

## Narcolepsy and the Seasons

By Cassandra  
Perez

### **Emerging research supports the theory that the onset of narcolepsy is more common at certain times of the year.**

Narcolepsy is a chronic sleep disorder characterized by overwhelming daytime drowsiness and sudden attacks of sleep. The causes and triggers of this neurological condition are unknown; however, emerging research points to two infectious agents that may be involved in triggering the condition. Narcolepsy onset often follows a seasonal pattern of higher rates in spring and early summer following winter upper airway infection season.<sup>1</sup> Also, researchers are investigating a possible link between narcolepsy onset and streptococcal infection.<sup>1</sup> This article will explore the research that provides support for the possible association between the seasons and the onset of narcolepsy as well as the implications for patients and sleep medicine professionals.

### **Research Study: Narcolepsy in Beijing**

A 2011 study published in the *Annals of Neurology* showed that the occurrence of narcolepsy in China was highly linked to a seasonal pattern. The study, led by Fang Han, MD, included a retrospective analysis of narcolepsy onset in patients diagnosed between 1998 and 2011 in Beijing. Data on the month and year of narcolepsy onset were collected from 629 patients who were a part of the Stanford-Beijing University Chinese narcolepsy study cohort, and a vaccination history was provided by 182 participants who developed narcolepsy after October 2009.<sup>2</sup>

The results showed that the onset of narcolepsy was least frequent in November and occurred most often in April, with an almost sevenfold increase from lowest point to peak time. In a release, Han says, “Our findings show a seasonal variation in narcolepsy onset in a Chinese population, occurring most frequently in late spring and early summer.”<sup>3</sup>

The research team also studied year-to-year variations and identified 173 cases of narcolepsy following the 2009-2010 H1N1 flu pandemic, representing a threefold increase in the sleep disorder. “The increase in narcolepsy incidence was unlikely caused by increased vaccination as only 6% of study narcolepsy participants reported receiving a vaccination against H1N1,” says coauthor Emmanuel Mignot, MD, PhD, of the Stanford Center for Sleep Sciences and Medicine, in the release.<sup>3</sup> In addition, a 5- to 7-month delay between the seasonal peak in flu and peak in narcolepsy onset was observed.

Mignot adds, “These findings are reminiscent of the encephalitis lethargica epidemic that followed the great Spanish influenza pandemic of 1917-1918. Not only narcolepsy, but also psychosis and Parkinson’s disease may follow winter infections, and further research is needed in the area of autoimmune diseases of the brain.”<sup>3</sup>

Via e-mail, Han explains: “Narcolepsy-cataplexy was due to the loss of hypocretin cells in brain. Our finding that narcolepsy onset is highly correlated with seasonal and annual patterns of upper airway infections fits the model that the patients may get virus infection in winter, [which] triggers immunological infection several months later, therefore destroying the cells in brain.”

## Related Research

The relationship between the seasons of the year and the onset of narcolepsy is a newer theory, although several studies have explored this connection and found supporting evidence. In the book *Neurology of Brain Disorders: Biological Basis of Neurological and Psychiatric Disorders*, the authors note that the onset of narcolepsy has been shown to be highly seasonal in children developing the disease, with a sixfold higher incidence in April than December, which suggests occurrence typically 5 to 6 months after winter.<sup>4</sup>

In another study, a notable six to ninefold increase in the risk of developing narcolepsy was reported in northern Europe, which followed a campaign of pandemic H1N1 vaccination using Pandemrix after the 2009-2010 H1N1 influenza pandemic.<sup>4</sup> The retrospective population-based cohort study included narcolepsy cases with onset from April 2009 to December 2010, and narcolepsy incidence was 5.7 per 100,000 children and adolescents vaccinated with Pandemrix and 0.4 per 100,000 unvaccinated children and adolescents.<sup>5</sup> The *Eurosurveillance* study confirms the basic association between Pandemrix vaccination and narcolepsy as observed in Finland and Sweden.

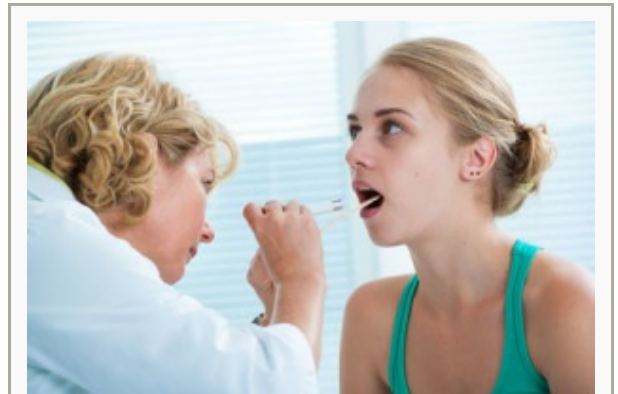
## Upper Airway Infections and Narcolepsy

There is published data that indicate a role for upper airway infections in triggering narcolepsy, Han says. “Of course, this is just an association study based on epidemiology research. Another clue from our study was that H1N1 virus per se other than vaccine might be linked to narcolepsy,” he says. “The peak seasonal onset of narcolepsy was phase delayed by 6 months relative to winter H1N1 infections...indicating that H1N1 virus infection is one of the major triggers.”

Along with other published data, Han says the seasonal pattern indicates the role of upper airway infection in triggering narcolepsy, especially the close link to the H1N1 pandemic. “[It] also supports that H1N1 virus might be the antigen to trigger the immunological process,” Han says. However, Han adds whether or not this means narcolepsy is an autoimmune disorder needs to be further proved.

Kiran Maski, MD, says via e-mail that because the onset of narcolepsy was found to be strongly seasonal in the Beijing study, it “suggests that infections acquired during the winter (such as influenza and *Streptococcus pyogenes*) could initiate an immune response that leads to an autoimmune attack of hypocretin neurons in susceptible individuals.” Maski, instructor at Harvard Medical School and director of sleep neurology clinics at Boston Children’s Hospital, says there have been studies showing a high incidence of *S. pyogenes* infection preceding the onset of narcolepsy, which suggests a role of upper airway infection as a trigger for narcolepsy.

Patients with *S. pyogenes* infection have a higher risk of being diagnosed with narcolepsy, and approximately two-thirds of patients with new onset of narcolepsy had high ASO antibody titers, which is a marker of a streptococcal infection, according to Maski. Also, even in H1N1 cases of narcolepsy, 69% of patients were positive for ASO, suggesting concurrent *S. pyogenes* infection. Maski says, “Streptococcus releases superantigens, molecules that bridge HLA and T-cell receptors, so this may cause a more robust immune response that potentially attacks hypocretin neurons and other brain tissue.”



One theory of narcolepsy’s increased spring onset prevalence is that upper airway infections in the winter may trigger an immunological response months later that then destroys hypocretin cells in the brain.

Additional research also supports the theory that narcolepsy onset is seasonal and associated with both streptococcus and H1N1 infections. Epidemiological population studies in King County, Washington, showed that the risk of narcolepsy is increased in individuals with a history of a physician-diagnosed streptococcal throat

infection.<sup>4</sup> Also, the involvement of streptococcal infections in the development of this disorder is supported by the presence of antistreptococcal antibodies in 65% of narcoleptic patients within 1 year of onset compared with 26% in age-matched controls in US studies.<sup>4</sup>

## Implications in Sleep Medicine

The possible relationship between the seasons and the onset of narcolepsy has implications for sleep medicine professionals, for diagnosing and treating this condition, and for patients who are at an increased risk of developing this disorder.

While there is not sufficient data to include seasonality in making a narcolepsy diagnosis, Maski says, “Physicians should query about potential triggers of narcolepsy including preceding infections such as pharyngitis and influenza, vaccinations, and head trauma.”

The possible link between the onset of narcolepsy and certain vaccines is also a consideration for medical professionals and guidelines. For patients who are genetically susceptible to narcolepsy, there is currently not sufficient data to make recommendations about vaccination schedules for this patient population. Maski does note, however, that this is “an active area of research...given the outbreak of narcolepsy cases with Pandemrix vaccinations against the H1N1 influenza strain in Northern European countries.”

Han affirms that high-risk cases can include those with a family history of narcolepsy, although even in his study’s Chinese cohort who had a higher rate of familial narcolepsy, less than 5% of the cases had more than one cause of typical narcolepsy. Additionally, Han explains it is not clear what kind of flu besides H1N1 is related to narcolepsy. The other major risk factor is HLADQ0602; however, in Chinese and Caucasians, one-fourth of the population has these markers, Han says. Overall, Han says, “It is hard to say any specific group of people needs to be protected.”

## Considering the Seasons in Narcolepsy

The link between the seasons of the year and narcolepsy warrants future research in order to establish a resolute connection and understand this relationship. Han says the major indication of the findings of his 2011 study is that additional research is needed to determine the mechanisms of narcolepsy-cataplexy to prove a causal relationship.

Han says, “In clinical practice, we do see more close to onset patients in the last half of the year annually. As [a] close to onset case generally has more severe symptoms, and may have higher rate of positive markers... we may look for more diagnostics biomarkers in these cases.” In addition, Han says future research should also explore the interaction between environmental and genetic factors.

Maski suggests future research on this subject should focus on immune mechanisms in the development of narcolepsy and genetic and environmental modifiers of disease severity. “Understanding the cause of narcolepsy and being able to identify early immune mechanisms would allow for early immunomodulating treatments for patients that would potentially alter disease course,” says Maski.

Cassandra Perez is associate editor of Sleep Review. CONTACT [cperez@nullallied360.com](mailto:cperez@nullallied360.com)

## References

1. “What Is Narcolepsy?” Wake Up Narcolepsy Inc, nd. [www.wakeupnarcolepsy.org/about-narcolepsy/what-is-narcolepsy](http://www.wakeupnarcolepsy.org/about-narcolepsy/what-is-narcolepsy) Accessed October 9, 2015.
2. Han F, Lin L, Warby SC, et al. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. *Ann Neurol*. 2011;70:410–417.
3. Press release: Study finds narcolepsy cases in China peak in early spring.

[www.eurekalert.org/pub\\_releases/2011-08/w-sfn081811.php](http://www.eurekalert.org/pub_releases/2011-08/w-sfn081811.php)

4. Zigmond MJ, Coyle JT, Rowland LP. *Neurobiology of Brain Disorders: Biological Basis of Neurological and Psychiatric Disorders*. London: Academic Press; 2014.
5. O'Flanagan D, Barret AS, Foley M, et al. Investigation of an association between onset of narcolepsy and vaccination with pandemic influenza vaccine, Ireland April 2009-December 2010. *Euro Surveill*. 2014;19(17):15-25.