

Narcolepsy Onset Is Seasonal and Increased following the 2009 H1N1 Pandemic in China

Fang Han, MD,¹ Ling Lin, MD, PhD,² Simon C. Warby, PhD,² Juliette Faraco, PhD,² Jing Li, BS,¹ Song X. Dong, MD,¹ Pei An, BS,¹ Long Zhao, BS,¹ Ling H. Wang, MD,¹ Qian Y. Li, MD,¹ Han Yan, MD,¹ Zhan C. Gao, MD,¹ Yuan Yuan, MD,¹ Kingman P. Strohl, MD,³ and Emmanuel Mignot, MD, PhD²

Objective: Narcolepsy is caused by the loss of hypocretin/orexin neurons in the hypothalamus, which is likely the result of an autoimmune process. Recently, concern has been raised over reports of narcolepsy in northern Europe following H1N1 vaccination.

Methods: The study is a retrospective analysis of narcolepsy onset in subjects diagnosed in Beijing, China (1998–2010). Self-reported month and year of onset were collected from 629 patients (86% children). Graphical presentation, autocorrelations, chi-square, and Fourier analysis were used to assess monthly variation in onset. Finally, 182 patients having developed narcolepsy after October 2009 were asked for vaccination history.

Results: The occurrence of narcolepsy onset was seasonal, significantly influenced by month and calendar year. Onset was least frequent in November and most frequent in April, with a 6.7-fold increase from trough to peak. Studying year-to-year variation, we found a 3-fold increase in narcolepsy onset following the 2009 H1N1 winter influenza pandemic. The increase is unlikely to be explained by increased vaccination, as only 8 of 142 (5.6%) patients recalled receiving an H1N1 vaccination. Cross-correlation indicated a significant 5- to 7-month delay between the seasonal peak in influenza/cold or H1N1 infections and peak in narcolepsy onset occurrences.

Interpretation: In China, narcolepsy onset is highly correlated with seasonal and annual patterns of upper airway infections, including H1N1 influenza. In 2010, the peak seasonal onset of narcolepsy was phase delayed by 6 months relative to winter H1N1 infections, and the correlation was independent of H1N1 vaccination in the majority of the sample.

ANN NEUROL 2011;00:000–000

Narcolepsy-cataplexy affects approximately 0.03% of the population in various countries and ethnic groups, including Asians.^{1–3} When cataplexy is present, the disorder is tightly associated with the human leukocyte antigen (HLA) DQA1*01:02/DQB1*06:02 haplotype and the loss of approximately 70,000 neurons in the brain producing the wake regulatory peptide hypocretin (orexin). Other genetic associations identified through recent genome-wide association studies include the T-cell receptor (TCR) alpha, and the P2RY11 receptor loci,^{4,5} supporting the notion that narcolepsy is an autoimmune disease affecting hypocretin

neurons. Despite numerous efforts, however, the definitive proof for autoimmunity, the presence of autoantibodies or T-cell responses directed toward hypocretin cell antigens, has been lacking. Recent studies found autoantibodies against the protein TRIB2, but this finding was replicated only in a subset of recent onset patients.^{6–9}

Interestingly, studies have also found evidence for recent *Streptococcus pyogenes* infections preceding the onset of narcolepsy in Caucasians, suggesting a role for upper airway infections in triggering narcolepsy.^{9–11} Furthermore, cases of narcolepsy/hypocretin deficiency have been reported

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.22587

Received Jun 3, 2011, and in revised form Jul 31, 2011. Accepted for publication Aug 2, 2011.

Address correspondence to Dr Han, Department of Pulmonary Medicine, Beijing University People's Hospital, Xi Chen Qu, Beijing 100044, China. E-mail: hanfang1@hotmail.com; or Dr Mignot, Stanford University Medical Center, Center for Narcolepsy, Stanford, CA 94304, E-mail: mignot@stanford.edu

From the ¹Department of Pulmonary Medicine, Beijing University People's Hospital, Beijing, China; ²Stanford Center for Sleep Sciences and Medicine, Palo Alto, CA; ³Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Case Western Reserve University and Cleveland Louis Stokes Veterans Administration Medical Center, Cleveland, OH.

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following H1N1 influenza vaccination or infections,^{9,12} although 69% of the 12 published post-H1N1 cases were positive for the antistreptolysin O (ASO) antibody, suggesting a role for past strep throat infections even in post-H1N1 cases. The World Health Organization (WHO) review of data from Finland's National Institute of Health and Welfare indicated a 9-fold increased risk of narcolepsy in children and adolescents aged 4 to 19 years following H1N1 vaccination with Pandemrix, a squalene/ α -tocopherol (AS03) adjuvanted H1N1 vaccine.¹² Available data on a few individuals suggest that the onset of narcolepsy occurred approximately 8 weeks following these vaccinations.⁹ More recently, the Swedish Medical Products Agency found that the relative risk of narcolepsy was 6.6 \times higher in vaccinated children and adolescents (aged 19 years and younger) compared to unvaccinated individuals.¹³

The diagnosis of narcolepsy in China has been increasing since the initiation of a Stanford-Beijing University research collaboration in 1998 to study the disorder and raise public awareness. Currently, the Chinese narcolepsy cohort consists of 906 well-characterized patients, most of whom were diagnosed as children. In this population, we found that the onset of narcolepsy occurs at an early age, and that development of symptoms is frequently abrupt.¹⁴ Using data collected in 629 patients with documented month of onset information, we examined seasonal fluctuations in narcolepsy onset and relationship with 2009 H1N1 infections.

Patients and Methods

Study Design

The study is a retrospective analysis of narcolepsy onset dates in subjects diagnosed from September 1998 to February 2011 at the People's Hospital, Beijing University, China. In the first analysis, the patient's self-reported month and year of onset of cataplexy and sleepiness (1996–2011) were determined independently by chart review by 2 of us (F.H. and L.H.W.). Year of onset of all symptoms was confirmed using the Stanford Sleep Inventory (SSI), a validated questionnaire focusing on narcolepsy symptoms, with results entered into a database. Discrepancies or absence of information in the chart were labeled as data missing. In a second analysis, we performed a brief scripted telephone interview with narcolepsy patients, asking for recent history of seasonal influenza or H1N1 vaccinations and other diseases (October 2009–present). We called 182 patients with known narcolepsy onset from October 2009 (the date of first H1N1 vaccination administered in China) to February 2010, and successfully interviewed 154 patients (85%).

Patients

The patient population was comprised of 906 subjects with narcolepsy/hypocretin deficiency, successively presenting over a period of \sim 11 years at People's Hospital, Beijing University,

Beijing. Ninety-seven percent of these subjects were seen by 1 of us (F.H.); most of these subjects are Han (97.0%) and come from the north of the country (89.8%; see also Supplementary Fig 1). Narcolepsy/hypocretin deficiency was defined either by measured hypocretin deficiency in the cerebrospinal fluid (CSF) or the presence of clear cataplexy and HLA-DQB1*06:02 (if CSF hypocretin-1 measurements were unavailable). Approximately 98% of patients with clear cataplexy and HLA-DQB1*06:02 are predicted to have CSF hypocretin deficiency.^{4,15} Evaluation procedures for this cohort included: nocturnal sleep recordings, Multiple Sleep Latency Tests (MSLTs), SSI assessments, CSF hypocretin-1 measurements, and DQB1*06:02 typing studies as described previously.¹⁴ In adults, consent was obtained for all subjects. For children, the child gave written assent and parents consented for inclusion into this study. The local institutional review boards of Beijing University and Stanford University approved the study. A subsample of 629 subjects was compiled for which disease onset (cataplexy, sleepiness) was documented to the exact month and year from January 1996 onward based on the clinical chart and the SSI. These cases were mostly children (69%), many of whom were prepubertal (60%) at evaluation. Data from 277 patients (31%) were not included due to missing information, discrepancies, or no recall. The 277 cases without this information were most often adults (89%) with a long diagnostic delay, probably partially explaining a poorer recall of the exact month of onset (see Supplementary Table for comparison of these samples). Older onset age remained significant in subjects without exact recall even when corrected for age, suggesting that recall is perhaps better in subjects with younger onset (see Supplementary Table). Other clinical differences, such as fewer MSLT sleep-onset rapid eye movement periods and increased sleep paralysis, disappeared when the 2 groups were controlled for age, as expected, as these occur in narcolepsy with increased age.^{14,16}

Control Data

Control data included statistics on monthly national births (1970–2000, $n = 2,028,714$, Population Census Data, Beijing, China), the number of total nocturnal sleep polysomnography studies occurring monthly at the People's Hospital, Beijing University, Beijing (2002–2009), and government statistics on influenza/cold and H1N1 influenza cases reported by China (entire country) to the Center for Disease Control in 2004–2010 (yearly for 2004–2010, monthly for 2009–2010, provided by Y.Y.).

Data and Statistical Analysis

Concordance of onset data was 95.6% between the 2 chart scorers; monthly and yearly occurrences were corrected for variation in days per month and for leap years. Data are reported as raw data, means \pm standard error of the mean, or percentages as appropriate. Analyses were performed using SYSTAT 10.0. Chi-square or t tests were used for 2-group comparisons (see eg Supplementary Table). Graphical analysis of the data included plotting time series, autocorrelation and partial autocorrelation plots, and Fourier analysis of adjusted monthly or yearly onset counts. To assess statistical significance of onset seasonality, we also calculated a multiway chi-square of

narcolepsy onset occurrences across 12 months against the null hypothesis (similar sample size equally distributed across 12 months) or against monthly polysomnography studies conducted in the same clinic. Our primary measure was month of disease onset, calculated as the earlier date of either cataplexy or sleepiness (Table); onset month of cataplexy or sleepiness individually were also studied with similar results. To reduce the possibility of recall bias for disease onset, a subanalysis of the same parameters was also performed in 403 patients diagnosed within 12 months of onset, and in 453 patients with onset prior to 2010 (thus excluding post-2009–2010 winter cases). Because of prior reports suggesting seasonal fluctuations in birth month of narcolepsy, the distribution of patient birth months was also examined versus expected and national birth counts (see Table). Finally, seasonal fluctuations of H1N1 and influenza/cold statistics were also compared against the null hypothesis. Reported p values were Bonferroni corrected for 15 comparisons.

To test whether occurrences of narcolepsy onset per year varied significantly across successive years (1996–2010), we conducted a 15-way chi-square against the null hypothesis (similar sample size equally distributed across 12 months). Additionally, autoregressive integrated moving average (ARIMA) models were used on the differenced annual 1996–2009 series (autoregression = 1, moving average = 1) to forecast 2010 occurrences with 95% confidence intervals (CIs). The forecasted 2010 number was then compared to the actual number of 2010 new onset cases recorded. Finally, cross-correlations between narcolepsy onsets versus H1N1 or influenza/cold counts were performed to study temporal relationships between these phenomena.

Results

Narcolepsy Onset Occurs Most Frequently in the Late Spring and Early Summer

In our sample, narcolepsy onset occurrences demonstrated a circannual cycle, as graphically depicted in the Figure. Seasonal variation was evident when onset was defined by the appearance of either sleepiness or cataplexy, a more objective symptom. It was also present in cases reporting onset within a year of diagnosis and in cases diagnosed prior to 2010 (see Table). Occurrences of onset were typically lowest in fall and winter months (shaded gray) and highest in spring and summer (see Fig. A; see also Supplementary Fig 2). Fourier analysis indicated a peak frequency of 0.08, which is consistent with an annual cycle in the onset data ($1/0.08 = 12$ months). Monthly means of occurrences in spring–summer versus fall–winter are depicted in panel B of the Figure. Onset was least frequent in November (0.9 ± 0.4 occurrences/month) and highest in April (6.0 ± 2.1). This is a 6.7-fold increase from trough to peak ($p < 0.01$). The Table reports 12-way chi-square values indicating strong statistical significance of monthly variation in all categories except for narcolepsy birth. Most notably, narcolepsy onset

occurrences were statistically different from expected distribution (null hypothesis) and from monthly polysomnography counts, a measure of sleep patient volume at the sleep clinic (comparison also shown in Supplementary Fig 2).

Although not nominally significant, we found weak evidence for more frequent narcolepsy births in the fall–early winter (Supplementary Fig 3; $p = 0.09$ without Bonferroni correction compared to national births). This is consistent with a recent report in Hong Kong Chinese patients,¹⁷ but opposite to findings reported in Europe and the United States.^{18,19} Seasonality of month of birth has been reported in various other autoimmune disorders, notably multiple sclerosis, another disease associated with the DRB1*15:01, DQB1*06:02 haplotype.²⁰

Narcolepsy Onset Increased Several-Fold following the 2009-2010 Winter Season

Yearly narcolepsy onset counts increased several-fold in 2010 following the H1N1 2009–2010 pandemic season (depicted with a blue dashed line in Fig. A, from data presented in the Table). A linear trend line for diagnosed cases was constructed using successive yearly counts from 1996–2009 (see Fig. C). The slope of the trend line is positive (occurrences = $3.06 \cdot [\text{years since 1996}] + 7.82$; $r^2 = 0.4812$, $p < 0.001$) and projects 53.77 new narcolepsy cases in 2010 in this population, based on the 1996–2009 data. The nonlinear best fit equation was $y = 7.2476 \times 0.6851^x$, with a projected number of 46.32 cases in 2010. Similarly, ARIMA modeling forecasts 47.42 diagnoses for 2010 (95% CI, 34.19–107.70). The observed 173 narcolepsy cases identified in 2010 are $3.2 \times$ greater than the linear forecast and 3.7 -fold greater than the ARIMA forecast ($p < 0.001$).

Correlations between Governmental Statistics on Monthly H1N1 and Influenza/Cold Occurrences in 2009 and 2010 and Narcolepsy Onset Occurrences during the Same Period

The sudden increase in narcolepsy onset occurred approximately 6 months after the H1N1 pandemic peak in China, based on governmental statistics (see Fig. A; Table). To examine this relationship, we used cross-correlation plots between cold/influenza occurrences, H1N1 occurrences, and narcolepsy occurrences in 2009–2010. Influenza/cold and H1N1 occurrences were highly and significantly cross-correlated without any time lag. In contrast, narcolepsy occurrences correlated significantly with both H1N1 and influenza/cold counts, with the highest correlation coefficient at lag times of 5 and 6 months, respectively (significant cross-correlation coefficients, $r^2 \sim 0.5$ – 0.6 , observed from 5–7 and 4–7 months delay, respectively).

TABLE: Month of Onset in Different Subdiagnostic Groups

Group	Month of Occurrence												Chi-Square ^a	Chi-Square ^{b,c}	p ^{a,b}	p ^{b,c}	
	January	February	March	April	May	June	July	August	September	October	November	December					Total Count
Disease onset 1996-2010, ^d No. (%)	25 (4.0)	45 (7.2)	68 (10.9)	90 (14.4)	77 (12.3)	67 (10.7)	85 (13.6)	56 (8.9)	56 (8.9)	32 (5.1)	10 (1.6)	15 (2.4)	629	91	1.9 × 10 ⁻¹³	128.7	5.8 × 10 ⁻²¹
Disease onset 1996-2009, ^d No. (%)	17 (3.8)	32 (7.1)	50 (11.0)	56 (12.4)	48 (10.6)	44 (9.7)	56 (12.4)	46 (10.2)	52 (11.5)	30 (6.6)	8 (1.8)	14 (3.1)	453	53.1	3.2 × 10 ⁻⁶	76.4	1.3 × 10 ⁻¹⁰
Disease onset 1998-2010, ^e No. (%)	17 (4.2)	29 (7.2)	49 (12.2)	68 (16.9)	55 (13.6)	52 (12.9)	55 (13.6)	30 (7.4)	22 (5.5)	10 (2.5)	6 (1.5)	10 (2.5)	403	82	10.8 × 10 ⁻¹²	124	5.0 × 10 ⁻²⁰
Cataplexy onset 1996-2010, No. (%)	24 (4.7)	33 (6.4)	48 (9.3)	76 (14.8)	65 (12.6)	65 (12.6)	58 (11.3)	44 (8.5)	47 (9.1)	26 (5.0)	13 (2.5)	16 (3.1)	515	60.1	1.7 × 10 ⁻⁷	97.9	8.2 × 10 ⁻¹⁵
Sleepiness onset 1996-2010, No. (%)	21 (3.5)	41 (6.9)	66 (11.0)	84 (14.0)	76 (12.7)	63 (10.5)	77 (12.9)	56 (9.4)	58 (9.7)	32 (5.4)	10 (1.7)	14 (2.3)	598	87.9	8.5 × 10 ⁻¹³	125	3.2 × 10 ⁻²⁰
Narcolepsy birth 1956-2010, No. (%)	83 (10.0)	56 (6.7)	63 (7.6)	58 (7.0)	66 (7.9)	65 (7.8)	53 (6.4)	80 (9.6)	60 (7.2)	85 (10.2)	88 (10.6)	74 (8.9)	831	11.7	n.s.	17.4	n.s.
Polysomnographic examinations 2002-2009, No. (%)	398 (8.0)	391 (7.8)	522 (10.4)	525 (10.5)	367 (7.3)	360 (7.2)	430 (8.6)	381 (7.6)	402 (8.0)	377 (7.5)	434 (8.7)	419 (8.4)	5,006	37.2	1.8 × 10 ⁻³		
National birth 1970-2000, No. (%)	185,735 (9.2)	173,156 (8.5)	176,071 (8.7)	158,841 (7.8)	154,187 (7.6)	160,207 (7.9)	171,805 (8.5)	171,067 (8.4)	155,550 (7.7)	179,119 (8.8)	177,316 (8.7)	165,660 (8.2)	2,028,714	3,334.1	<10 ⁻³⁰		
H1N1 2009	0	0	0	0	22	544	1,021	1,583	17,553	32,943	44,270	28,779	126,715	118,679.8	<10 ⁻³⁰		
H1N1 2010	5,931	834	415	123	48	544	101	105	63	18	17	146	8,345	8,257.2	<10 ⁻³⁰		
Influenza/cold 2009	3,397	4,395	7,889	6,707	7,688	7,871	7,682	14,449	42,312	24,412	41,817	29,977	198,596	6,271.0	<10 ⁻³⁰		
Influenza/cold 2010	10,415	6,595	8,488	6,357	3,865	7,999	2,627	3,588	5,114	4,121	5,323	6,529	71,021	47,741.5	<10 ⁻³⁰		

^aVersus expected if evenly distributed across 12 months.

^bBonferroni corrected for 14 comparisons.

^cVersus polysomnographic examinations.

^dSleepiness or cataplexy, whichever came first.

^eWith diagnosis within 1 year of onset.

n.s. = not significant.

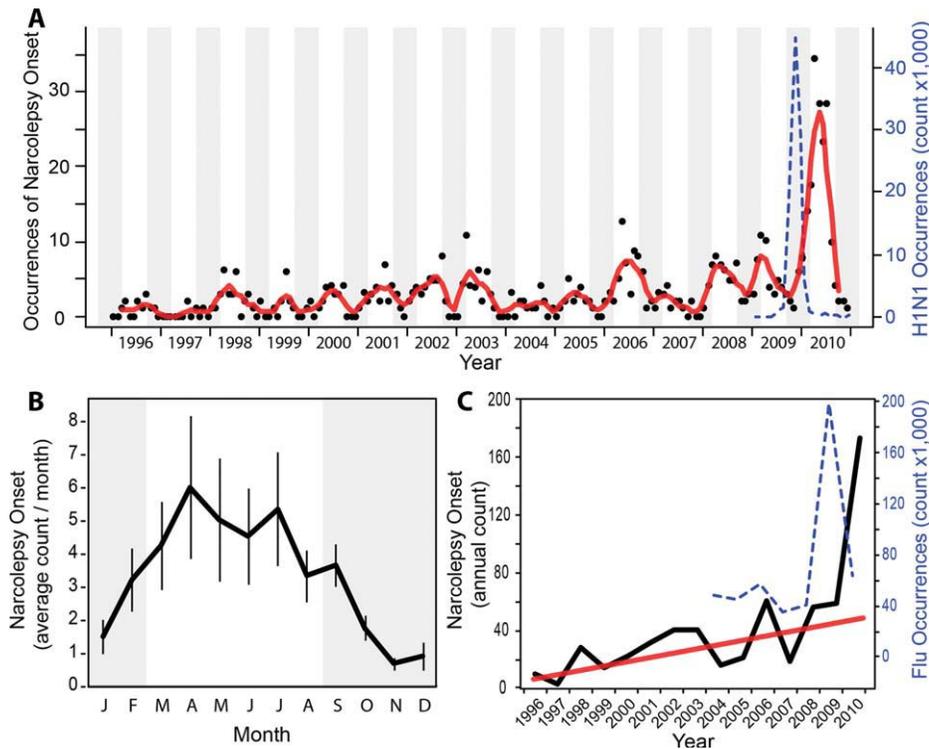


FIGURE: Narcolepsy onset occurrences over the past 15 years in 629 patients with narcolepsy/hypocretin deficiency diagnosed at the People's Hospital, Beijing University, China. (A) Monthly counts of onset occurrences over a 15-year period (raw data) with 3-month moving average trend line depicted in red. Note clear seasonal fluctuations of the trend line, with lower onset counts in fall and winter (shaded gray), and higher onset counts in spring and summer. The number of H1N1 infections documented by governmental statistics is depicted in blue. The peak of infections was followed by a large increase in incident narcolepsy cases in 2010, approximately 6 months later (see text). (B) Mean \pm standard error of the mean of monthly occurrences (corrected by the number of days per month and leap years) in percentage of 12 months across the year (mean of 15-year data). Onsets are approximately 6- to 7-fold more frequent in the late spring/early summer versus late fall/early winter (shaded in gray; see also Table). (C) Yearly counts of narcolepsy onset (corrected for leap years), with a linear trend line (red) depicting modest yearly increases from 1996 to 2009, also projected to 2010 (occurrences = $3.06 \cdot [\text{years since 1996}] + 7.82$; $r^2 = 0.4812$, $p < 0.001$). Projected value for the trend line was 53.77 cases for 2010, a value well below the 173 observed (3.2-fold higher). Autoregressive integrated moving average modeling forecast for 2010 counts gave similar results and indicated a statistically significant increase from expected (see text). The number of yearly 2004–2010 influenza infections documented by governmental statistics is depicted in blue.

Vaccination History in Cases with Onset since October 2009

Twelve of 154 cases (mean age, 8.99 ± 0.49 years) recontacted did not recall whether they had an H1N1 vaccination, leaving 142 cases for analysis. Eight of 142 (5.6%) reported a prior H1N1 vaccination (10.2 ± 2.7 weeks delay between vaccination and symptoms). Similarly, 10 of 154 did not recall whether they had a seasonal influenza vaccination, leaving 144 subjects, 14 of whom (9.7%) recalled an influenza vaccination (12.9 ± 2.6 weeks delay in 10 subjects between vaccination and symptoms). In this sample, 27 (25%) of 150 cases recalled having been sick with an infection a few months prior to the onset of narcolepsy (2.9 ± 0.1 weeks prior; range, 3 days to 2.5 months), 23 of whom (85%) reported symptoms of upper airway infection (runny nose, coughing or/and sore throat), with 2 cases recalling "flu" and 2 "strep throat"; very few reported other infec-

tious symptoms (1 case with diarrhea, 1 case with a skin infection, and none with urinary infections).

Discussion

Using data collected over more than a decade in China, we observed that the onset of narcolepsy is strongly seasonal, peaking in April–July (see trend lines in Fig. A and B). As previously reported,¹⁴ most of our sample was constituted of children, many of whom were prepubertal (see Supplementary Table). These prepubertal cases often had a rapid and catastrophic onset, likely facilitating recall of exact onset dates by the parents. We also found that the occurrence of narcolepsy onset was 3–4-fold greater than predicted following the 2009–2010 winter season (see Fig. A and C), when the H1N1 pandemic was at its peak. The majority (96%) of new narcolepsy patients in 2010 did not report a prior H1N1

vaccination. Most of these cases were young children, as also observed prior to the 2009–2010 H1N1 pandemic.¹⁴ Together with recent findings, these results strongly suggest that winter airway infections such as influenza A (including H1N1), and/or *S. pyogenes* are triggers for narcolepsy. Winter infections would initiate or reactivate an immune response that leads to hypocretin cell loss and narcolepsy in genetically susceptible individuals. Based on animal studies, approximately 80% cell loss is needed to exhibit symptoms, possibly explaining the 4- to 6-month delay between winter airway infection and narcolepsy onset occurrence.

Last year, reports of sudden onset narcolepsy cases following H1N1 vaccinations using the adjuvanted vaccine Pandemrix were reported by the press in Finland, raising alarm. Pandemrix is a split-virion inactivated vaccine containing A/California/7/2009 derived H1, N1, and PB1 antigens re-assorted into a PR8 backbone strain. It is adjuvanted with a proprietary adjuvant called AS03 that includes squalene (also commonly used in other vaccines) and alpha-tocopherol (specific of AS03). Increased occurrences of recent onset narcolepsy cases following the winter of 2009–2010 and after H1N1 vaccination were also recently reported in the United States, France, and Canada.⁹ A review of 16 identified post-H1N1 cases with definite narcolepsy/cataplexy (all DQB1*06:02 positive, and several with documented low CSF hypocretin-1) in these countries suggested a strong association with Pandemrix or Arepanrix, both AS03 adjuvanted vaccines, whereas we found almost no cases following nonadjuvanted vaccination in the United States (Pandemrix or other adjuvanted H1N1 vaccines have not been used in the United States). We also reported that 2 cases with recent onset occurred abruptly after an actual H1N1 infection, and that more recent onset cases had been identified by the Stanford Narcolepsy Center in the United States in the spring of 2010 than in previous years,⁹ suggesting that the H1N1 pandemic also had an effect.

Since these reports, the association between Pandemrix and narcolepsy has been strengthening, whereas data are less clear with other vaccines, suggesting that the combination of the nonspecific immune-stimulating effects of adjuvant and of the H1N1 antigen may be important. The WHO, reviewing the unpublished Finnish evidence, now suggests a 9-fold increase in risk for children and adolescents occurred following vaccination with Pandemrix in Finland.¹² More recently, the Swedish Medical Products Agency also found that the relative risk of narcolepsy was 6.6× higher in Pandemrix-vaccinated children and adolescents (aged 19 years and younger) compared to unvaccinated individuals.¹³ Interestingly, however, incidence rates

for narcolepsy irrespective of vaccination status were similar to historical national registry-based rates during the years before the pandemic period in adults, suggesting preferential effects in younger subjects, and no effects of the pandemic. This contrasts with what we observed in our preliminary post-H1N1 vaccination case series involving both unusually younger and older individuals⁹ and the data from China presented here. Further, data suggest that the association is not only stronger with Pandemrix but may be more evident in northern European countries than in southern Europe. A recent review of Scandinavian pharmacovigilance data following pandemic vaccination with other vaccines either unadjuvanted or containing another squalene-based adjuvant (MF59) did not reveal increased narcolepsy.²¹ In our data, only a very small subset of subjects diagnosed in 2010 (5.6%) reported a prior H1N1 vaccination (using a nonadjuvanted H1N1 monovalent vaccine²²), suggesting that H1N1 vaccination is not the culprit for increased narcolepsy onsets in China.

In prior studies, Aran et al had found that about 2/3 of Caucasian patients with narcolepsy onset within 1 year had high titers of ASO antibody (>200), a marker of *S. pyogenes* infections, primarily strep throat.^{9,10} This finding was complemented by epidemiological findings showing a 5.4-fold higher risk of developing narcolepsy among people reporting a physician-diagnosed strep throat before the age of 21 years.¹¹ As *S. pyogenes* is known to be associated with the onset of other autoimmune diseases, notably rheumatic heart fever and Sydenham chorea,^{23,24} it was a prime candidate as a potential autoimmune trigger for narcolepsy. Other brain-related autoimmune conditions have been suggested to be post-streptococcal, including chronic tic disorder, obsessive compulsive disorder, and recent cases of postinfectious encephalitis reminiscent of von Economo encephalitis (1915–1923).^{25,26} It is however notable that in most of these instances (and as in most autoimmune disorders), the exact immune mechanism involved is still uncertain (eg, the originator and target of molecular mimicry, if any), such that it is difficult to determine whether *Streptococcus per se* is involved, or an associated infection. Indeed, numerous studies have shown that upper airway infections often involve multiple viral²⁷ and bacterial coinfections or superinfections²⁸ including *S. pyogenes*.²⁹ In this context, the prior association with ASO and strep throat may reflect coinfections or superinfections of influenza-like illness with *S. pyogenes*. Alternatively, *S. pyogenes* may increase narcolepsy risk in conjunction with influenza or other upper airway infections. Even in our previously published post-H1N1 related cases, 69% were positive for ASO, suggesting concurrent strep infections.⁹ *S. pyogenes*

infections release superantigens, molecules known to bridge HLA and TCR molecules independently of antigen presentation, allowing the global stimulation of a broad range of T-cell clones.

Based on the data available, 2 factors may be needed for the development of narcolepsy³⁰:

- A specific immune-mimicry component, mediated through the presentation by DQB1*06:02/DQA1*01:02³¹ of a particular autoantigen to a specific TCR idiotype.⁴ This would explain the need for a very specific DQA1 and DQB1 peptide binding groove sequence and the TCRA genetic association. The specific autoantigen may or may not be related by mimicry to an H1N1-related antigen.
- Nonspecific factors, such as adjuvants, influenza or strep infections, streptococcus superantigens, and other factors. The importance of these cofactors may vary depending on latitude and other local factors. These nonspecific factors may act through reactivation of dormant T-cell clones (including through bystander activation) or increase blood–brain penetration of peripheral immune responses, or could involve novel HLA–immune interactions specific to the brain, as suggested recently by HLA class I expression in neurons and interactions with natural killer cell or immunoglobulinlike receptors.³²

Studies are ongoing to test these hypotheses.

This study has several limitations. First, the sample used patients from a single center in Beijing, China³³; this could explain why most of our patients are from northern rather than southern China. Second, the study is a cross-sectional retrospective case series based on chart review. This observational, ecological design may be difficult to generalize and can be subject to the ecological fallacy, an erroneous interpretation of aggregate data.^{34,35} This design can, however, still generate hypotheses, and is often a good choice for underdiagnosed disorders with low prevalence such as narcolepsy. Unbiased population-based designs would have needed ascertainment of >3 million individuals to reach a similar sample size. Finally, it is also clear that the sample of narcolepsy patients collected in this study is not representative of the country at large, representing at most 1/400 of the total number of patients who have the disorder. The sample is primarily composed of children, many of whom are prepubertal, whereas narcolepsy is a lifelong disorder. As discussed in 2 prior articles,^{14,36} narcolepsy may be more easily recognized in children than in adults in China for cultural reasons, genetic and environmental factors, or/and because the onset may be more abrupt and dramatic than in adolescence or adulthood.

Despite these limitations, our study supports the concept that H1N1 and/or other winter infections are associated with the onset of narcolepsy in a temporal manner, suggesting causality. Lifelong risk may potentially be increased, or H1N1 infection or vaccination may simply precipitate narcolepsy in subjects who would have developed the disorder later, and with a slower and less abrupt onset. The new finding of an association with infection, and not vaccination, is important as it suggests that limiting vaccination because of a fear of narcolepsy could actually increase overall risk. Philosophically, there has to be a lower threshold of proof for reporting potential adverse events than for advising therapy, not to mention the relevance of this work for future medicolegal claims. Epidemiological assessments of narcolepsy risk following vaccination with adjuvanted versus unadjuvanted formulations are ongoing in various countries of different latitudes, and will help answer these questions.

The findings that winter upper airway infections are triggers for narcolepsy, a brain autoimmune disease, may have implications for other diseases of the central nervous system. Recently, weak HLA association signals have been identified through genome-wide association studies in schizophrenia³⁷ and Parkinson disease,³⁸ suggesting a potential role for autoimmune/infectious pathology in a subset of cases. In this context, it is notable that the great H1N1 pandemic of 1918 was followed by a seasonal disease known as von Economo encephalitis lethargica.³⁹ Symptoms were very polymorphic, reflecting the location of brain lesions, and included extreme somnolence and ophthalmoplegia (associated with lesions of the posterior hypothalamus and upper brainstem), insomnia and sleep inversion (associated with lesions of the anterior hypothalamus), psychosis, chorea type movement disorders (reminiscent of Sydenham chorea, with lesions of the basal ganglia), and a residual form, postencephalitis Parkinsonism. In light of our present findings, this may indicate that a range of autoimmune pathologies of the brain (including narcolepsy, psychosis, and Parkinson disease) may follow winter infections. In support of this, recent cases of von Economo-like encephalitis have also shown increased ASO titers²⁵; furthermore, near onset narcolepsy cases share clinical features with Sydenham chorea, a poststreptococcal disorder, especially when patients are ASO positive.⁴⁰

Acknowledgments

This work was supported by research grants from the National Science Foundation of China (81070069), Sino-German Center for Research Promotion (GZ538), and Beijing Municipal Science and Technology Commission (D1011000050010029) to F.H. and grant NIH-

NS23724 to E.M. K.P.S. was supported in part by the Veterans Administration Research Service.

We thank the parents and most importantly the children for their participation.

Potential Conflicts of Interest

E.M.: consultancy, Jazz Pharmaceutical, Merck; expert testimony, Mead, Federal Trade Commission. Since submission of this article, E.M. has been in discussion with GlaxoSmithKline, the maker of Pandemrix, regarding the funding of contractual research to be conducted at Stanford University, aimed at better understanding the association of narcolepsy with Pandemrix.

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