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PART III

Other aspects of narcolepsy





Month of birth is not a risk factor for narcolepsy with cataplexy in the Netherlands

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ABSTRACT

The month of birth has been proposed as a risk factor for narcolepsy, suggesting a harmful influence during early development. Several authors have described an excess of births in March in those developing narcolepsy later. Analysis methods in published studies varied, but no study corrected completely for possible changes in seasonal birth pattern over time in the appropriate population. The present study describes changes in seasonal birth pattern of the entire Dutch population over a 79-year span and compared the monthly birth pattern of Dutch narcoleptics with the population data. Month and year of birth were noted for 307 patients with non-familial narcolepsy with cataplexy, born in the Netherlands between 1923 and 2001. The numbers of live births per month and per year from the entire Dutch population for the same period were used to calculate a virtual data set of expected births per month with exactly the number of cataplexy cases, but with the birth pattern of the Dutch population. Observed and expected numbers per month were compared using the chi-square test. In the 1970s the peak of births shifted from spring to autumn, confirming the need to correct for changing seasonal patterns. There was no significant difference between observed and expected birth numbers per month. An effect of birth month on the occurrence of narcolepsy with cataplexy was not found in a study of 307 cases after adjusting for changing birth patterns in the general population.

INTRODUCTION

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness, cataplexy and nocturnal sleep disturbances.¹⁰² Narcolepsy with cataplexy is associated strongly with a loss of hypocretin-producing neurones in the hypothalamus.⁴⁷ The exact aetiology of this cell loss is unknown.²⁴² The strong association of narcolepsy with cataplexy with several human leucocyte antigen (HLA) subtypes suggested that autoimmune processes play a role in the pathogenesis of narcolepsy.²⁴³ However, searches for evidence to support the autoimmune hypothesis, for instance the detection of autoantibodies or inoculation with immunoglobulins, have failed.^{242;244} The recent discovery of circulating anti-Tribbles homologue 2 (TRIB2) antibodies reactive with hypocretin neurones strongly supports the autoimmune nature of narcolepsy.⁵⁹ Another approach to demonstrate autoimmune involvement involves studying the distribution of births over the months of the year. For some disorders with a presumed autoimmune origin (multiple sclerosis, type I diabetes and inflammatory bowel disease), seasonal birth patterns were found to differ from those of the population as a whole.^{245;246} The underlying concept is that exposure to various environmental factors such as viruses may vary during the course of the year. An exposure in early life may later set events in motion leading to the development of a specific disease. Several studies have addressed seasonal birth patterns in narcolepsy.^{170;247-251} A relative abundance from March to June as well as a relative paucity in September has been described in a study of 555 German cases.²⁴⁸ A similar pattern was also described for 886 cases, from French, Canadian and Californian sources combined.²⁴⁹ This type of study is not without potential problems. First, birth data from the narcolepsy population under study should ideally be compared with an appropriate control population, as the putative environmental risk factors might depend upon the geographical origin of the populations, as well as on cultural habits or racial susceptibility. Secondly, seasonal birth patterns in a population may well differ over time under the influence of factors such as changes in contraceptive use or in cultural attitudes towards procreation, as these may affect a priori chances of risk exposure. Hence, any comparison should correct for changes in birth patterns over years or decades. None of the above-mentioned studies corrected completely for both sources of potential error. In the present study we first investigated if and how the distribution of births over the year changed between 1923 and 2001 in the entire population of the Netherlands. Then, we compared the birth pattern of Dutch narcoleptic patients with that of the entire Dutch population, taking account of changes in birth pattern over time in the general population.

METHODS

Patient data

Data from 337 Dutch narcolepsy patients with cataplexy were available from The Leiden University Medical Centre narcolepsy database. Diagnostic criteria were those of the International Classification of Sleep Disorders.¹¹⁸ Thirty cases were excluded to improve the homogeneity of the study group; reasons for exclusion were being born outside the Netherlands ($n = 9$), atypical cataplexy ($n = 10$) and familial cases ($n = 8$). Three cases, born before 1923, were excluded because complete birth data were not available for the Dutch population prior to that year.

Statistical analysis

The month and year of birth were noted for 307 (146 men) patients with narcolepsy with typical cataplexy, born 1923–2001. The number of live births for each month in the period 1923–2001 was obtained from The Dutch Central Bureau of Statistics (Voorburg, The Netherlands). We first assessed whether the distribution of births over the months of the year changed during the 79 years of study.

To do so, the numbers of births per month in any given year were divided by the total number of births of that year, resulting in a series of 12 fractions of that year's births. The fractions were then plotted as a function of month and year, allowing any changes to be visualized. The second step of analysis concerned the comparison of birth distribution of narcoleptics with that of the population. Two tables were formed containing the absolute number of births by month and by year; one table concerned narcoleptics, the other the Dutch population. The narcolepsy table was used to add the number of births per month, resulting in 12 totals for January–December: this was the observed monthly birth distribution for the narcolepsy group. The same table was also used to calculate the number of births of narcoleptics for each of the 79 years. Both tables were used to arrive at the expected monthly birth distribution for narcoleptics, as follows. For each year, the population table was used to calculate which fraction of that year's births occurred in each of the 12 months. These 12 fractions were multiplied by the number of births of narcoleptics of that year, resulting in 12 virtual birth numbers. In this way, the number of births per year was the same in the virtual group as in the narcolepsy group, but their distribution over the months was exactly that of the general population. Adding the calculated virtual birth numbers over all 79 years for each month

resulted in 12 numbers: expected monthly birth distribution. The observed and expected monthly birth distributions were compared with the chi-square test. This technique was also used to study seasonal patterns instead of months, by pooling data from three consecutive months, starting with winter (January–March), analogous to the approach taken by other authors.²⁴⁸ Finally, odds ratios were calculated per month, comparing the number of births in the particular month to the pooled number of births in the other 11 months, with the expected number of births as reference category.

RESULTS

A total of 16 699 889 live births were recorded in the 79 years of study in the Netherlands. The monthly distribution of these births did not remain stable over the years: during the 1970s the birth peak shifted from spring to autumn (Figure 8.1). The figure also shows a profound disruption for the period during World War II, which in the Netherlands lasted from May 1940–May 1945. The observed monthly birth distribution of the narcolepsy with cataplexy group did not differ significantly from the expected monthly birth distribution ($\chi^2 = 8.350$, $df = 11$, $P = 0.681$; Figure 8.2). This also held for the secondary analyses when births were grouped per season ($\chi^2 = 1.229$, $df = 3$, $P = 0.745$). None of the calculated odds ratios per month differed significantly from one.

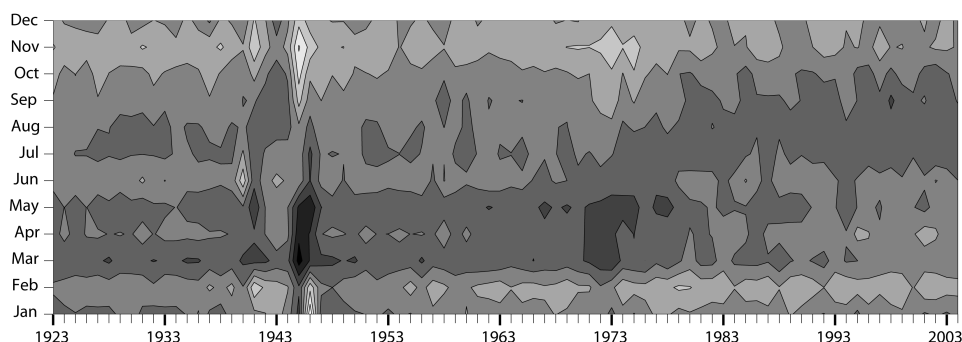


Figure 8.1 Distribution of births in the Netherlands 1923–2003. The number of births per year and month were calculated on a yearly basis to obtain the fractions of each year's births per month. The resulting table of 79 years x 12 months were used to calculate a filled contour plot, in which the range of fraction (0–1) was divided into bands of similar colour. Darker colours indicate higher fractions of births. Note the shift of birth peak from spring to autumn during the 1970s and the abrupt upheavals in birth pattern during World War II (1940–1945) (note also that the statistical analysis concerned the years 1923–2001).

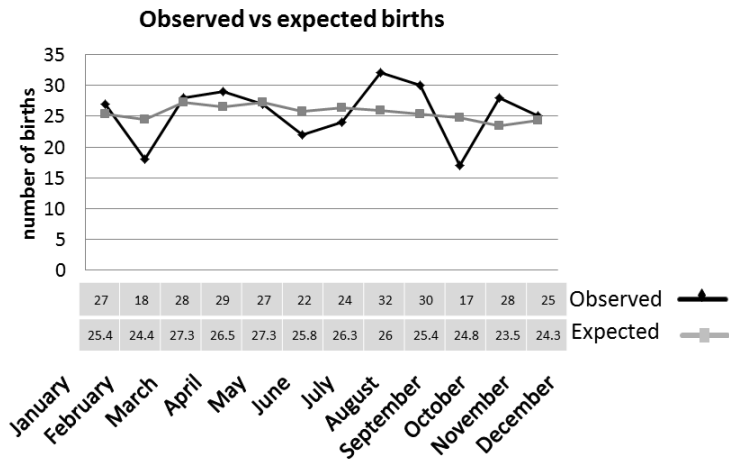


Figure 8.2 Observed versus expected births by month. The total number of births for each month over 79 years are shown for the narcolepsy group and the calculated expected number, matched for birth year. See the text for an explanation. The distributions did not differ significantly ($P = 0.94$).

DISCUSSION

This is the first study on birth month patterns in narcolepsy that takes geographical and temporal criteria fully into account. The method of analysis corrects for changes in birth patterns that occurred in the general population. Such corrections were necessary, as shown by the shift in peak from spring to autumn occurring in the 1970s, and by the marked changes occurring during the World War II. The descriptive nature of the study means that the causes of the change in the 1970s cannot be identified, even though social changes and changes in methods of contraception may have contributed.

No effect of birth month on the occurrence of narcolepsy was observed, in contrast to some earlier reports. Some authors reported a significantly different seasonality of birth month compared to that of the general population,²⁴⁸⁻²⁵¹ whereas others mentioned a predilection for births in March without stating statistical significance.^{170,247} It is possible that correction factors explain the discrepancy, but this remains uncertain.

A limitation of this study is the relatively small size of the patient group. Despite this, the method used in this study has advantages over those used in previous studies. Compared to previous studies in this field, the ascertainment percentage of narcolepsy patients in our group is the highest. Furthermore, the study was performed on a very homogeneous group of narcolepsy patients. In addition, the Netherlands is a relatively small country with a high

population density and no pronounced climatic or other geographical differences between areas, providing even more uniform conditions. Finally, we suggest that the methods used in this study to correct for changing birth patterns may be used also to research birth month patterns for other diseases.

