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ACUTE ENCEPHALOMYELITIS SYNDROMES ASSOCIATED WITH H1N1 09 INFLUENZA VACCINATION

Case reports. *Case 1.* A previously healthy 38-year-old man presented with acute urinary retention and constipation after 4 days of progressive weakness affecting all 4 limbs and patchy sensory disturbance over the trunk and upper arms. Ten days prior to the onset of symptoms, he had received H1N1 09 influenza (Panvax H1N1, CSL Biotherapies, Parkville, Australia) vaccination and had experienced a spontaneously resolving febrile reaction 24–48 hours following administration.

MRI of the brain, cervical, thoracic, and lumbar spine was performed (figure, A). Several areas of central cord T2 signal hyperintensity were demonstrated, extending from C3 to C6 and from T7 to L1, and a diagnosis of longitudinally extensive transverse myelitis was made. Serologic investigations for infective and autoimmune etiologies were unremarkable. CSF demonstrated an inflammatory pattern, with $80 \times 10^6/L$ lymphocytes and 0.78 g/L total protein.

The patient received IV methylprednisolone (1 g/d for 3 days), with resolution in power and sphincter function over the following 10 days.

Case 2. A previously healthy 19-year-old woman presented with a 7-day history of progressive weakness of all limbs, 21 days after vaccination for H1N1 09 influenza. Symptoms progressed until the patient was unable to walk, and were associated with urinary retention, constipation, and paraesthesia over the trunk and legs.

MRI spine demonstrated a transverse myelitis, with high T2 signal and swelling of the cord extending from C2 to C7 and areas of T2 hyperintensity through the proximal thoracic segments (figure, B). Etiologic investigations were unremarkable, with $10 \times 10^6/L$ lymphocytes and 0.52 g/L total protein in CSF.

IV methylprednisolone was administered for 3 days, with resolution of weakness but persistent parasthesia 3 weeks after treatment.

Case 3. A 30-week pregnant 37-year-old woman developed an acute ataxia syndrome 14 days after receipt of the H1N1 09 influenza vaccine. On examination, there was horizontal opsoclonus (ocular flutter) and disrupted smooth pursuit in the

horizontal plane. There was marked dysmetria in the upper limbs and broad-based ataxic gait. The patient exhibited tremor and myoclonus, and the remainder of the examination was normal.

MRI of the brain and spine was unremarkable, as were serologic investigations for infective etiologies. A diagnosis of opsoclonus myoclonus syndrome was made and IV methylprednisolone was administered for 5 days. Symptoms improved and had resolved by day 14 of her illness.

Discussion. We have described 3 cases of acute encephalomyelitis syndromes associated with H1N1 (pandemic) 09 vaccination. Transverse myelitis and opsoclonus myoclonus syndrome are part of a spectrum of neuroinflammatory disorders that have been associated with autoimmune diseases and following viral infections.¹ Transverse myelitis is an acute inflammatory disorder of the spinal cord, characterized by neurologic abnormalities related to segmental spinal cord lesions.² Estimates of population prevalence are based on small numbers of cases, but range from 1 to 8 cases per million/year.³ Opsoclonus myoclonus syndrome is a rare neuroinflammatory disorder that has been described in the setting of CNS malignancies and following viral infection. Clinical features of involuntary saccades, myoclonus, and ataxia are pathognomic for this condition, which may be reversible with steroid or IV immunoglobulin therapy.⁴ While definitive identification of antecedent causes is usually not possible in either condition, the temporal association and exclusion of alternative etiologies raise the possibility that our patients' neuroinflammatory disorders may be related to H1N1 09 vaccination.

Neurologic complications such as encephalitis and Guillain-Barré syndrome have been reported in recent series of acute H1N1 09 infection.⁵ Influenza virus infection has a recognized association with neurologic complications; however, with the exception of the 1976 swine influenza vaccine (A/New Jersey/76 H1N1), influenza vaccination has been shown not to be significantly associated with such adverse events.⁶ The connection between Guillain-Barré syndrome and A/New Jersey/76

(A) MRI thoracic spine, demonstrating extensive longitudinal intramedullary T2 hyperintensity. (B) MRI cervical spine, demonstrating multilevel cord edema and hyperintensity of proximal thoracic segments.

H1N1 vaccination has been well-described, leading to concerns in relation to possible adverse neurologic side effects of H1N1 09 vaccination. Although much of this attention has been directed toward a potential association with Guillain-Barré syndrome, our report highlights the fact that other serious neurologic adverse events should not be neglected.

Currently, large-scale vaccination programs are being implemented worldwide. Prospective surveillance networks of adverse effects of H1N1 09 vaccination have been established in many countries and potential complications are currently being assessed. As with all vaccines, accurate prospective monitoring is essential for establishing both the true incidence of various neurologic events and the relative risk associated with vaccination.⁷ We urge clinicians to be aware of serious neurologic side effects potentially complicating H1N1 09 vaccination and to report suspected adverse events promptly to relevant local organizations such as the Food and Drug Administration/ Centers for Disease Control and Prevention Vaccine Adverse Event Reporting System (United States) or the Medicine and Healthcare Products Regulatory Agency (United Kingdom).

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AN INDEPENDENT REPLICATION OF PARK16 IN ASIAN SAMPLES

Parkinson disease (PD) is the most common neurodegenerative movement disorder with age-related prevalence. Approximately 1% of the population is affected at 65 years, which increases to 4%–5% in 85-year-olds.¹ To date, several loci containing pathogenic or risk variants have been identified; the most recent, *PARK16*, was nominated through 2 genome-wide association studies (GWAS) using samples of Japanese and European ancestry.^{2,3} This new locus, located in 1q32, was originally identified in the Asian study with *p* values ranging from 10^{-7} to 10^{-12} . *PARK16* did not reach significance level in the European GWAS or its replication (*p* value $>10^{-4}$); however, combining samples from stage I and II indicated an association. The most significant SNP in the European study (rs823128) showed a 1% difference in minor allele frequency (MAF) between patients with PD (4%) and control subjects (3%), resulting in an odds ratio (OR) of 0.66 (*p* value = 7.3×10^{-8}) (of note, the allele frequencies seem to have been mistakenly switched in the combined analysis).³ In contrast, the MAF of rs823128 appears to be more common in the Japanese population, with a lower frequency in patients with PD (10%) vs control subjects (14%), resulting in an OR of 1.41 (confidence interval 1.26–1.58; *p* value = 4.9×10^{-7}). Interestingly, rs947211 presents the highest level of significance in the Asian study (*p* value = 1.5×10^{-12}); however, it did not replicate in the European GWAS (uncorrected *p* value = 0.01, OR = 0.93).

In this study, we attempted to replicate this association in 7 independent patient–control series from Asia, Europe, North Africa, and North America (table e-1 on the *Neurology*® Web site at www.neurology.org). Genotyping of rs823128 was performed on the Sequenom platform with a call rate of $>95\%$ for all series. All genotypes were in Hardy-Weinberg equilibrium; allele and genotype frequencies for each series and a combined analysis are displayed in table 1.

We could replicate the association observed in the Japanese population in our Taiwanese series of ethnic Chinese ancestry (OR = 1.46 modeled over the major allele, confidence interval 1.05–2.04; *p* value = 0.015) despite the relatively small sample size of this

series (*n* = 751). In contrast, neither the Tunisian series nor any of the Caucasian samples of European ancestry from North America or Europe, individually or combined, showed evidence for association (*p* value >0.05). The allele frequency for rs823128 is similar in the Taiwanese and Tunisian samples (13%), but low in all the Caucasian series (2%–5%), resulting in decreased statistical power to identify true associations.

This study confirmed the presence of *PARK16* in Taiwanese ethnic Chinese samples. Additional population studies are needed to discern whether *PARK16* is a global risk locus, and to identify the functional variants responsible in Asia.

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Supplemental data at
www.neurology.org

Table 1 Association of rs823128 with Parkinson disease in populations of Asian, Arab-Berber, and European ancestry^a

	rs823128					p Value	
Ancestry/origin	AA	AG	GG	MAF	Power, %	Genotype	Allele
Chinese							
Taiwan							
Controls	247	97	4	0.151	69	0.015 ^b	0.051
Cases	315	82	6	0.117			
Arab-Berber							
Tunisia							
Controls	232	62	8	0.129	42	0.59	0.88
Cases	122	34	3	0.126			
European							
United States							
Controls	935	71	3	0.038	85	0.83	0.97
Cases	1,774	137	5	0.038			
Canada							
Controls	308	22	1	0.036	34	0.25	0.96
Cases	390	30	0	0.036			
Norway							
Controls	554	27	1	0.025	40	0.20	0.70
Cases	638	37	0	0.027			
Ireland							
Controls	343	28	1	0.040	36	0.37	0.39
Cases	328	34	1	0.050			
Poland							
Controls	324	23	1	0.036	32	0.13	0.16
Cases	331	16	0	0.023			
Combined							
Controls	2,464	171	7	0.035	99	0.29	0.83
Cases	3,461	254	6	0.036			

^a Genotype frequencies, estimated p values under genotypic and allelic model are given for 7 independent populations, and combined populations of European ancestry. Power to detect statistically significant associations ($p < 0.05$) for rs823128 in each series is given. Calculations used the observed minor allele frequencies (MAF) and population sizes for each series, and assumed an odds ratio of 1.5, a disease prevalence of 1%, and a dominant model.

^b Significant.

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