Post-H1N1 Narcolepsy-Cataplexy

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NARCOLEPSY-CATAPLEXY, A DISEASE CAUSED BY THE LOSS OF ~70,000 HYPOCRETIN CELLS IN THE HYPOTHALAMUS AFFECTS ~20 PER 100,000 INDIVIDUALS, with an incidence of ~ 0.3-0.6 per 100,000 person-years.[1,2] Onset is most typically in the teens, and cases with onset before age 6 or after 40 are rare in Western Europe and North America.[3] The disease is extremely tightly associated with human leukocyte antigen (HLA) DQB1*0602[4], so that DQB1*0602 negative cases without documented loss of hypocretin cells, as measured by cerebrospinal fluid (CSF) hypocretin levels, are exceptional; only 5 such cases have been reported in the literature. The cause of narcolepsy is likely autoimmune based on the HLA association, association with T-cell receptor polymorphisms,[5] and recently reported Tribbles 2 autoantibodies.[6] As for most autoimmune diseases, twin pairs are most often discordant (65% to 80%), and environmental triggers are suspected to play a critical role.[1] Most notably, two recent reports have found an association with past streptococcus infections,[7,8] leading to the speculation that upper airway infections could be involved in many cases as a cofactor.

The possibility that narcolepsy could be a rare side effect of H1N1 flu vaccination was first reported by the Swedish Medical Product agency in August 2010 (6 cases). Additional cases (up to 14) were also reported in Finland, potentially linked to Pandemrix vaccination, an H1N1 vaccination formulation containing the adjuvant ASO3. Vaccination has been suspended in these countries.[9]

In three major centers of reference for narcolepsy—Montpellier, France; Montreal, Canada; and Stanford University, United States—we noticed in the first months of 2010 an unusual increase in abrupt onset narcolepsy-cataplexy diagnosed within a few months of H1N1 onset. These observations were made independently and first discussed among directors of the 3 centers at a sleep meeting in spring 2010, prior to any media attention. From September 2008 to August 2009, 9 recent-onset cases (symptoms of less than one year duration before being diagnosed) were identified in the 3 centers. The following year (September 2009-August 2010), 31 recent onset cases were identified (8 cases in Montpellier, 9 in Montreal, 14 at Stanford). These cases were examined for past H1N1 exposure or vaccination by review of clinical charts, and when possible additional interviews by phone or in person. Of the 31 cases, 14 post-vaccination cases were identified at Montpellier (n = 6), Montreal (n = 4), and Stanford University (2 of 4 US cases were vaccinated in Europe). In addition, 2 cases following H1N1 infection (as opposed to vaccination) were also reported at Stanford. These patients were interviewed to specify the date of cataplexy onset. Information regarding date of vaccination and type of vaccine was also obtained in all cases. Multiple sleep latency tests (MSLTs) were performed in all cases older than 9 years old. Serum, CSF, and DNA were collected for biochemical measurements. Serum samples were tested for the presence of antistreptolysin O (ASO).[7] The presence of anti-TRIB2 antibodies was tested in Lausanne, Switzerland, for the 6 French cases[6] or at Stanford, USA, for the remaining cases.[10] DNA was tested for the presence of DQB1*0602. CSF hypocretin-1 levels were measured as previously described.[11]

A summary description of the 16 post-H1N1 cases is reported in Table 1. All cases were HLA DQB1*0602 positive with severe sleepiness and definite/severe cataplexy. All were Caucasian except case 3 (African American), and 50% were male. In 10 cases, CSF hypocretin-1 was found to be extremely low (< 110 pg/mL; normal value > 200 pg/mL). MSLTs were performed in 11 cases, with confirmation of diagnosis in all cases, i.e., mean sleep latency < 8 minutes and ≥ 2 SOREMPs. The post streptococcal marker ASO was positive in 11 cases (68.7%), confirming a previous report in recent-onset cases.[7] None of our post-H1N1 subjects were anti-TRIB2 positive, in contrast to recent-onset cases collected in prior years.[6,10,12] Brain MRI (performed in 6 cases) were unremarkable except for the presence of a pineal cyst in 2 cases. The most striking features of our sample were the abrupt onset and the unusual severity of both sleepiness and cataplexy. Rapid weight gain was frequently noted, as is typical with abrupt onset cases. Finally, we noted that age at onset was often atypical, with 5 cases with onset after age 38, and 2 with very early onset (under 5 years of age from the United States). Of the 14 post-vaccination cases, 11 cases followed adjuvanated vaccination, while 3 were vaccinated without adjuvant. Delay between vaccination and cataplexy onset in these cases ranged from 2 days (strong local response followed by a generalized reaction following vaccination) to 5 months, although in 9 of the 14 post-vaccination cases the onset occurred 2-8 weeks following vaccination. As the de-

Submitted for publication September, 2010
Accepted for publication September, 2010
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Table 1—Characteristics of post H1N1 narcolepsy patients

Case#	Referral/Country	Age at diagnosis (years)	Time between H1N1 exposure to cataplexy onset	H1N1 exposure (vaccine manufacturer)	Date of Vaccine	Date of EDS	Date of Cataplexy
1	Stanford/Switzerland	10	4 weeks	H1N1 with adjuvant: AS03 (Pandemrix)	12/09	1/5/10	1/5/10
2	Mayo Clinic/US	3	6 weeks	H1N1/no adjuvant (MedImmune-mist and Panenza)	11/09 (mist); 1/10 (injectable)	2/26/10	3/3/10
3	Stanford/US	9	2 weeks	H1N1/no adjuvant (injectable)	12/09	1/10	1/10
4	Stanford/UK	3.5	15 weeks	H1N1 with adjuvant: AS03 (Pandemrix)	1/10	4/10	4/10
5	Montpellier/France	38	2 days	H1N1 with adjuvant: AS03 (Pandemrix)	12/09	12/09	12/09
6	Montpellier/France	19	16 weeks	H1N1 with adjuvant: AS03 (Pandemrix)	12/09	3/10	5/10
7	Montpellier/France	14	5 weeks	H1N1 with adjuvant: AS03 (Pandemrix)	1/10	2/10	3/10
8	Montpellier/France	14	20 weeks	H1N1/no adjuvant (Panenza)	11/09	3/10	4/10
9	Montpellier/France	13	8 weeks	H1N1 with adjuvant: AS03 (Pandemrix)	12/09	12/10	3/10
10	Montpellier/France	49	4 weeks	H1N1 with adjuvant: AS03 (Pandemrix)	1/10	2/10	2/10
11	Montreal/Canada	17	3 weeks	H1N1 with adjuvant: AS03 (Arepranrix)	12/09	1/10	1/10
12	Montreal/Canada	41	13 weeks	H1N1 with adjuvant: AS03 (Arepranrix)	11/09	1/10	3/10
13	Montreal/Canada	11	4 weeks	H1N1 with adjuvant: AS03 (Arepranrix)	12/09	12/09	12/09
14	Montreal/Canada	51	4 weeks	H1N1 with adjuvant: AS03 (Arepranrix)	12/09	1/10	1/10
15	Stanford/Hong Kong	45	8 weeks	H1N1 infection likely (positive daughter)	No vaccination	10/09	1/10
16	Stanford/US	5	6 weeks	H1N1 infection documented	No vaccination	10/09	10/09
Mean		21.5	7.4 weeks				
SE		4.3	1.4 weeks				

lay between onset and diagnosis is often long,[1,13] more cases are likely to be identified in the future.

How could H1N1 vaccination or infection trigger narcolepsy? Possible hypotheses include a specific immune response to H1N1 (and possibly subsequent molecular mimicry) or generalized stimulation of the immune system. In Europe and Canada, as well as the cases reported in Scandinavia, most cases followed vaccination with ASO3. This vaccine has been reported to be associated with side effects suggestive of stronger immune stimulation.[14] In the United States, where vaccination did not contain the ASO3 adjuvant, only 2 post-vaccination cases were documented. The strength of the immune response (higher with adjuvant, or after actual infections), rather than the specificity of the immune response to H1N1, may thus be involved. Several of our patients showed high ASO titers, suggesting that they had recent or recurrent streptococcus infections. An association between streptococcal infection and recent-onset narcolepsy was reported previously, in the absence of H1N1 vaccination. One possibility is that streptococcus infection could also act as a nonspecific immune trigger, for example via superantigen stimulation of dormant autoreactive T-cell clones. It is possible that these factors increase brain inflammation or blood brain penetration nonspecifically, allowing the autoimmune process to reach hypocretin cells. Fever and the administration of various adjuvants have been reported to increase blood brain penetration and activate brain microglia in animal models.[15]

Cases reported here with their temporal link between vaccination and disease onset and unusual clinical presentation, with rapid development and severity of both excessive daytime somnolence and cataplexy, suggest that H1N1 vaccination or exposure may trigger narcolepsy. However, there are several limitations and potential confounding factors, such as increased awareness of narcolepsy and more efficient diagnostic processes leading to faster diagnosis and increased identification of recent-onset cases. Another limitation is that a large portion of the population was either vaccinated or had H1N1 infection, including many unrecognized instances of infection, increasing the difficulty to document a specific association between narcolepsy onset and H1N1 infection or vaccination. Nevertheless, these correlative findings indicate an urgent need for further examination of a possible link. Even if confirmed, as for other better-established post-vaccination autoimmune reactions such as Guillain-Barré, post-flu vaccination narcolepsy is likely to be an exceptionally rare complication.[16-18] To our knowledge, vaccination has not previously been reported as a triggering factor for narcolepsy. The consequences of withholding vaccination should be weighed against the risk of potentially lethal H1N1 infections (that may also trigger narcolepsy based on our data). Considering that all cases reported here were HLA DQB1*0602 positive, HLA typing prior to vaccination could be considered in the future and would represent the first vaccinogenomic intervention.

DISCLOSURE STATEMENT

Dr. Dauvilliers is consultant for UCB Pharma, Cephalon, and Bioprojet. Dr. Monaca served on the scientific advisory board for UCB Pharma. Dr. Montplaisir received research grants/support from Boehringer Ingelheim, Sanofi-Aventis and Merck, served as an advisor for Boehringer Ingelheim, Merck and Servier, and received honoraria for speaking engagements from Valeant Pharmaceutical, Boehringer Ingelheim, Sanofi-Aventis and GlaxoSmithKline. Dr. Mignot is a consultant for Merck and Jazz Pharmaceuticals and has been contacted by GlaxoSmithKline for consulting on post vaccination narcolepsy cases. The other authors have indicated no financial conflicts of interest. GSK is the primary manufacturer of Pandemrix and Arepranrix.

REFERENCES

1. Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. Lancet 2007;369:499-511.
2. Longstreth WT Jr, Koepsell TD, Ton TG, et al. The epidemiology of narcolepsy. Sleep 2007;30:13-26.
3. Dauvilliers Y, Montplaisir J, Molinari N, et al. Age at onset of narcolepsy in two large populations of patients in France and Quebec. Neurology 2001;57:2029-33.
4. Mignot E, Lin L, Rogers W, et al. Complex HLA-DR and -DQ interactions confer risk of narcolepsy-cataplexy in three ethnic groups. Am J Hum Genet 2001;68:686-99.
5. Hallmayer J, Faraco J, Lin L, et al. Narcolepsy is strongly associated with the T-cell receptor alpha locus. Nat Genet 2009;41:708-11.
6. Cvetkovic-Lopes V, Bayer L, Dorsaz S, et al. Elevated Tribbles homolog 2-specific antibody levels in narcolepsy patients. J Clin Invest 2010;120:713-9
7. Aran A, Lin L, Nevsimalova S, et al. Elevated anti-streptococcal antibodies in patients with recent narcolepsy onset. Sleep 2009;32:979-83.
8. Koepsell TD, Longstreth WT, Ton TG. Medical exposures in youth and the frequency of narcolepsy with cataplexy: a population-based case-control study in genetically predisposed people. J Sleep Res 2010;19:80-6.
9. http://www.thl.fi/en_US/web/en/pressrelease?id = 22930
10. Kawashima M, Lin L, Tanaka S, et al. Anti-Tribbles homolog 2 (TRIB2) autoantibodies in narcolepsy are associated with recent onset of cataplexy. Sleep 2010;33:869-74.
11. Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 2002;59:1553-62
12. Toyoda H, Tanaka S, Miyagawa T, Honda Y, Tokunaga K, Honda M. Anti-Tribbles homolog 2 autoantibodies in Japanese patients with narcolepsy. Sleep 2010;33:875-8.
13. Morrish E, King MA, Smith IE, Shneerson JM. Factors associated with a delay in the diagnosis of narcolepsy. Sleep Med 2004;5:37-41.
14. Waddington CS, Walker WT, Oeser C, et al. Safety and immunogenicity of AS03B adjuvanted split virion versus non-adjuvanted whole virion H1N1 influenza vaccine in UK children aged 6 months-12 years: open label, randomised, parallel group, multicentre study. BMJ 2010 May 27;340:c2649. doi:10.1136/bmj.c2649.
15. Ankeny DP, Popovich PG. The blood-brain barrier and immune function and dysfunction. Neurobiol Dis 2010;37:26-32.
16. Gadoth A, Aizenstein O, Mosek A. Influenza a/h1n1 encephalitis. Neurology 2010;75:666-7
17. Lehmann HC, Hartung HP, Kieseier BC, Hughes RA. Guillain-Barré syndrome after exposure to influenza virus. Lancet Infect Dis 2010;10:643-51.
18. Salemi S, D'Amelio R. Could autoimmunity be induced by vaccination? Int Rev Immunol 2010;29:247-69.