Waking Up to Narcolepsy

Narcolepsy with cataplexy, certainly one of the most fascinating problems in medicine, always seemed (to us) an unlikely candidate for an autoimmune or infectious etiology. In typical cases, the CSF is bland and MRI unrevealing. Powerful evidence (summarized in reference 1) that abnormalities of the hypocretin system contribute to narcolepsy came initially from genetic studies revealing that canine narcolepsy-cataplexy was caused by mutations in the hypocretin receptor 2 gene and that narcolepsy-like behavior followed knock-out of the hypocretin gene in mice. These findings were essential to progress in human narcolepsy, as they helped to focus attention on the hypocretin system in the hypothalamus. Diminished hypocretin levels were found in the CSF of narcoleptic patients, and limited pathologic data suggested that hypocretin containing neurons were selectively lost. However, unlike the single gene model for narcolepsy in dogs, in humans narcolepsy behaves as a complex trait, with both genetic and environmental factors at play. In only one case of human narcolepsy was a hypocretin mutation found; by contrast, most genetic data now point to an immunologic cause. These genetic factors include the class II HLA molecule DQA1*01:02/DQB1*06:02 involved in presenting peptide antigens to T-cells, and more recently the T-cell receptor alpha chain (TCRα) gene,[2] and the P2RY11 receptor,[3] an immune modulatory molecule. With respect to specific infectious agents associated with narcolepsy, the strongest clues to date have implicated streptococcal infections (especially strep throat) and development of antistreptolysin O (ASO) antibodies.[4]

The medical community is with good reason alert to the possibility that neurologic complications might accompany infection with the H1N1 strain of influenza. In 1916-1923, roughly coincident with a global H1N1 flu pandemic that affected several hundred million people worldwide, a curious form of seasonal encephalitis, "encephalitis lethargica," led to somnolence or residual Parkinson's disease in tens of thousands of patients.[5] In 1977, an H1N1 vaccination program was followed by an increase in cases of Guillain-Barré syndrome (GBS), and in 2009 there was concern that vaccination against the new "swine flu" H1N1 strain might also lead to GBS. Fortunately, this did not happen. However, cases of acute narcolepsy-cataplexy began to appear, initially as case reports following H1N1 vaccination or active infection, and the link strengthened following more systematic assessments of vaccination outcomes in Finland and Sweden.[6,7] Could these adverse outcomes represent the beginning of a new sleep disorder associated with H1N1, more than 90 years after "encephalitis lethargica?"

In this issue of the *Annals*, Fang Han and colleagues from Beijing University People's Hospital, in collaboration with Emmanuel Mignot at Stanford University, report that a surge of narcolepsy occurred in 2009-2010 in China that was also remarkable for its seasonal fluctuation, occurring in the late spring and early summer months.[8] The authors propose the H1N1 pandemic (pH1N1) flu virus was responsible for the narcolepsy, but in fact there is little evidence to support this claim beyond the fact that pH1N1 infection had been prevalent the previous winter. In fact, any number of other viruses, bacteria, or even toxins could have been responsible. Vaccination against pH1N1 did not appear to explain the variation in narcolepsy rates. This was a retrospective study that carried the potential for biases in recall and ascertainment, and will need to be replicated and confirmed. However, the data add to evidence of a possible association between infection and narcolepsy, and could point to pH1N1 - in addition to streptococcal infection - as a potential environmental culprit. If specific peptides of pH1N1 are demonstrated to interact with narcolepsy-associated HLA and TCRα genes, we may finally begin to understand the triggers of narcolepsy and this could suggest new approaches for prevention and treatment.

Previously reported associations between administration of some pH1N1 vaccines (e.g. those that contain adjuvant) and the subsequent development of narcolepsy, especially in children, have generated concerns in

the lay public regarding the safety of pH1N1 vaccination programs in Scandinavia, but have not reached the United States. In the US, pH1N1 and seasonal flu vaccines are not adjuvanted, perhaps explaining why associations have not yet been found. Han and colleagues raise the possibility that community acquired H1N1 and flu infection might also cause the same adverse neurologic outcome – narcolepsy – suspected to occur rarely in vaccine recipients. If true, this could reflect a common immune response to a similar antigenic challenge. For example, acute disseminated encephalomyelitis (ADEM) can occur following native infection with measles virus or after administration of measles vaccine; with infection, the risk of ADEM is 1 in 1,000, whereas it is 1-2 per million with vaccination. Thus, although some individuals will develop ADEM from a measles vaccine, a vaccination program that eradicates measles in the community will still reduce the overall incidence of ADEM 1,000-fold if everyone in a population would eventually be expected to be infected. Clearly, we need to insure that all flu vaccines, including those containing pH1N1, are as safe as possible; however, we need also to keep in mind that the risk of any adverse outcome related to vaccination must be balanced against the known risk of community-acquired infection. For H1N1 and narcolepsy, the verdict is not yet in, and more data are sorely needed. Whatever the final answer, the evolving narcolepsy story reminds us once again how easily entrenched concepts of pathogenesis can be turned upside down by new data.

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