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Title

Month of birth in multiple sclerosis with and without longitudinally extensive spinal cord lesions: A study of a Japanese national survey

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Key Words

Multiple sclerosis; Month of birth; Longitudinally extensive spinal cord lesions; Environmental factors; Cohort study; Prevalence

Abstract

Objectives: Month of birth has been associated with the environmental factors for multiple sclerosis (MS). This study aimed to investigate whether individuals with MS had significantly different frequencies of birth in a particular month of the year, and whether month-of-birth patterns were influenced by the longitudinally extensive spinal cord lesions (LESCL) status relative to the general population in the same Japanese birth cohort.

Methods: In this study, performed as a part of the fourth Japanese nationwide survey of MS, patients were divided into two groups according to the presence (n = 307) or absence (n = 906) of LESCLs that were diagnosed on the basis of magnetic resonance imaging findings. The number of births in every month was counted for both groups. Control data were obtained from birth records of the Japanese general population of the median years of birth of each group. Differences in the month-of-birth distributions between the patients and the general population were assessed using the chi-square test.

Results: In MS patients without LESCLs, significantly more patients were born in January and June, whereas significantly fewer patients were born in May, compared to the general population. The seasonal patterns of birth were not in association with those of ambient ultraviolet (UV) radiation. No significant differences were found for the month-of-birth distributions between MS patients with LESCLs and the general population.

Conclusions: A different distribution of month of birth in Japanese MS patients without LESCLs from the general population, but not in those with LESCLs, suggests some role for environmental factors in the pathogenesis of the former group. Environmental factors other than UV radiation should be further elucidated in Japanese and other Asian MS cohorts.

Introduction

It is widely believed that multiple sclerosis (MS) results from the interplay between environmental and genetic factors. (1) Strong evidence connects environmental factors such as latitude of birthplace, Epstein-Barr virus (EBV) exposure, smoking, and vitamin D deficiency with MS. (2-10) The investigation of seasonal birth patterns is one of the classic epidemiological approaches to seek the early-life environmental influences on disease process and to suggest seasonally-variable risk factors. (11) Seasonal birth patterns in MS, epilepsy, and amyotrophic lateral sclerosis patients vary from the general population. (11-22) Previous studies, primarily from northern/western countries, suggest that birth in spring and summer is associated with a subsequent occurrence of MS. (11-19) A study of seasonal birth patterns for a certain disease in areas with different seasonality can potentially add new information about environmental factors associated with that disease. Japan is generally a rainy country with high humidity, has four distinct seasons and the marked rainy season, and has a variety of climates because of its wide range of latitude stretching from 24° to 46°N. The temperature fluctuates between extremes, ranging from freezing in the winter to sweltering in the summer.

Compared with MS patients in Europe, MS patients in Japan are characterized by more frequent involvement of the spinal cord and binocular optic nerve, leading to severe visual impairment at disease onset; however, the cerebellum is less frequently involved. (23) After the

discovery of anti-aquaporin 4 antibodies in 2004, these manifestations were often shown to be associated with neuromyelitis optica (NMO), characterized by severe optic neuritis, and longitudinally extensive spinal cord lesions (LESCLs) extending over three or more vertebral segments. (24, 25)

To investigate the role of environmental factors in Asian MS patients whose clinical manifestations differ from those of Western MS patients, we evaluated whether the month-of-birth effects found in Western MS patients could be also found in Japanese MS patients, with special emphasis on the presence or absence of LESCLs.

Methods

Survey procedures

This study was performed as part of the fourth nationwide survey of Japanese MS, which was conducted by the Research Committees of Neuroimmunological Diseases and of Epidemiology of Intractable Diseases, sponsored by the Ministry of Health, Labour and Welfare, Japan. The study was approved by the Kyushu University Ethics Committee. The general findings of the survey have been reported previously. (26, 27) In brief, the survey was undertaken in the following two steps: first, a preliminary survey was undertaken to ascertain the approximate

number of MS patients in Japan and second, a survey was conducted using a questionnaire sheet for each patient. The hospitals randomly selected from the directory of all of the registered hospitals throughout Japan were included in the study. The study also included all university hospitals, in which council members of the Japanese Society of Neurology and members of the Committees of Medical Facilities for Children and the Japanese Society of Child Neurology practiced. In January 2004, a preliminary survey questionnaire for MS patients who visited hospitals because of MS from 1 January 2003 to 31 December 2003 was mailed to 6708 departments together with the diagnostic criteria. A second questionnaire was forwarded to those institutions who reported patients during the first survey. The second survey requested detailed clinical information on individual patients, including age at onset and examination, sex, birthplace, present address, symptoms based on history and signs based on physical examination, laboratory findings, course, treatment and prognosis. Patients who were reported by more than one hospital or department were treated as duplicates, and when discordance occurred between data sources, the earliest data of the patient were used. The patients were divided into two groups according to the presence or absence of LESCLs on the basis of magnetic resonance imaging (MRI) findings, to ascertain whether individuals with MS had significantly different frequencies of birth in the months of the year relative to the general population in the same birth cohort and whether this differed according to the LESCLs status. The two groups were further

subdivided on the basis of sex and birthplace location (i.e. north or south) relative to the approximate midpoint (37°N) of the mainland. (27) The number of birth in every month was counted about each patient group.

Control data of the Japanese general population were obtained from the national vital statistics of the Japanese government agencies available from 1972 to 1997. (28) The total number of births and their annual monthly distribution corresponding to the median year of birth in each group served as the control data.

Diagnostic criteria

The diagnostic criteria for MS in the present survey were as follows: [1] symptoms and signs owing to multifocal inflammatory lesions in the CNS (dissemination in space); [2] remissions and exacerbations (dissemination in time); and [3] other diseases such as acute disseminated encephalomyelitis were excluded. (26) Although the diagnostic criteria were originally adopted for clinically definite MS, they were also applicable in patients with NMO. At the time of the survey in 2004, we were unable to measure anti-aquaporin 4 antibodies or exclude patients with NMO.

MRI finding-based classification

In the present study, patients were divided into subgroups according to the presence or absence of LESCLs on the basis of MRI findings-based classification as previously described. (13, 26) LESCLs were defined as those extending over three or more vertebral segments in MRIs performed during the entire clinical course.

Statistical analysis

We examined the null hypothesis that the monthly birth rate in each patient group did not differ from that in the Japanese general population. The chi-square test (Microsoft Excel 2010, Microsoft Japan, Tokyo) was used and the significance level was set at $p = 0.05$.

Results

Data for birth year and birth month were available for 1,213 MS patients born between 1927 and 1997. The median year of birth of the group of patients without LESCLs was 1964, whereas that of the group of patients with LESCLs was 1957. The total number of births in Japan and the annual birth month distribution are shown in Table 1.

Relative to the general population, patients without LESCLs ($n = 906$) showed a significantly increased frequency of birth in January and June and decreased frequency of birth in May (Table 2). In addition, patients without LESCLs had a statistically insignificant trend

towards a lower birth rate tendency in October (autumn) and higher birth rate in August (summer). In contrast, no difference in month-of-birth distribution was found between MS patients with LESCLs (n = 307) and the general population (Table 3).

In patients without LESCLs (250 males and 656 females), male patients were significantly more frequently born in June (Table 4), whereas females patients were more frequently born in January and less frequently in May (Table 5), compared with the general population. Birthplace information was obtained for 711 patients without LESCLs (306 northern born and 405 southern born). Compared with the general population, a significant more number of northern-born patients were born in January and fewer in November (Table 6), whereas fewer southern-born patients were born in May (Table 7).

Discussion

The present study of Japanese MS patients has identified a significantly different month-of-birth pattern in MS patients without LESCLs, but not in those with LESCLs, compared with the general population. To the best of our knowledge, this is the first study to demonstrate a difference in the month-of-birth pattern for persons with MS without LESCLs from the general population, suggesting some role for environmental factors in this group.

In our study, MS patients without LESCLs were born more frequently in January and less frequently in May, compared with the general population. Japan is at a lower latitude than European countries and the seasonal solar radiation widely varies; solar ultraviolet (UV) radiation is the lowest in January and a long spell of fine weather lasts in May with the maximum global solar radiation. (29)

Varying seasonal maternal epidermal exposure to solar UV radiation and subsequent synthesis of the hormonally active metabolite 1,25-dihydroxyvitamin D during gestation is one of the theorized pathways of the month of birth to cause MS. (6, 10, 30) Previous studies in Europe and Australia have demonstrated that early gestation during winter months and birth during summer months are associated with an increased frequency of subsequent MS, whereas early gestation during summer months and birth during winter months are associated with a decreased frequency of subsequent MS. (11-19) However, data of the present study are in conflict with those reported in previous studies. In addition, the monthly birth distribution pattern in the present study differs from a sinusoidal pattern that is known to be in agreement with seasonal UV changes. (19) Although our data reflect a similar tendency of increased birth frequency of MS patients without LESCLs in June and August and decreased birth frequency in October, and also in November in northern-born patients, our data suggest a need to consider other kind of environmental factors.

Considering the inconsistent direction of effect and absence of a particular seasonal effect identified by previous studies in this area, the possible role of the type 1 error to explain our findings cannot be dismissed. One limitation of the current study is the possible inclusion of NMO cases in the cohort. Unlike MS, no UV effect for NMO has been identified in the literature; therefore inclusion of these cases may have obscured any possible month-of-birth effect.

In conclusion, the present study finds some evidence for a month-of-birth effect for MS patients without LESCLs in Japan; however the pattern of month-of-birth in this group was not explicable by a seasonal UV pattern as found in previous studies. Further research is required to elucidate whether a role exists for environmental factors in the aetiology of MS in Asian populations.

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Table 1. Total number of births in Japan and its monthly distribution in 1964 and 1957

	Reference population for LESCLs (-) group	Reference population for LESCLs (+) group
Month	All births in 1964 (n=1,716,761)	All births in 1957 (n=1,566,713)
Jan	162,209	173,807
Feb	144,454	140,230
Mar	148,384	141,302
Apr	147,115	135,916
May	137,133	123,946
Jun	129,003	115,280
Jul	142,853	125,564
Aug	142,802	126,730
Sep	141,225	119,002
Oct	139,839	118,866
Nov	134,631	120,378
Dec	147,113	125,692

Table 2. LESCLs (-) patients (n = 906). Observed and expected births in each month

Month of birth	Estimated month of conception	Observed births	Expected births	Ratio, Observed/Expected	Chi-square test, p
Jan	Apr	104	86	1.21	0.038
Feb	May	74	76	0.97	0.78
Mar	Jun	82	78	1.05	0.66
Apr	Jul	75	78	0.96	0.74
May	Aug	55	72	0.76	0.033
Jun	Sep	86	68	1.26	0.024
Jul	Oct	69	75	0.92	0.43
Aug	Nov	89	75	1.19	0.10
Sep	Dec	72	75	0.96	0.74
Oct	Jan	59	74	0.80	0.07
Nov	Feb	61	71	0.86	0.21
Dec	Mar	80	78	1.03	0.78

Table 3. LESCLs (+) patients (n = 307). Observed and expected births in each month

Month of birth	Estimated month of conception	Observed births	Expected births	Ratio, Observed/Expected	Chi-square test, p
Jan	Apr	36	34	1.06	0.72
Feb	May	26	27	0.96	0.77
Mar	Jun	25	28	0.89	0.58
Apr	Jul	23	27	0.85	0.45
May	Aug	21	24	0.88	0.49
Jun	Sep	19	23	0.83	0.42
Jul	Oct	24	25	0.96	0.89
Aug	Nov	29	25	1.16	0.38
Sep	Dec	29	23	1.26	0.21
Oct	Jan	24	23	1.04	0.87
Nov	Feb	21	24	0.88	0.57
Dec	Mar	25	25	1.00	0.94

Table 4. LESCLs (-) males (n = 250). Observed and expected births in each month

Month of birth	Estimated month of conception	Observed births	Expected births	Ratio, Observed/Expected	Chi-square test, p
Jan	Apr	25	24	1.04	0.77
Feb	May	15	21	0.71	0.16
Mar	Jun	13	22	0.59	0.05
Apr	Jul	20	21	0.95	0.75
May	Aug	23	20	1.15	0.48
Jun	Sep	29	19	1.53	0.014
Jul	Oct	19	21	0.90	0.67
Aug	Nov	23	21	1.10	0.61
Sep	Dec	23	21	1.10	0.58
Oct	Jan	17	20	0.85	0.44
Nov	Feb	19	20	0.95	0.87
Dec	Mar	24	21	1.14	0.55

Table 5. LESCLs (-) females (n = 656). Observed and expected births in each month

Month of birth	Estimated month of conception	Observed births	Expected births	Ratio, Observed/Expected	Chi-square test, p
Jan	Apr	79	62	1.27	0.023
Feb	May	58	55	1.05	0.69
Mar	Jun	69	57	1.21	0.08
Apr	Jul	56	56	1.00	0.97
May	Aug	32	52	0.62	0.003
Jun	Sep	57	49	1.16	0.25
Jul	Oct	50	55	0.91	0.51
Aug	Nov	66	55	1.20	0.10
Sep	Dec	49	54	0.91	0.48
Oct	Jan	42	53	0.79	0.10
Nov	Feb	42	51	0.82	0.17
Dec	Mar	56	56	1.00	0.97

Table 6. LESCLs (-) northern-born patients (n = 306). Observed and expected births in each month

Month of birth	Estimated month of conception	Observed births	Expected births	Ratio, Observed/Expected	Chi-square test, p
Jan	Apr	42	29	1.45	0.011
Feb	May	26	26	1.00	0.96
Mar	Jun	25	26	0.96	0.77
Apr	Jul	30	26	1.15	0.43
May	Aug	18	24	0.75	0.17
Jun	Sep	26	23	1.13	0.51
Jul	Oct	26	25	1.04	0.90
Aug	Nov	26	25	1.04	0.90
Sep	Dec	30	25	1.20	0.31
Oct	Jan	16	25	0.64	0.06
Nov	Feb	13	24	0.54	0.019
Dec	Mar	28	26	1.08	0.71

Table 7. LESCLs (-) southern-born patients (n = 405). Observed and expected births in each month

Month of birth	Estimated month of conception	Observed births	Expected births	Ratio, Observed/Expected	Chi-square test, p
Jan	Apr	40	38	1.05	0.76
Feb	May	33	34	0.97	0.84
Mar	Jun	41	35	1.17	0.28
Apr	Jul	30	35	0.86	0.40
May	Aug	21	32	0.66	0.038
Jun	Sep	37	30	1.23	0.21
Jul	Oct	32	34	0.94	0.75
Aug	Nov	42	34	1.24	0.13
Sep	Dec	33	33	1.00	0.95
Oct	Jan	28	33	0.85	0.36
Nov	Feb	31	32	0.97	0.88
Dec	Mar	37	35	1.06	0.68