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Original Article

Symptoms and occurrences of narcolepsy: a retrospective study of 162 patients during a 10-year period in Eastern China

Huijuan Wu [a,b], Jianhua Zhuang [a,1], William S. Stone [c], Lin Zhang [a], Zhengqing Zhao [a], Zongwen Wang [a], Yang Yang [a], Xiang Li [a], Xiangxiang Zhao [a,b], Zhongxin Zhao [a,b,*]

[a] Department of Neurology, Changzheng Hospital, Second Military Medical University, Shanghai, China
[b] Institute of Neuroscience and MOE Key Laboratory of Molecular Neurobiology, Neuroscience Research Center of Changzheng Hospital, Second Military Medical University, Shanghai, China
[c] Department of Psychiatry, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

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ABSTRACT

Objective: Our study was designed to assess symptomatology and occurrences of narcolepsy in Eastern China between 2003 and 2012. Herein we report the substantial changes in the occurrence and clinical features of narcolepsy over the last decade in China.
Methods: We performed a retrospective analysis of 162 Han Chinese patients with narcolepsy at Changzheng Hospital, Shanghai, China. Clinical histories and precipitating factors were recorded, in addition to narcolepsy and H1N1 winter flu pandemic (pH1N1) occurrences at Changzheng Hospital. The occurrences also were compared between the Changzheng Hospital and the People's Hospital, Beijing, China.
Results: In our sample, narcolepsy occurred 1.73 times more frequently in men than in women. Most of the participants were children, which peaked to 91% in 2010. Excessive daytime sleepiness (EDS), disrupted nocturnal sleep, cataplexy, and weight gain were the four major symptoms. We found that 40% of patients had identifiable precipitating factors. The occurrence of narcolepsy in 2010 showed an approximate three-fold difference from the baseline levels at the Changzheng Hospital, which showed positive relationships with occurrences of pH1N1 in Shanghai and the occurrence of narcolepsy at the People's Hospital.
Conclusions: Our findings show the interactive effects of geography and H1N1 disease in relation to narcolepsy in Han Chinese populations, and strengthen the theoretic hypothesis that immune and mental factors facilitate the onset of narcolepsy.

1. Introduction

In 1880 narcolepsy was first reported as an independent syndrome by Gélineau, a French physician [1]. Narcolepsy was known as "an excessive daytime sleepiness (EDS), accompanied typically by cataplexy attacks, and the symptoms associated with rapid eye movement sleep, such as sleep hallucinations and sleep paralysis" [2,3]. However, narcolepsy is now understood to affect multiple functions in addition to sleep. It has been estimated that the core pathologic mechanism of narcolepsy is the loss of large quantities of hypocretin (orexin) neurons in the hypothalamus [4–7]. Narcolepsy not only destroys orexin system, but also considerably affects endocrine, metabolism, and mood regulation systems [8–11].

Narcolepsy is not a common disease, and the prevalence of narcolepsy with cataplexy varies from 0.002% to 0.167% worldwide [12,13]. The prevalence of narcolepsy in Hong Kong, a Southern Chinese city, is approximately 0.033% [14]. It is suspected that racial difference and latitude/climate factors may contribute to these variances [15]. However, in 2010 many studies from Northern Europe reported a worldwide increased occurrence of narcolepsy following the H1N1 winter flu pandemic (pH1N1) of 2009 [16–20]. Groups in Finland and Sweden reported that children vaccinated with adjuvanted AS03 flu vaccine, a combination of squalene and α-tocopherol, had a six- to nine-fold increased risk for narcolepsy [17–19]. No association was seen between influenza A (H1N1) vaccinations and narcolepsy in Asia [20,21]. A large retrospective study in the north of China [20] revealed that pH1N1 virus

* Corresponding author at: Department of Neurology, Neuroscience Research Center of Changzheng Hospital, Second Military Medical University, 415 Fengyang Road, Shanghai 200003, China. Tel./fax: +86 21 81885451.
E-mail address: zhaozx@medmail.com.cn (Z. Zhao).
[1] Equal contribution.

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infections or winter infections might increase susceptibility to narcolepsy in children, but there was no significant correlation between the increased incidence of narcolepsy and pH1N1 vaccinations in China. These studies strengthen the hypothesis that narcolepsy is associated with immunologic mechanisms [15–22].

During the review of the clinical data in our study, we found significant fluctuations in narcolepsy rates of occurrence at the Changzheng Hospital, Shanghai in Eastern China during the last 10 years. Our study was reported 3 years after the 2009 H1N1 winter flu pandemic, which was long enough to review its effects and begin to consider its relationships with other conditions. The purposes of our study were as follows. First, we examined symptoms and rates of narcolepsy based on the accumulated cases of narcolepsy at the Changzheng Hospital. Second, we examined several precipitating factors for onset of narcolepsy including the pH1N1 and other infections, in addition to emotional stimulation. Finally, we compared the trend of narcolepsy occurrence at the Changzheng Hospital with the occurrences of pH1N1 in the Shanghai area, as well as with the occurrence at the People's Hospital, Beijing, China, to represent hospitals in Eastern and Northern China, respectively.

2. Material and methods

2.1. Patients

Patients diagnosed with narcolepsy at the Changzheng Hospital, Second Military University, Shanghai, China were included in our study from March 2003 to December 2013. Standard nocturnal polysomnography (nPSG) and multiple sleep latency tests (MSLT) were used to diagnose narcolepsy. Diagnosis of narcolepsy was based on the International Classification of Sleep Disorders: Diagnostic and Coding Manual, second edition, criteria [2]. Due to a lack of cerebrospinal fluid of orexin detections, we used the same criteria to diagnose narcolepsy with or without cataplexy. Besides the defined history of EDS or cataplexy, the diagnosis of narcolepsy with and without cataplexy was confirmed by nPSG (NIHON KOHDEN Inc, Polysmith 3.0 sleep analysis system) followed by an MSLT. The mean sleep latency on MSLT was less than or equal to 8 min, and two or more sleep onset rapid eye movement periods were observed following sufficient nocturnal sleep (minimum of 6 h) during the night before the test. Hypersomnia was diagnosed if the symptoms could not be better explained by alternative sleep disorders, medical or neurologic disorders, mental disorders, medication use, or substance use disorders. For those patients who had clinical symptoms less than 3 months and suspected narcolepsy, we retested with nPSG and MSLT to confirm the final diagnosis.

2.2. Study design

The study was a retrospective analysis of participants with narcolepsy. Participants' history was reported by either the patients or their parents and was recorded by two doctors, Drs. Wu and Wang, to ensure consistent historical content. For inconsistent or incomplete histories, outpatient interviews or telephone interviews were performed to confirm historical details. Participants were not included when histories were unavailable. All participants or their parents provided written informed consent before participation and the research was approved by the ethics committee of the Changzheng hospital.

2.3. Clinical data

All narcoleptic participants had complete clinical data, including clinical manifestations, disease onset time, onset age, family history of sleepiness, history of fever, respiratory infections and infections of the digestive system within 6 months prior to disease onset, history of influenza vaccination, and precocious puberty. Major clinical manifestations included EDS, attacks of cataplexy, nocturnal sleep disturbances, hypnogogic hallucinations, sleep paralysis, considerable weight gain, mood disturbances, or irritability. Because one of the symptoms of narcolepsy is nocturnal sleep disturbance, we used the criterion for nocturnal sleep disturbance as defined for insomnia [2]. Nocturnal sleep disturbance was defined as fragmented sleep during the night, night sleep awakening 2 times or more for durations longer than 30 min, or sleep efficiency less than 90% [2]. Weight gain was defined as considerable weight gain after narcolepsy onset, weight increase of more than 5% per month, or weight gain of more than 30% a year, with an increased body mass index. The clinical manifestations of precocious puberty included premature breast and pubic or axillary hair development before the age of 8 years in girls [23] and 9 years in boys [24]. Some of the younger participants also were examined for serum gonadotropic hormone stimulation curves and X-rays of the wrist to determine bone age and chronologic age ratios.

2.4. Control data

The control data for our study involved the occurrences of narcolepsy from 2003 to 2012 at the Sleep Center of People's Hospital [25], Beijing University (permitted by F. Han), and the occurrences of pandemic H1N1 infection between 2009 and 2012 from the Shanghai municipal center for disease control and prevention (provided by H.L. Su).

2.5. Statistical analysis

Means ± standard error of the means were presented to show yearly rates of occurrence. Inductive analysis was processed by statistical description using SPSS 18.0 statistical software. Pearson product moment correlation analysis was used to analyze relationships between the occurrence of narcolepsy at the Changzheng hospital and People's Hospital from 2003 to 2012 and the relationships between the occurrences of narcolepsy of Changzheng hospital from 2009 to 2012, as well the cases of pH1N1 infection in the Shanghai municipal center for disease control and prevention from 2009 to 2012.

3. Results

3.1. Data of narcoleptic participants

A total of 162 participants met the diagnostic criteria of narcolepsy and were included in this study. Among them, 12 participants had clinical symptoms and met the criteria on nPSG and MSLT but could not be diagnosed as having first-time narcolepsy as the symptoms had not persisted for 3 months. However, all 12 of these participants were finally diagnosed as narcolepsy after 3 months. All the participants were Han Chinese and 141 participants (87.04%) were from the Eastern China area. Narcolepsy occurred 1.73 times more frequently in men (63.36%) than in women (36.64%). Among them, 75% were children. In our study, the gaps between the emergence of initial symptoms and the diagnosis varied from 2 weeks to 12 years, with an average of 2.75 ± 3.63 years. There were 135 participants diagnosed with narcolepsy with cataplexy (83.3%), and 27 participants were diagnosed with narcolepsy without cataplexy (16.7%) (Table 1).