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Is season of birth associated with multiple sclerosis?

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Objective – To compare the monthly distribution of multiple sclerosis (MS) patients' births with that of the Sicilian population. *Background* – Studies on the association between season of birth and risk of MS are scanty and controversial. *Design and methods* – Archives of the Institute of Neuropsychiatry of the Universities of Palermo and Catania were searched up to 1995 for definite MS patients (McDonald & Halliday criteria). The monthly distribution of MS patients' births ($N=965$) was compared with that of the Sicilian population ($N=5{,}608{,}307$). *Results* – The distribution of births among MS patients compared with the general population was not different when tested by the χ^2 statistic ($P>0.25$). The Hewitt's non-parametric test for seasonality showed an excess of births between June and November among MS patients ($P=0.004$). *Conclusion* – A different pattern of MS patients' births is observed in Sicily and in Northern countries.

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Many reports on the influence of the month of birth on human development (1, 2) and on disease risk have been published (3–5). The prevalence of the season of birth on the risk of schizophrenia (6–8) and of amyotrophic lateral sclerosis (9) has been reported.

Concerning multiple sclerosis (MS), two studies, one conducted in Denmark by Templer et al. (10), and one in Canada by Sadovnick & Yee (11), investigated the monthly distribution of births among MS patients. The results of these two studies were conflicting. The Danish study found a statistically significant difference in seasonal pattern of births among MS patients whereas the Canadian study was unable to find any significant seasonal difference. Recently, James (12) critically reanalysed these two studies, and, using a different statistical approach, suggested a similar seasonal pattern in both populations.

The Danish and Canadian studies were performed in countries with comparable latitude, meteorological, and ecological features. Data from the Mediterranean area, a region with different climatic features, should be of interest. For this reason, we designed a study aimed to investigate the month of birth of MS patients' in Sicily, Italy.

Materials and methods

Subjects affected by MS were identified by searching the archives of the neurological departments of the Universities of Palermo and Catania. Clinical records were available from the 1950s. In order to classify patients born and diagnosed in a wide range of years and consequently with different diagnostic approaches, we used McDonald & Halliday (13) criteria to identify all cases. Only definite cases born in Sicily between 1900 and 1982, and diagnosed with MS not later than 1995 were included. Data on the monthly distribution of births in Sicily for the general population were obtained from the Monthly Statistical Bulletin of the ISTAT, the Italian Statistical Bureau (14). Complete information was available since 1927. The study population was compared with people born in Sicily from 1927 to 1995 ($N=5{,}608{,}307$).

Seasonality was assessed using the χ^2 test and the Hewitt's test. The latter is a non-parametric alternative to the Edwards' test for seasonality, considered by many authors to be more appropriate for sinusoidal patterns as monthly births usually are (15–17). Briefly, estimates of relative incidence were calculated for each month and ranked from 1 to 12 according to magnitude. Then, the 6-month segment, which yields the highest value of rank-sum, was identified. Finally, the statistical significance of the maximum value of rank-sum was determined by a table of cumulative probability (15). In other words, the Hewitt's test compares all possible consecutive 6-month segments moving from 1 month to the next.

Results

We ascertained 965 definite MS patients fulfilling the diagnostic criteria, born between 1900 and 1982, and diagnosed not later than 1995 as having MS.

The monthly distribution of MS births among the Sicilian population and the expected number based on the general population pattern of monthly births are summarized in Table 1.

The distribution of births of the whole sample compared with the general population ($N = 5{,}608{,}307$), analyzed by χ^2 test, did not show any statistically significant difference ($P > 0.25$). However, the grouping of data into the 4 seasons and the calculation of a χ^2 value with 3 degrees of freedom would be suggestive of a seasonal effect ($\chi^2 = 7.36$, $P = 0.06$). Finally, the analysis of the seasonal aggregation by Hewitt's non-parametric test showed that in Sicily an excess of births of MS patients occurred between June and November ($P = 0.004$) (Fig. 1, Table 2).

Table 1. Monthly distribution of MS births in Sicily

Month	Multiple sclerosis (1900–1982) Observed	Multiple sclerosis (1900–1982) Expected	Sicilian population (1927–1995)
January	96	95.9	557542
February	80	81.3	472483
March	75	87.2	506638
April	67	77.2	448527
May	73	77.1	448079
June	84	73.8	428840
July	85	77.8	452057
August	91	78.6	456886
September	88	83.4	484938
October	86	80.8	469797
November	75	77.9	452883
December	65	73.9	429637
Total	965		5608307

$\chi^2 = 9.08$, d.f. = 11, $P > 0.25$.

Table 2. Analysis by Hewitt's non parametric test of MS births in Sicily

A. Determination of ranks Month	Relative Incidence × 100,000	Rank
January	17.2	7
February	16.9	6
March	14.8	1
April	14.9	2
May	16.3	4
June	19.6	11
July	18.8	10
August	19.9	12
September	18.1	8
October	18.3	9
November	16.6	5
December	15.1	3

B. Hewitt's test Six month segments	Rank-sum	*P*
January to June	31	> 0.5
July to December	47	0.120
February to July	34	> 0.5
August to January	44	0.242
March to August	40	0.469
September to February	38	> 0.5
April to September	47	0.120
October to March	31	> 0.5
May to October	54	0.008
November to April	24	> 0.5
June to November	55	0.004
December to May	23	> 0.5

Discussion

To assert that a given event has a seasonal pattern of occurrence is hazardous even when supported by statistics. Which statistic is to be preferred for the analysis of seasonal conditions is debatable. The χ^2 test seems insensitive to variations of moderate amplitude, particularly when the sample size is not large and when changes in disease frequency or in denominators could occur (15–17). Parametric and non-parametric tests designed for the analysis of seasonal events would be more appropriate to study these phenomena (15–19). The present study is

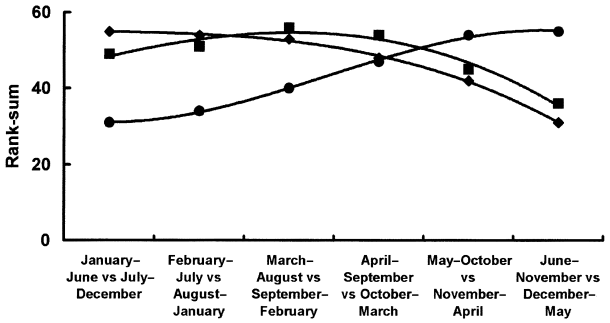

Fig. 1. Comparison of monthly distribution of MS patients' birth, according to Hewitt's non-parametric test, in Sicily (current study) (•), Denmark (■) and Canada (◆).

characteristic in showing how different statistical approaches may lead to different results.

Our findings suggest that in Sicily, an excess in births of MS patients occurred in summer, with a peak in August. Two studies, one conducted in Denmark (10) and the other in Canada (11), published on this topic reached conflicting results. The Danish study indicated a higher risk of developing MS among people born in springtime. The Canadian study was unable to find any statistically significant seasonal pattern. Both investigations used the same statistical analysis (i.e. the χ^2 test). James (12) critically analyzed the data of both studies by using a test specifically designed for seasonal events: the Hewitt's non-parametric test (15). By applying this test, both the Danish and the Canadian data reached a statistically significant association between season of birth and MS (12). Moreover, the season at risk (spring with a peak around May) was the same for both the Danish and the Canadian MS patients (Fig. 1).

Results differing according to the statistics used may suggest that association between season of birth and risk of MS may simply be a statistical artifact. Assuming that the results of the present and previous studies are true, then spring and summer could be respectively the season at risk for Northern and Southern regions of the western hemisphere. However, the association between MS and season of birth is more likely to be a spurious association.

Finding a biological plausibility for seasonal associations is a more challenging task. Templer et al. (10) suggested that infection's patterns at birth could provide a rationale for the association. This interpretation was criticized by Sadovnick & Yee (11); moreover a search recently performed to analyze whether infectious events around the time of birth could be relevant for MS failed to find any association (20). Other studies performed both in animal models (21, 22) and in humans (1) observed an association between environmental variables related to seasons (day length and temperature) and some aspects of the differentiation of the immune system. However, current knowledge of the aetiology of MS is so meager that it is hazardous to offer hypotheses.

Additional efforts to provide a rationale for seasonal associations with risk of MS are warranted.

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