Comment on the Letter to the Editor By Dr. Marcus on the Association between Narcolepsy and H1N1 Exposure

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We thank Dr. Marcus for her insightful comment.1 There is no doubt that the association reported between H1N1 and narcolepsy could still be chance, although we find it increasingly unlikely. Ongoing epidemiological studies will answer this question this year. As described in our article,2 the association was more evident following Squalene-Tocopherol adjuvanted H1N1 vaccines (Pandemrix or Arepanrix). The association with other vaccines or post H1N1 infection per se was deemed less strong, but possible, as we reported a surge of recent onset cases in early 2010 (similar to Dr. Marcus). A large portion of the population was infected with H1N1 during the 2009-2010 winter without reporting any symptoms, thus the post-H1N1 narcolepsy is harder to document.

Since we first reported this observation, the association between Pandemrix and narcolepsy has become even more likely. Of 33 million Europeans vaccinated with Pandemrix, approximately 160 have already developed narcolepsy, leading to an incidence of 0.36/100,000, a figure close to habitual yearly incidence of narcolepsy. As it takes years before narcolepsy is diagnosed, many more cases are likely to be present in this sample. Reviewing current evidence, the WHO is now suspecting a 9-fold increase in incidence in Finish children and adolescents.3

Surprisingly, we also found that many post-H1N1 subjects were positive for ASO4 (as in prior samples5) suggesting a role for recent strep throat infections.6,7 We suggest that two factors are needed for the development of narcolepsy: (1) a specific immune–mimicry component, mediated through the presentation by DQB1*0602/DQA1*01026 of a particular antigen to a specific TCR idiotype,7 and (2) nonspecific factors, such as adjuvants, flu or strep infections, streptococcus superantigens, and other factors. These nonspecific effects may reactivate dormant T cell cones, increase blood brain penetration of peripheral immune responses, or could involve novel HLA immune interactions specific to the brain, as suggested recently by HLA class I expression in neurons and interactions with natural killer cell or immunoglobulin-like receptors.8

Interestingly, Genome Wide Association studies in schizophrenia9 and Parkinson’s disease10 have recently shown a weak HLA association signal. This HLA association likely reflects disease heterogeneity and the involvement of autoimmune/infectious diseases in some cases for these diseases. Intriguingly, it has long been forgotten that Von Economo’s encephalitis lethargica, a seasonal disease that followed the great 1918 H1N1 flu pandemic, was a very polymorphic disorder at the symptomatic level.11 Symptoms included extreme somnolence and ophthalmoplegia (associated with lesions of the posterior hypothalamus and upper brainstem), insomnia and sleep inversion (associated with lesions of the anterior hypothalamus), psychosis, movement disorders (chorea type, as seen in post-streptococcal Sydenham’s Chorea, with lesion of the basal ganglia) and a residual form: post-encephalitis parkinsonism. These recent findings increasingly suggest that narcolepsy may be the tip of the iceberg and that a much broader phenotype involving post-infectious autoimmune pathologies of the brain persists in the population at large. Recent cases of Von Economo’s-like encephalitis have also shown increased ASO titers.12

DISCLOSURE STATEMENT

This was not an industry-supported study. Dr. Dauvilliers is consultant for UCB Pharma, Cephalon, Bioproject. 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. GSK is the primary manufacturer of Pandemrix and Arepanrix.

REFERENCES