Association between H1N1 vaccination and narcolepsy–cataplexy
Flu to sleep

After the beginning of the influenza A (H1N1 pdm09) pandemic in 2009, several monovalent pandemic H1N1 vaccines were licensed using fast track procedures, with limited safety data in children and adolescents. Nonadjuvant monovalent vaccines were used in the United States and Australia, and on a limited scale, in Europe (France, Spain) and other countries. Within the European Union (EU), 2 different vaccines with adjuvant were licensed, both containing a new generation of squalene-based adjuvant: Focetria (Novartis, Philadelphia, PA), with the MF59 adjuvant, and Pandemrix (GSK, Philadelphia, PA), containing AS03 (squalene and α-tocopherol). Arepanrix, similar to Pandemrix, was used in Canada and Brazil. The vaccine program started in the EU by September 2009; concurrently, the European Center for Disease Prevention & Control (ECDC), Vaccine Adverse Event Surveillance and Communication, and other agencies initiated an active surveillance program to monitor safety and adverse events associated with this vaccine.

In 2010, there was intense media coverage of case reports of new-onset narcolepsy as a side effect of the vaccine. Subsequent epidemiologic studies showed a 6- to 12-fold increased risk of narcolepsy in children and adolescents following Pandemrix H1N1 vaccination in Finland and Sweden but no increased risk in other countries that used the Pandemrix vaccine, such as Norway, France, and Ireland. Interestingly, none of the EU countries reported cases of narcolepsy following H1N1 infection itself. However, a recent case series from China reported a threefold increase in narcolepsy onset following the 2009 H1N1 winter influenza pandemic.

In this issue of Neurology®, Szakács et al. present additional corroborative evidence on the association of narcolepsy after H1N1 vaccination with Pandemrix from western Sweden. They calculated the incidence of new-onset narcolepsy based on the onset of hypersomnia, and compared the rates from January 2000 to August 2009 (prevaccination) to those from October 2009 to December 2010 (postvaccination). All cases had confirmatory multiple sleep latency tests (MSLT). They identified 9 children with narcolepsy prior to the H1N1 vaccination, compared to 28 children after the initiation of the vaccination, with a 25-fold increase in the incidence of narcolepsy in children 17 years and younger. The median age was 10 years, and all cases except one occurred within 12 weeks of getting the vaccine. All cases were human leukocyte antigen (HLA) DQB1*0602 positive and had low CSF orexin/hypocretin levels.

The study has a few limitations. Identifying cases by onset of hypersomnia brings an element of subjective bias; in addition, cases identified after the 2010 media attention could result in overreporting because of increased awareness by patients and providers. Small sample size, retrospective nature of the analysis, and lack of comparison between the prevaccination and postvaccination group are other limitations. In addition, the authors did not perform an overnight sleep study prior to the MSLT, but relied on actigraphy data, thereby possibly missing alternate causes of hypersomnia such as obstructive sleep apnea. Nevertheless, the study has strengths: population-based observation, robust 25-fold increase in incidence of narcolepsy after vaccination, and low CSF orexin levels, along with HLA DQB1*0602 positivity in all cases.

What have we learned? Narcolepsy, with an incidence of 0.3–0.6 per 100,000 person-years, has an increased incidence after Pandemrix vaccination in some children and adolescents. The reasons for this increase are not well-determined. Attribution to a specific vaccine component is difficult since approved monovalent H1N1 vaccines differed in the techniques for virus growth and inactivation, antigen preparation and amount, adjuvant use and type, and other constituents. Possible explanations include molecular mimicry, but there is no evidence of homology between H1N1 virus and brain-specific proteins.

There are additional questions. Is it possible that the vaccine accelerated the degenerative process of the hypocretin/orexin neuronal loss, with earlier emergence of narcolepsy in those who were destined to develop it? Why were adults not affected? Why did countries like Norway and Ireland, where Pandemrix was used, not signal an increase in the incidence of postvaccine narcolepsy as

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occurred in Sweden and Finland? Would cases in these countries emerge with continued surveillance? Why didn’t all children with HLA DQB1*0602 develop narcolepsy after Pandemrix vaccination? Is there an additional factor that is needed for narcolepsy onset? Should the implicated vaccine be withdrawn from use or does it offer a benefit that exceeds the reported association with narcolepsy?

Broader lessons apply to the issue of vaccine safety. Passive reports by medical providers triggered efforts to investigate this previously unrecognized potential adverse event. Similarly, ongoing recognition of future potential neurologic adverse events following immunization requires reports by neurologists and other providers to passive monitoring systems such as the US Vaccine Events Reporting System and other worldwide programs. If warranted, further investigations can occur through established active surveillance systems such as the Vaccine Safety Datalink and Post-licensure Rapid Immunization Safety Monitoring project. When an investigation is initiated, it is important that investigators use a common language to document the adverse event to allow comparison among reports: this has been developed by the Brighton Collaboration, a worldwide consortium of professionals. In this case, the peer-reviewed Brighton Collaboration narcolepsy definition was used by Nohynek et al. in Finland and by the ECDC to compare reports from 8 European countries.

Many questions remain unanswered. What these studies tell us is that there is a clear association between H1N1 vaccination and development of narcolepsy–cataplexy. However, we cannot be sure of causality, and it would be imprudent and simplistic to blame it exclusively on the adjuvant and squalene, which have been used in other vaccines in the past without the adverse event of hypersomnia. This experience should prompt other studies to understand the basic mechanisms in the development of human narcolepsy, including the development of animal models.

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**REFERENCES**