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SCIENTIFIC INVESTIGATIONS

The month of birth has a seasonal effect in Chinese patients with narcolepsy and cataplexy

Jingjing Guo, PhD, MD[1]; Liyue Xu, MD[1]; Jingyu Wang, PhD, MD[1]; Chenyang Li, PhD[2]; Chi Zhang, MPH[1]; Xiaosong Dong, MD[1]; Yuhua Zuo, BS[1]; Yongfei Wen, MD[1]; Fulong Xiao, MD[1]; Karen Spruyt, PhD[3]; Fang Han, MD[1]

[1]*Sleep Medicine Center, Department of Respiratory and Critical Care Medicine, Peking University People's Hospital, Beijing, China;* [2]*Peking University School of Nursing, Beijing, China;* [3]*University Claude Bernard Lyon 1, Lyon, France*

Study Objectives: We assessed the yearly seasonal, environmental effects on birth pattern in Chinese patients later diagnosed with narcolepsy and cataplexy and explored if this effect persisted in patients with symptoms onset date before, following, and after the 2009 H1N1 pandemic.

Methods: A total of 1,942 patients with birth data information and diagnosed narcolepsy with cataplexy were included in this study. The birth month and seasonal effect of 1,064 patients born from 1970 to 2000 were compared to controls (n = 2,028,714) from the general population. Furthermore, birth season effect in 1,373 patients with definite disease onset month were compared among patients with onset date before (n = 595), following (from January 2010 to December 2010) (n = 325), and after (n = 453) the H1N1 pandemic.

Results: Patients with narcolepsy and cataplexy had a significantly different seasonality from the general population (P = .027). The monthly distribution of birth month yielded a peak in November (odds ratio = 1.23 [95% confidence interval, 1.01–1.49], P = .042) and a trough in April (odds ratio = 0.68 [95% confidence interval, 0.52–0.88], P = .004). No significant difference was observed in the birth month across patients with symptom onset dates before, following, and after the 2009 H1N1 pandemic (P = .603).

Conclusions: This finding across many years of seasonal effect in Chinese narcolepsy cataplexy supports a role for early-life environmental influences on disease development.

Keywords: autoimmune, narcolepsy, seasonality

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Seasonality as indicated by birth month could be a clue for the role of early-life and potential environmental factors in narcolepsy with cataplexy .

Study Impact: Seasonal effect of birth month in a well-defined large Chinese cohort with narcolepsy and cataplexy was revealed, with a peak in November (winter) and a trough in April (spring), which are different from that reported in White cohorts. This pattern was not influenced by the 2009 H1N1 pandemic, a time point for a spike of new onset disease. The differences in birth month peak-and-trough here from prior Western cohorts could represent a gene-by-environment interaction.

INTRODUCTION

Narcolepsy is characterized by excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis, and nocturnal sleep disturbances.[1] Patients with type 1 narcolepsy (NT1) had low or undetectable concentrations of hypocretin-1 in the cerebrospinal fluid (CSF), which was caused by the destruction of the hypocretin (orexin)-producing neurons in the lateral hypothalamus,[2] indicative of both genetic and environmental factors.[3] Genetic studies have shown association of NT1 with human leukocyte antigen (HLA)-DQB1*0602 and other immunological genes.[3,4] Environmental factors like upper airway infection may trigger the immunological process, destroying hypocretin neurons in NT1.[5,6] There was a remarkable increase in narcolepsy cases following 2009 H1N1 Influenza A pandemic (pH1N1), associated with H1N1 vaccine in Northern Europe,[7] and with virus infections in nonvaccinated people in China,[8] respectively. Narcolepsy incidence variations across populations therefore represent both genetic and environmental influences.

Another potential way to assess the role of early-life environmental factors is to look at the effect of birth season, as early developmental programming prepares offspring for the environmental challenges they may face. Season of birth is known to play a pathogenic role in development of autoimmune disorders[9,10] and is a factor found in sleep timing[11,12] and susceptibility to insomnia in the UK Biobank cohort.[13] While seasonal birth patterns seemed to have no effect on narcolepsy onset in the White people,[14–17] 1 study conducted in South China reported peak of January births in a group of 54 patients with narcolepsy.[18] This small sample size in a relatively rare disease, together with potential heterogeneity of the sample indicated that this issue needs to be further addressed. Furthermore, as

H1N1 virus infection was found to be a strong trigger for narcolepsy, at least in Chinese,[8,19] there is the opportunity to determine if a birth month effect could be found in patients following the 2009 H1N1 pandemic.

This report utilizes a national network providing data on a well-defined large Chinese cohort with narcolepsy with cataplexy to assess correlation of birth month distribution to the subsequent diagnosis and, because of the length of time in this reporting, evaluate whether birth pattern is different among patients with disease onset date before, following, and after the 2009 H1N1 pandemic.

METHODS

Patients

A total of 1,942 patients with narcolepsy and cataplexy with known birthdate and diagnosed from August 1998 to August 2018 at Peking University People's Hospital's sleep center were recruited in the study. The patients (1,064) born between 1970 and 2000 were used for analysis of birth month distribution. A total of 1,373 patients had definite onset month information that was included to compare the birth pattern before, following, and post H1N1 pandemic. The onset month was calculated as the earlier date of either cataplexy or sleepiness.[8] According to the period of the H1N1 pandemic, patients were divided into 3 groups: 595 participants with onset date before December 2009, 325 between January 2010 and December 2010, and 453 after January 2011.

All the patients had typical cataplexy with irrepressible sleepiness for more than 3 months associated with cataplexy and abnormal Multiple Sleep Latency Test (mean sleep latency ≤8 minutes and more than 2 sleep onset rapid eye movement periods) according to standard techniques. They met the diagnosis of narcolepsy with cataplexy according to the *International Classification of Sleep Disorders*, second edition,[20] and were regrouped following *International Classification of Sleep Disorders*, third edition.[21] Diagnostic criteria for NT1 were defined either by measured hypocretin deficiency in the CSF (CSF hypocretin-1 <110 pg/mL, n = 140) or the presence of clear cataplexy and HLA-DQB1*06:02 (if CSF hypocretin-1 measurements were unavailable). It was considered that more than 96% of patients may have hypocretin deficiency, ie, NT1.[22–24] The details of our narcolepsy database were reported in a previous study.[8]

For adults, consent was obtained for all participants. For children, the child gave written assent, and parents consented for inclusion into this study. The local institutional review boards and Peking University People's Hospital approved the observational study.

General population

The number of live births at each month of the general population between January 1970 and December 2000 were obtained from Population Census Data, Beijing, China (n = 2,028,714, men 51.4%).

Statistical analysis

Summary statistics are presented using means and standard deviations for continuous data and frequencies and percentages for categorical data.

First, to understand the birth month distribution of narcolepsy in China, 878 patients born before 1970 or after 2000 were excluded. Chi-square analysis was performed to compare the observed number of births of narcolepsy with cataplexy (n = 1,064) to the number of births of the general population in each month between 1970 and 2000. Results were expressed as odds ratios and their 95% confidence interval (95% CI). The odds ratio with 95% CI was then defined as follows: for each month, we compared the observed number of births of patients to the population against 1 of the 11 other months. We also pool data into 4 seasonal periods delineated by groups of months (Winter: November, December, January; Spring: February, March, April; Summer: May, June, July; and Autumn: August, September, October).[18] Data were analyzed by χ^2. Also, the effect of sex on the birth month distribution in patients with narcolepsy and cataplexy was evaluated using χ^2.

Next, to understand whether the months of birth differ among patients with onset date (n = 1,373) before, following, and after H1N1 pandemic, we used χ^2 analysis to compare the observed number of patients born at each month among 3 groups (before, following, or after 2009 H1N1 pandemic). Patient onset following the 2009 H1N1 pandemic was defined as onset just following 2009 H1N1 (from January 2010 to December 2010),[23] whose onset may have been affected by the 2009 H1N1 pandemic.

All statistical analyses were performed with SPSS 25.0 for windows (SPSS Inc, Chicago, IL). Statistical significance was set at a P value < .05.

RESULTS

Demographics

The demographics of all patients (n = 1,942, 86.9% children) are shown in **Table 1**. On average, participants were young (17.5 ± 12.8 years), with an onset age 12.1 ± 9.3 years with more males (67.7%). A majority of the patients (98.8%) had positive DQB1*0602. See details for demographics of patient subgroup (born during 1970 to 2000 [n = 1,064] or with onset month information [n = 1,373] in **Table 1**.

A subsample of 1,373 patients with disease onset month information were divided into before (n = 595), following (n = 325), and after (n = 453) the 2009 H1N1 pandemic. No significant differences were observed in sex, ethnicity, and DQB1*0602 positivity percentage (see **Table 2**). The onset age was significantly younger in the group of patients with disease onset following the H1N1 pandemic due to a narrow time window (P < .001).

Monthly distribution of birth

The percentage of general population birth differ over the months (P = .02), with lowest birth percentage in May (7.6%) and highest birth percentage in January (9.15%).

The observed monthly distribution of birth in the patients with narcolepsy and cataplexy significantly differs from that in the general population (χ^2 = 21.6, df = 11, P = .027; see **Figure 1A**). November was the birth month in which the highest number of those diagnosed with narcolepsy and cataplexy were born compared with the general population (χ^2 = 4.2, df = 1, P = .042); the number born in April was significantly

Table 1—Demographic and clinical features of each data sample.

	All Patients (n = 1,942)	Patients Born During 1970–2000 (n = 1,064)	Patients With Onset Month Information (n = 1,373)	Birth Year Before 1970 or After 2000 (n = 878)	*P**
Age, y	17.5 ± 12.8	20.3 ± 9.2	13.9 ± 10.6	14.1 ± 15.4	<.001
Onset age, y	12.1 ± 9.3	13.1 ± 6.8	11.2 ± 9.3	10.9 ± 11.6	<.001
Male sex, %	67.7	68.5	67.4	66.7	.830
BMI, kg/m^2	23.1 ± 6.5	25.2 ± 5.0	22.8 ± 5.3	21.7 ± 5.2	<.001
Children (<18 y), %	86.9	84.9	90.0	89.4	<.001
Clinical presentation, %					
EDS	100	100	100	100	>.050
Cataplexy	100	100	100	100	.050
Sleep paralysis	34.7	47.0	28.4	19.7	<.001
Hallucination	47.3	52.2	47.2	41.5	<.001
MSLT					
SL, min	2.6 ± 2.0	3.0 ± 1.8	2.6 ± 1.7	2.5 ± 1.7	.042
SOREMPs	4.3 ± 0.9	4.1 ± 0.9	4.4 ± 0.8	4.3 ± 0.9	.051
SL ≤8 min and SOREMPs ≥2, %	100	100	100	100	>.050
Laboratory testing					
HLA-DQB1*0602+, %	98.8	98.7	99.0	97.3	.784
HCRT-1, pg/mL	23.0 ± 17.0	22.8 ± 15.6	21.2 ± 15.7	23.8 ± 20.5	.860
	(n = 140)	(n = 104)	(n = 64)	(n = 36)	
HCRT-1 <110 pg/mL, %	100	100	100	100	>.050

*Group comparison: *P* from analysis of variance or χ^2. BMI = body mass index, EDS = excessive daytime sleepiness, HCRT = hypocretin, HLA = human leukocyte antigen, MSLT = Multiple Sleep Latency Test, SL = sleep latency, SOREMP = sleep onset rapid eye movement period.

lower (χ^2 = 8.3, df = 1, *P* = .004). The maximal calculated odds ratio for the month of birth was 1.23 (95% CI, 1.01–1.49) was observed in November, and the minimal relative risk was in April (odds ratio = 0.68 [95% CI, 0.52–0.88], see **Figure 1A**).

Similar results were obtained in the secondary analyses of birth seasons (χ^2 = 12.2, df = 3, *P* = .007). When compared to the general population, excess winter birth (χ^2 = 4.9, df = 1, *P* = .027) and trough spring birth (χ^2 = 9.4, df = 1, *P* = .002; see **Figure 1B**) were observed. The risk of individuals born in Winter with a diagnosis of narcolepsy and cataplexy was 1.16 times (95% CI, 1.02–1.33) than the individuals born in other seasons (see **Figure 1B**). No significant difference in the birth month (*P* = .903) and birth season (*P* = .504) were observed between male and female patients.

Differences among patients with onset date before, following, and after H1N1 pandemic

The monthly distribution of birth months did not differ significantly between before, following, or after the H1N1 pandemic groups (χ^2 = 19.7, df = 22, *P* = .603; see **Figure 2**).

DISCUSSION

This study used a homogeneous cohort with narcolepsy and cataplexy to quantitate birth month patterns of patients in China. We observed significant seasonality of birth month with narcolepsy and cataplexy compared to birth months in the general population. The birth month number of people with narcolepsy and cataplexy was highest in November and the winter season and lowest in April and the spring season. Furthermore, the birth month of narcolepsy was not different among individuals with onset date before, following, and after the 2009 H1N1 pandemic.

It is well known that narcolepsy has ethnic differences, traditionally attributed to genetic variations.[24] Recent studies indicated environmental risk may also affect population incidence, for example, the H1N1 virus infection association with narcolepsy onset in Chinese[8,19] and the emphasis of H1N1 vaccine linked to narcolepsy in the White people in Europe. Prior streptococcal infection as a causal element is suspected by immunologic tests in the White race[5] but not in Chinese.[25] Three previous studies addressed unusual birth patterns in patients with narcolepsy from the Northern hemisphere.[14–16] Okun et al[14] first reported the birth peak in winter (January to March) and a trough in September in 484 narcolepsy patients from an international patient cohort. Dauvilliers et al[15] had similar findings in 886 patients with narcolepsy from North American and French; however, 377 patients from the United States were overlapped the previous study.[14] Dahmen et al[16] reported an excess of birth in Winter and Spring in 555 patients in an independent group of patients from Germany. In addition, season of

Table 2—Demographics and clinical features of 1,373 patient subgroups with symptom onset before, following, and after pH1N1.

	Onset Before H1N1 Pandemic (n = 595)	Onset Following H1N1 Pandemic (n = 325)	Onset After H1N1 Pandemic (n = 453)	*P**
Age, y	15.7 ± 10.7	11.0 ± 8.1	13.7 ± 11.7	<.001
Onset age, y	11.0 ± 8.0	9.6 ± 7.7	12.3 ± 11.6	<.001
Male sex, %	67.2	64.6	69.5	.351
BMI, kg/m^2	23.8 ± 5.3	21.9 ± 5.4	22.2 ± 4.7	<.001
Children (<18 y), %	89.9	93.5	87.6	.025
Clinical presentation, %				
EDS	100	100	100	>.050
Cataplexy	100	100	100	>.050
Sleep paralysis	33.3	23.4	25.8	.002
Hallucination	54.8	45.5	34.8	<.001
MSLT				
SL, min	2.9 ± 1.7	2.4 ± 1.4	2.3 ± 1.8	<.001
SOREMPs	4.4 ± 0.8	4.6 ± 0.7	4.3 ± 0.9	<.001
SL ≤ 8 min and SOREMPs ≥ 2, %	100	100	100	>.050
Laboratory testing				
HLA-DQB1*0602+, %	99.3	99.4	98.4	.290
HCRT-1, pg/mL	21.4 ± 16.3	13.9 ± 10.2	23.6 ± 15.5	.446
	(n = 44)	(n = 6)	(n = 14)	
HCRT-1 <110 pg/mL, %	100	100	100	>.050

*Group comparison: *P* from ANOVA or χ^2. BMI = body mass index, EDS = excessive daytime sleepiness, HCRT = hypocretin, HLA = human leukocyte antigen, MSLT = Multiple Sleep Latency Test, SL = sleep latency, SOREMP = sleep onset rapid eye movement period.

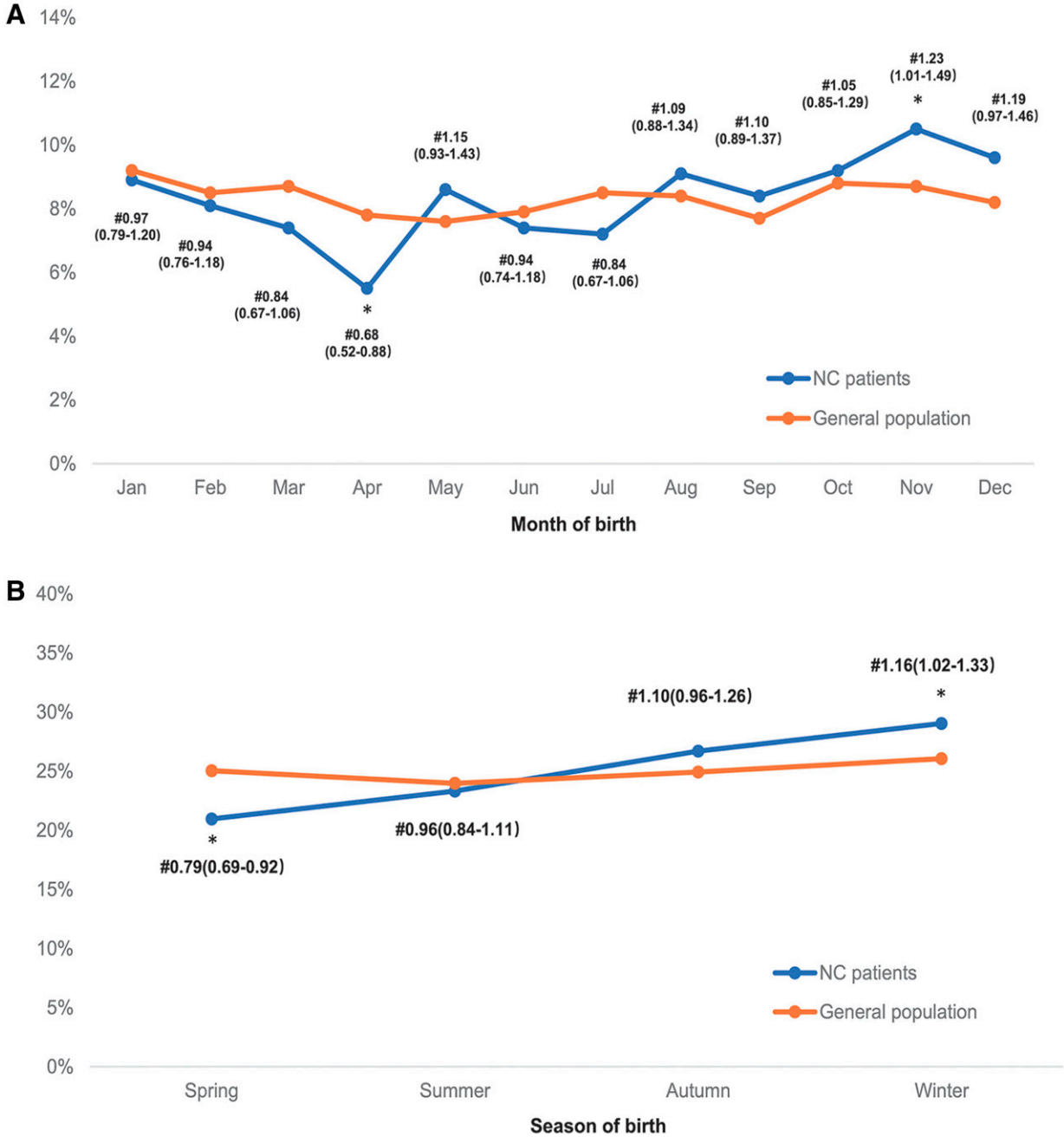
birth may influence both the likelihood of developing the disease and narcolepsy severity in a way independent of HLA-DQB1*0602 status.[17] A significant seasonality of birth effect on narcolepsy with cataplexy was observed in this large Chinese patient cohort, extending observations on a smaller South China cohort.[18] The data support an environmental effect on narcolepsy in Asians. A majority of our patients with narcolepsy were children (89%), extending the findings of previous studies in adults and a role for early-life influences. However, the birth month's exact peak in our study was different from previous reports providing data suggestive of a March peak and September fall-off in the White people from the United States, Canada, France, and Germany.[14–17] We showed that the peak of the birth in the current study was November (Winter) and the trough birth was April (Spring). A small sample study (n = 54) from South China reported a birth peak in January.[18] It seems that a consistent excessive number of people with narcolepsy born in winter was observed in the Chinese population.

The discrepancy of birth month peak and nadir between Chinese in the current study and data from White race reported in the previous studies might be explained by the different effects of climate, the temperature on various geographical areas, and the food nutritional supplements. Indeed, taking geographical and temporal criteria fully into account, one recent study yielded no effect of birth month on the occurrence of narcolepsy in the White people.[26]

Narcolepsy onset has a strong seasonality effect.[8] Interestingly, a comparison of patients to controls found out that Spring season has more frequent narcolepsy onset but less frequent birth and Winter season had the opposite change (see **Figure S1** in the supplemental material). Winter might be a favorable birth period for narcolepsy. There might be a seasonal programming as a compensatory mechanism, as indicated by the UK Biobank cohort analysis,[13] which reported that insomnia was more frequent in autumn-winter but autumn-winter season of birth was associated with less frequent insomnia. Other physiological parameters such as reaction speed, height, and basal metabolic rate had the similar changes.[13] These are supported by findings that seasonal programming may influence brain development, and structure of the superior temporal gyrus was associated with season of birth.[27] However, a biological interpretation of the relationship between birth and onset month in narcolepsy remains to be determined.

The H1N1 pandemic was reported as an important environmental factor for narcolepsy onset.[8,28,29] A similar birth seasonality among narcolepsy with disease onset following the 2009 H1N1 pandemic in comparison with before and after pandemic, indicated that the birth pattern maintained the same even facing the challenge of the stronger trigger. Other studies also found that patients with narcolepsy having disease onset following the 2009 H1N1 pandemic did not differ in regard to both clinical and polysomnographic presentations.[23,30] Thus, the finding of same birth pattern in the current study indicated again that

Figure 1—Birth month and season distribution of patients with narcolepsy cataplexy vs general population, both were born during 1970–2000.

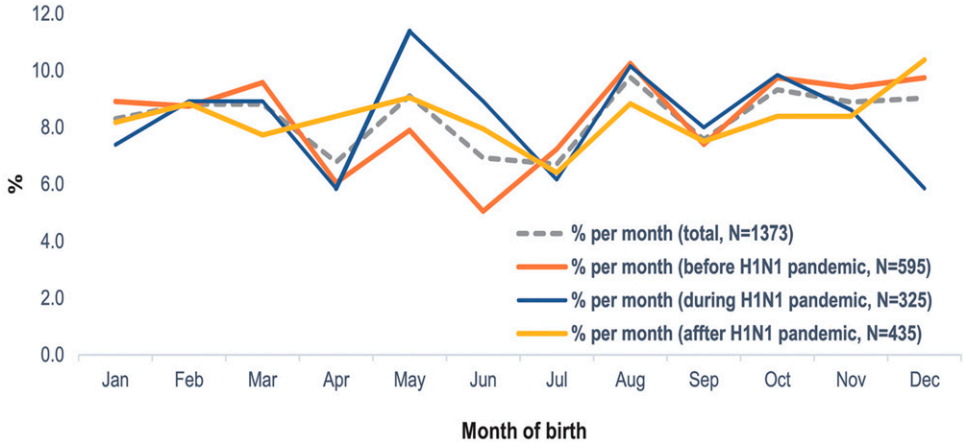


(A) Birth month. **(B)** Birth season. **P* value < .05 compared between the patients and general population. #Data presented as odds ratios with 95% confidence intervals. NC = narcolepsy cataplexy.

H1N1 infection might be an important trigger for narcolepsy. Although after the 2009 H1N1 pandemic, H1N1 occurred in the setting of common flu and the H1N1 vaccine, a recent study by the European Narcolepsy Network found another peak in 2013 in children/adolescent narcolepsy,[31] this increase in patients may not relate to H1N1 infection or H1N1 vaccine, which supports that there is a common trigger in addition to H1N1 virus that existed to mediate the occurrence of narcolepsy.

This study has certain limitations. In the current study, we selected a period of birth between year 1970 to 2000 for first analysis, as we were able to get population birth data during that period, to provide a control group. Around 878 cases born before 1970 or after 2000 were excluded for analysis, a larger patient sample would be better to interpret the findings, although the comparison between the excluded and the included patients had similarity in many aspects (**Table 1**). The birth

Figure 2—Distribution of birth month for patients with narcolepsy and cataplexy before, following, and after the 2009 pH1N1.



No significant differences were found between the patients before, following, or after the 2009 pH1N1 (P = .603).

patterns between year 1970 and 2000 may be affected by the 1-child policy in China. A significant birth rate variation in our population over the months may reflect this policy. However, numbers in both controls and patients were similar in direction in the same time window, which would minimize this influence. Only 10 patients were born during the year of 2010, which limited us to evaluate directly the effect of the 2009 H1N1 virus infection on the patients at the fetal or perinatal stage. Finally, the ascertainment of a disease was by medical testing, but in regard to symptoms there can be a recall bias on onset.[8] The latter would influence the period around the N1N1 pandemic; however, the continued strong association to birth month in the face of this extreme, sudden risk mitigates this concern.

In conclusion, we found an excess of births in November and a decrease of births in April in Chinese patients with narcolepsy and cataplexy, and this is not affected by the 2009 H1N1 pandemic. A different birth peak and trough across ethnic groups indicated that, in addition to genetic background, different environmental factors may also exist. Future studies are warranted to elucidate the interaction between environmental and genetic vulnerability factors in narcolepsy.

ABBREVIATIONS

CI, confidence interval
CSF, cerebrospinal fluid
HLA, human leucocyte antigen
NT1, type 1 narcolepsy

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Address correspondence to: Fang Han, MD, Sleep Medicine Center, Department of Respiratory and Critical Care Medicine, Peking University People's Hospital, Beijing, 100044, China; Email: hanfang1@hotmail.com

DISCLOSURE STATEMENT

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