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Season of birth and multiple sclerosis in Tunisia

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ABSTRACT

Background: Recent studies on date of birth of multiple sclerosis (MS) patients showed an association between month of birth and the risk of developing MS. This association has not been investigated in an African country.
Objective: We aimed to determine if the risk of MS is associated with month of birth in Tunisia.
Methods: Data concerning date of birth for MS patients in Tunisia ($n=1912$) was obtained. Birth rates of MS patients were compared with all births in Tunisia matched by year of birth ($n=11{,}615{,}912$). We used a chi-squared analysis and the Hewitt's non-parametric test for seasonality.
Results: The distribution of births among MS patients compared with the control population was not different when tested by the chi-squared test. The Hewitt's test for seasonality showed an excess of births between May and October among MS patients ($p=0.03$). The peak of Births of MS patients in Tunisia was in July and the nadir in December.
Conclusion: Our data does support the seasonality hypothesis of month of birth as risk factor for MS in Tunisia. Low vitamin D levels during pregnancy could be a possible explanation that needs further investigation.

1. Introduction

An association between month of birth and the risk of later developing a disease that affects the central nervous system has been reported for many diseases. These include schizophrenia, brain tumors, amyotrophic lateral sclerosis (ALS), epilepsy and multiple sclerosis (MS) (Brenner et al., 2004; Torrey et al., 2000). Several studies of MS patients have suggested a birth excess in spring or late summer (Salemi et al., 2000; Bayes et al., 2010; Becker et al., 2013) and a significant nadir in November and December (Torkildsen et al., 2012). These findings of seasonal birth patterns in MS patients that differ significantly from the general population suggest that environmental factors acting in early life or in the intrauterine period are important for disease susceptibility (Ramagopalan et al., 2010).

This issue, however, had not been confirmed in other studies (Salemi et al., 2000; Sadovnick and Yee, 1994) and has not been researched in African countries. Data from the North African area, a region with different climatic features and a closer location to equator, should be of interest. We thus aimed to elucidate the relationship between season of birth and risk of MS in the Tunisian population.

2. Materials and methods

2.1. Patients and general population

Data on month of birth and sex of patients with MS were collected from the register of the Tunisian National Health Insurance Fund (NHIF). We obtained all cases of definite MS registered in the NHIF. Only patients having health insurance are included in the register. Seventy percent of the Tunisian population is eligible for NHIF. MS is considered as a long-term illness with 100% health insurance coverage. The NHIF register included all insured MS patients in Tunisia. Patients were identified by searching the keyword “multiple sclerosis” in the register. Included patients in the study have an MS diagnosis according to the McDonald criteria (2001) or the modified McDonald criteria (2005 and 2010); or according to the Poser criteria (1983), for those patients who were only monitored up till the year 2000. The study was approved by the NHIF scientific committee. We used the anonymized registry data, therefore, ethical approval of the study was neither required nor was it solicited.

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Data on the monthly distribution of births in Tunisia for the control population were obtained from the National Institute of Statistics (NIS). The control population was matched to the year of birth of the included MS population. Complete information was available since 1948.

2.2. Statistical analysis

The data were analyzed using SPSS software for Windows (version 18.0). Seasonality was assessed using the chi-squared test and the Hewitt's test (Hewitt et al., 1971). We analyzed the month-specific risk of MS compared with the other 11 months, in terms of odds ratios (ORs) and 95% confidence intervals (CI) using the 2×2 chi-squared test as reported by Salzer et al. (2010). The Hewitt's test 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 (Marrero, 1981; Walter, 1982). In brief, estimates of relative incidence were calculated for each month and ranked from 1 to 12 according to magnitude (12=highest; 1=smallest). Then all possible sequences of six consecutive months were examined. Finally, the statistical significance of the maximum value of rank-sum was determined by a table of cumulative probability (Hewitt et al., 1971). Hence, the Hewitt's test compares all possible consecutive 6-month segments moving from one month to the next. Differences were considered significant at $p < 0.05$.

3. Results

We collected 1912 MS patients from the NHIF Register born between 1948 and 2008. The sex was known in 1732 patients. There were 545 males and 1187 females (ratio 1:2.18). The monthly distribution of MS births among the Tunisian population and the expected number based on the control population pattern of monthly births are summarized in Table 1. The distribution of births of MS patients compared with the control population (n=11,615,912), analyzed by chi-squared test, did not show any statistically significant difference. There were no significant differences between the sexes after correction for multiple analyses.

The analysis of the seasonal aggregation by Hewitt's non-parametric test showed that in Tunisia an excess of births of MS patients occurred between May and October (p=0.03). More (9.4%) cases with MS than expected were born in May–October as compared with November–April. The peak of Births of MS patients in Tunisia was in July and the nadir in December (Fig. 1).

Table 1
Observed number of cases of multiple sclerosis in Tunisia compared with expected number, according to month of birth.

Month	Control population 1948–2008 (n=11,615,912)	Observed no. of cases (n=1912)	Expected no. of cases	OR (95% CI)	p
January	1095721	173	180	1.04 (0.83–1.30)	0.69
February	977989	150	161	1.08 (0.85–1.36)	0.51
March	1023838	166	169	1.02 (0.81–1.27)	0.86
April	977369	170	161	0.94 (0.75–1.18)	0.6
May	1031490	178	170	0.95 (0.76–1.18)	0.65
June	970767	167	160	0.95 (0.76–1.19)	0.68
July	969816	180	160	0.87 (0.7–1.09)	0.25
August	983936	154	162	1.05 (0.83–1.33)	0.63
September	925970	155	152	0.97 (0.77–1.23)	0.85
October	904032	164	148	0.90 (0.70–1.12)	0.34
November	862441	133	142	1.07 (0.84–1.37)	0.57
December	892543	122	147	1.22 (0.95–1.56)	0.11

4. Discussion

This study suggests that in Tunisia, an excess in births of MS patients occurred in May–October, with a peak in July. These findings were significant using the Hewitt's test, but not the chi-squared test. Parametric and non-parametric tests designed for the analysis of seasonal events would be more appropriate to study these phenomena than the chi-squared test. The latter is insensitive to variations of moderate amplitude, particularly when the sample size is small and when disease frequency could change (Salemi et al., 2000; Rogerson, 1996).

Studies on season of birth in the Northern hemisphere have frequently reported an increased risk of MS in patients born in spring and summer and a decrease in MS births in autumn and winter months (Torkildsen et al., 2012; Templer et al., 1992; Sotgiu et al., 2006; Fernandes de Abreu et al., 2009; Dobson et al., 2013; Grytten et al., 2013). A pooled analysis in the largest study, based on datasets from Canada, Great Britain, Denmark and Sweden (n=42,045) showed an excess of MS among people born in May and a relative deficit among those born in November (Willer et al., 2005). In the Southern hemisphere, a reverse pattern was detected, with an excess in November–December and a decrease in May–June (Staples et al., 2010). This particular seasonal pattern could be explained by a protective effect of vitamin D and suggest a possible relation between decreased maternal exposure to sunlight, causing diminished vitamin D production, and an increased risk for MS in children born during the spring (Fernandes de Abreu et al., 2011; Fragoso et al., 2012).

Yet, some studies in non-European populations reported that month of birth interference with the development of MS is not consistent worldwide (Sadovnick and Yee, 1994; Givon et al., 2012; Barros et al., 2013). Interestingly, James WH (James, 1995) critically reviewed two studies published on this topic with conflicting results: one conducted in Denmark (Templer et al., 1992) and the other in Canada (Sadovnick and Yee, 1994). Using the same statistical analysis (chi-squared test), the Danish study reported a higher risk of developing MS among people born in springtime. The Canadian study was unable to find any statistically significant seasonal pattern. The author analyzed the data of both studies by using a test specifically designed for seasonal events: the Hewitt's non-parametric test. By applying this test, both the Danish and the Canadian data reached a statistically significant association between births in spring and MS. We found quite similar results in this study.

The significant month of birth effect on MS risk was criticized by Fiddes et al. (2013) for being false positive due to an inadequate control of confounding specifically by year and place of birth. Conversely, a limitation of the aforementioned study is that the researchers did not analyse data from the original studies that highlighted the month of birth effect in MS. Instead, they performed a separate study on national unweighted births statistics, thereby showing potential sources of bias in such studies (Hintzen, 2013).

In addition, one of the well-performed studies on seasonal birth patterns in MS, which was conducted in Australia, did correct not only for sex, but also for the confounders: region of birth and year of birth (Staples et al., 2010). This study showed a significant month of birth effect in MS risk. Also, in another study conducted in the small geographical area of Sardinia, where all cases and controls were by definition matched for the same latitude, a month of birth effect was again observed (Willer et al., 2005). In our study we used a control population matched by year of birth. We could not correct for the region of birth, but Tunisia has a relatively small latitudinal extent.

Disparate results due to the statistics used could suggest that association between MS and season of birth is more likely to be a