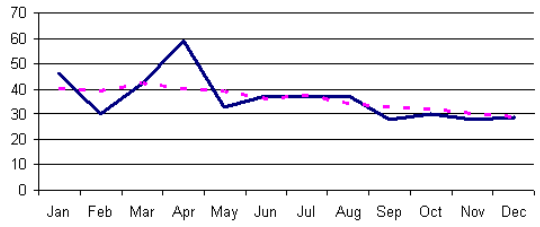

Fig. 1. *The number of monthly birth in observed multiple sclerosis patients (solid line) and the number of monthly birth in expected multiple sclerosis patients in the general population (dotted line). Birth data on 436 observed patients concern the years 1918-1995 and on expected patients the year 1960 in Poland*

Ryc. 1. *Liczba miesięcznych urodzeń obserwowanych chorych na stwardnienie rozsiane (linie ciągła) i liczba urodzeń oczekiwanych chorych na stwardnienie rozsiane w ogólnej populacji (linie kropkowana). Dane o urodzeniu 436 obserwowanych chorych dotyczą lat 1918-1995 i oczekiwanych chorych roku 1960 w Polsce*

As shown in fig. 1, important distortion of this distribution in MS was found in April. In particular, the April: November birth ratio (59:28) among MS patients significantly increased to 2.1:1.0; p=0.001. The ratio was also elevated in males (23:10; p=0.024) and in females (36:18; p=0.036). Generally, more MS people were born in spring them in autumn (134:86). Seasonal birth difference was also significant between the observed and expected MS groups; p=0.013. Data on seasonal birth are shown in tab. 2.

It is noteworthy that the spring: autumn birth ratio (observed 134/109 vs. expected 86/109) increased (p=0.001), but the spring: winter birth ratio (134/109 vs. 105/109) was not significantly raised (p=0.061); tab. 2.

The entire MS cohort was characterized by preponderance in women (ratio F/M 1.54). Female to male monthly birth ratio was atypically high in March (3.2) and very low in September (1.0); tab. 1. The question is whether seasonal birth distribution in females shows stronger association with MS development. Looking into seasonal birth frequency one may notice higher spring: autumn birth ratio among females (87:52) than among males (47:34). The ratio in the observed to expected women increased; p=0.033. Analogous ratio in the observed to the expected men decreased; p=0.149. The difference suggests that females were more susceptible to spring

Table 2. *Birth distribution of observed and expected multiple sclerosis patients according to season and gender. All patients died in the year 2007*

Tabela 2. *Rozmieszczenie urodzeń obserwowanych i oczekiwanych chorych na stwardnienie rozsiane (SR) według pory roku i płci. Wszyscy chorzy zmarli w 2007 roku*

Pora roku Season	Ogólna liczba urodzeń chorych na SR według pory roku Total number of seasonal birth in MS		Liczba sezonowych urodzeń chorych na SR według płci The number of seasonal birth in MS according to gender			
			mężczyźni		kobiety	
	obserwowani	oczekiwani	obserwowani	oczekiwani	obserwowane	oczekiwane
Zima Winter	105	109	44	42.75	61	66.25
Wiosna Spring	134	109	47	42.75	87	66.25
Lato Summer	111	109	46	42.75	65	66.25
Jesień Autumn	86	109	34	42.75	52	66.25
Ogółem Total	436	436	171	171	265	265

MS predisposing factors than males. These data are corroborated by the notable finding that seasonal birth distribution differed significantly in females (p=0.019), whereas distribution in males did not (p=0.476); tab. 2.

Monthly birth distribution in MS cohort was considered in relation to a place of the last residence. Monthly birth distribution in relation to residential province showed considerable variation (data not shown). The number of residential and non-residential provinces for April or November born MS people was presented in table 3.

As seen in tab. 3, the number of corresponding provinces for 54 MS women and for 28 MS men born in April or November were 1:15 and 7:9 or 4:12 and 10:6. In other words, there was the greater number of provinces in which April born MS people resided before death as compared to the smaller number of provinces inhabited by November born MS people; Fisher's exact test, p=0.025 for men and p=0.037 for women. The comparison suggests that April related environmental factors causing MS were more widely distributed than November related factors. The suggestion is valid only if the province of birth and early exposure are identical with the province of the last residence.

Table 3. *The number of residential and non-residential provinces for April or November born multiple sclerosis patients (the year 2007)*

Tabela 3. *Liczba zamieszkałych i niezamieszkałych województw przez urodzonych w kwietniu lub w listopadzie chorych na stwardnienie rozsiane (2007 rok)*

Liczba i płeć chorych The number and gender of patients	Chorzy urodzeni w kwietniu April born patients N = 59		Liczba i płeć chorych The number and gender of patients	Chorzy urodzeni w listopadzie November born patients N = 28	
	Liczba województw The number of provinces			Liczba województw The number of provinces	
	Niezamieszkałe województwa (2007 r.) Not inhabited provinces (yr. 2007)	Zamieszkałe województwa (2007 r.) Resided provinces (yr. 2007)		Nie zamieszkałe województwa (2007 r.) Not inhabited provinces (yr. 2007)	Zamieszkałe województwa (2007 r.) Resided provinces (yr. 2007)
N = 23 Mężczyźni Men	4	12	N = 10 Mężczyźni Men	10	6
N = 36 Kobiety Women	1	15	N = 18 Kobiety Women	7	9

DISCUSSION

The study of 436 MS people showed that the greatest proportion of patients was born in April (59/436); p=0.001. This result is corroborated by findings in Scandinavia, Canada and in other countries [4, 5, 6, 7, 8]. The association between birth season and MS concerned only affected people and not their siblings [8]. Monthly birth distribution of siblings in Sardinia showed almost reversed birth pattern with nadir in spring and excess in autumn [8]. No association between the month of birth and MS was found in the United States, Brazil, Israel and Canary Islands [14, 15, 16, 17]. The reason of this difference is unclear. Procreational and social habits of the parents in the USA must be taken into consideration. According to one of the hypothesis latitude below 40°N, longer solar radiation, climate, lifestyle and ethnic factors make south born Americans during springtime less susceptible to MS [18]. Lack of difference in monthly birth in Israelis, Brazilians and Spaniards from the Canary Islands may be due to relatively stable seasonal ultraviolet radiation B (UVB) and less fluctuating vitamin D serum concentration [15, 16]. South born

people enjoy also warmer air temperature which does not facilitate winter herpes simplex or parainfluenza viral infection. In addition, Brazilians less often carry allele HLA DRB1*15, which increases susceptibility to the disease [19]. The effect of this allele may be masked by sufficient vitamin D level and lower latitude [20].

April born people in Poland or May born people in northern countries might be exposed in prenatal period to insufficient solar radiation [18]. Diminished winter UVB radiation results in vitamin D deficiency and immune dysregulation [3, 21]. Spring born people show imbalance of T_H1:T_H2 cells, production of proinflammatory cytokines (IFN-gamma, IL-2, IL-17), maturation of dendritic cells presenting antigen and inhibition of T regulatory cell function [9, 18]. April born MS people are exposed also to other MS predisposing, environmental factors. Children and adolescents may be at risk of Epstein-Barr virus or herpesvirus type 6 infections [2, 16, 25]. They are not only exposed to pollens in springtime, but also to passive smoking at parental less ventilated homes [8, 22]. Smoking can be particularly dangerous if combined with anti-EBNA-1 antibodies and the presence of HLA DRB1*15 allele [23].

Fewer MS people were born in November in Scandinavia, Canada and Poland [4, 5]. However, the proportion of November born in Poland was not significantly lower (p=0.223). November births appear to have slightly protective effect against MS development. Autumn thinner layer of ozone absorbing UVB radiation can be taken into account [24]. Longer solar radiation in prenatal summer has possibly beneficial effect. There is no peak of infection with paramyxoviruses (measles, mumps) or pollen allergic reactions in November. Autumn newborns might instead have latent cytomegalovirus infection which significantly reduces MS risk (odds ratio 0.27), [25]. Nevertheless, children born in autumn are still exposed to highly prevalent EBV infection [8, 26].

Seasonal birth distribution in MS differs more among women than among men. The spring: autumn birth ratio was significantly higher in females (86:52; 1.65), but not in males (47:34; 1.38). This fact argues for greater sensitivity of women to insufficient UVB radiation, lower vitamin D level and to seasonal infections [3, 21].

Birth places of the Polish MS cohort were not examined in this study. Instead, present investigation of geographic distribution of the last residence concerning either April or November born people showed marked difference. The greater number of provinces was resided by April born than by November born MS people (for males p=0.037, for females p=0.025). One should notice that none of the April born MS women resided in southeastern province (Podkarpackie). This region is characterized by lowest latitude and longest December solar radiation in the country [24].

April births of MS people in Poland are associated with increased risk of the disease. It is not vet known whether seasonality is associated with maternal gestation, birth month, childhood, adult life or with each of these periods. It is also unclear whether spring birth related factors exert their action only during a month, season, year or a decade. Putative action of MS predisposing factors extends for March to June [27]. The association between spring birth and the disease does not reveal the magnitude of the effect. Factors might occur in winter, spring, throughout the year with peak in April or during couple of years. Adult blood donors had decreasing vitamin D level and increasing IgG antibody titer against EBV virus in preclinical latent phase of MS for lat least 2 years [8]. One can speculate upon the sequence of exposures to aetiological agents. Spring birth related deficiency in vitamin D level, late childhood paramyxovirus infection (after age of 5) and EBV virus infection (before age of 17) trigger slowly developing autoimmune response [2, 29]. Among these factors season related environmental events exert relatively small, but significant effect on pathophysiology of the disease.

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Received: 9.01.2012
Accepted for publication: 10.07.2012