### Background:
Although postvaccination Guillain-Barré syndrome is commonly reported, there have only been 2 previously reported cases of postvaccination Miller Fisher syndrome, and none in association with the novel influenza A(H1N1) vaccine.

### Objective:
To describe a case of Miller Fisher syndrome following receipt of the seasonal influenza and novel influenza A(H1N1) vaccine.

### Design:
Case report and literature review.

### Setting:
Vancouver General Hospital.

### Patient:
A 77-year-old Chinese woman.

### Results:
The patient presented with ophthalmoplegia, ataxia, areflexia, and a sensory neuropathy within 2 weeks of immunization. Findings of parainfectious evaluation were unremarkable. Treatment with 2 courses of intravenous immunoglobulin led to clinical improvement. Her presentation and natural history of disease were similar to the 2 previously published cases.

### Conclusions:
We present the third case of postvaccination Miller Fisher syndrome in the literature and the first associated with the novel influenza A(H1N1) vaccine.

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**THE BENEFITS OF THE DEVELOPMENT OF VACCINES AND THE ENSUING MODERN IMMUNIZATION PROGRAMS ARE OVERWHELMINGLY WITHOUT QUESTION. Nevertheless, there is a growing public concern surrounding the potential for postvaccination adverse events, a sentiment that has dwelled since their nascent.**

In view of the recent novel influenza A(H1N1) pandemic and scramble toward developing new vaccines for mass worldwide immunization campaigns, a better understanding of these potential adverse events is vital. We present a case of Miller Fisher syndrome (MFS) following seasonal influenza and novel influenza A(H1N1) vaccination, as well as a review of the literature on postvaccination MFS.

**METHODS**

Published cases of MFS associated with the receipt of a vaccine were obtained via a Medline search, with no date limitations, using the broad search terms (vaccine, vaccination, immunization, post-vaccination or post-immunization and Miller Fisher syndrome, Fisher or Guillain-Barré syndrome). Review articles on postvaccination autoimmunity and postvaccination neurological complications were compiled. The references of the resulting articles were screened for relevant articles.

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**REPORT OF A CASE**

A 77-year-old self-reported ethnic Chinese woman presented in January 2010 with a 6-day history of progressive ascending dysesthesia, unsteadiness, diplopia, and nausea that commenced 13 days after immunization with the seasonal influenza and novel influenza A(H1N1) vaccine. Pertinent findings on examination included complete external ophthalmoplegia, bilateral ptosis, anisocoria, appendicular and axial ataxia, areflexia, and a moderate symmetrical glove-and-stocking sensory deficit involving all 4 primary modalities. Her medical history was remarkable for hypertension and diabetes mellitus type II. Her medications were not contributory. She had no other recent illness or travel history in the preceding 24 months.

Findings of testing of initial cerebrospinal fluid collected 7 days after symptom onset were unremarkable. However, she later demonstrated cytoalbuminologic dissociation at 16 days, with a cerebrospinal fluid protein level of 595 mg/L and white blood cell count of 1/µL. Oligoclonal banding was negative. Findings of standard serum biochemistry screening including creatine kinase, thyroid stimulating hormone, cobalamin, and folate levels were unremarkable. Findings of parainfectious evaluation including cere-
brosplinal fluid herpes simplex virus and varicella-zoster virus as well as serology for human immunodeficiency virus, cytomegalovirus, syphilis, and Lyme disease were negative. Magnetic resonance imaging of the brain showed patchy periventricular and deep white matter T2 fluid-attenuated inversion recovery hyperintensities suggestive of chronic small-vessel ischemic disease. These were felt to be consistent with her ischemic risk factors and age. Furthermore, none of the lesions would account for her clinical presentation. Electrophysiology was consistent with a demyelinating sensory neuropathy, with sensory nerve conduction studies demonstrating prolonged distal latencies and conduction block. Results of testing for anti-GQ1b antibody in samples collected 14 days after symptom onset were negative.

It was felt that her clinical presentation was consistent with MFS. She was treated with 2 courses of intravenous immunoglobulin, separated by a 1-week interval. Dosing was 2 g/kg, administered over 2 to 3 days. She only improved with respect to her ataxia, with the remainder of her deficits persisting on transfer to a rehabilitation facility 4 weeks following presentation.

**COMMENT**

Miller Fisher syndrome is a variant of Guillain-Barré syndrome (GBS), accounting for 5% to 10% of cases, with higher incidences reported in Asian populations.²,³ It is characterized by the clinical triad of ophthalmoplegia, ataxia, and areflexia and is strongly associated with anti-GQ1b antibodies, which are present in excess of 90% of cases.³ Our patient developed MFS 13 days after immunization to both seasonal influenza and novel influenza A(H1N1). Results of testing for anti-GQ1b antibody were negative; however, the sample was collected later into the course of her illness, which can decrease its sensitivity.³,⁶ We were able to find 2 other cases of MFS following vaccination in the literature (Table). One occurred in a 64-year-old man 5 days after seasonal influenza vaccination and the other in a 66-year-old woman 1 week after receipt of the seasonal influenza and the Pneumovax vaccine.⁷,⁸ All cases occurred within a 2-week interval from vaccination and showed improvement following intravenous immunoglobulin treatment. Recovery was incomplete in all cases; however, this finding may be confounded by short follow-up durations. In our case, it is uncertain which vaccine, if either, was the offending agent.

Although postvaccination MFS specifically is rarely reported, GBS after vaccination is reported more frequently, particularly in association with the influenza vaccine. During the US novel influenza A(H1N1) vaccination campaign of 1976, the 45 million adults immunized with the A/New Jersey/8/76 swine flu vaccine were found to have a statistically significant 4- to 8-fold higher incidence of GBS than the general public. Cases occurred within 6 weeks of vaccination (P < .05), with a peak in the second and third weeks.⁹,¹⁰ Initially, subsequent studies spanning from 1978 to 1988 looking at the risk of post–seasonal-influenza-vaccination GBS found relative risks of 1.1 to 1.4 that were not statistically significant.¹¹-¹³ However, a review of cases

<table>
<thead>
<tr>
<th>Source</th>
<th>Sex/Age, y</th>
<th>Vaccine (Season)</th>
<th>Time to Symptom Onset</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoamanesh et al (current study)</td>
<td>F/77</td>
<td>Novel influenza A(H1N1) (2009-2010); seasonal influenza (2009-2010)</td>
<td>13 d: nausea, ascending dysesthesia, diplopia, ataxia</td>
<td>CSF: WBC, 1 µL; protein level, 595 mg/L; anti-GQ1b antibody; negative MRI: nothing significant Electrophysiology: demyelinating sensory neuropathy</td>
<td>IVIG</td>
<td>Persistent ophthalmoplegia at 1-mo follow-up</td>
</tr>
<tr>
<td>Blanco-Marchite et al, 2008</td>
<td>M/64</td>
<td>Seasonal influenza</td>
<td>5 d: diplopia, dizziness, unsteadiness</td>
<td>CSF: cytologic dissociation; anti-GQ1b antibody, positive CT: unremarkable</td>
<td>IVIG</td>
<td>Persistent ophthalmoplegia</td>
</tr>
<tr>
<td>Thaler, 2008</td>
<td>F/66</td>
<td>Seasonal influenza (2007-2008), Pneumovax</td>
<td>1 week: headache, dysarthria, dyphagia, ascending dysesthesia Followed by: facial weakness, neuropathic pain, autonomic instability</td>
<td>MRI: nothing significant</td>
<td>IVIG</td>
<td>Persistent ataxia, sensory neuropathy, and dysarthria</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; WBC, white blood cell count.
between 1992 and 1994 found a relative risk of 1.7 (confidence interval, 1.0-2.8; P < .04). Overall, influenza immunization is thought to cause approximately an additional 1 case of GBS per million vaccinations. Fifteen percent of these cases result in permanent disability and 4%, in death. With respect to the 2009-2010 novel influenza A(H1N1) vaccine campaign, there were 0.42 and 1.75 verified cases of GBS reported to the Vaccine Adverse Event Reporting System per million vaccinations for vaccine recipients younger than 25 years and those 25 years or older, respectively, from July 1, 2009, through January 31, 2010. Based on previous studies, these rates were deemed lower than the expected background rates of GBS. Specific background rates for the period studied were, however, not provided. Conversely, preliminary results from the Center for Disease Control and Prevention's Emerging Infections Program shows an age-adjusted rate ratio of 1.77 (confidence interval, 1.12-2.56) in comparing the incidence of GBS among patients hospitalized through March 31, 2010, who received the 2009 novel influenza A(H1N1) vaccine and those who did not. This would correspond to an attributable risk of 0.8 excess cases of GBS per million vaccinations. Guillain-Barré syndrome, including MFS, is thought to be an autoimmune disorder, with molecular mimicry serving as a potential mechanism. Influenza vaccination has been shown to increase autoantibodies in humans. More specifically, the injection of various influenza vaccines, including the 1976 novel influenza A(H1N1), induced experimental allergic neuritis-like disease in rabbits. Similarly, Nachamkin et al have shown that the 1976 novel influenza A(H1N1) vaccine can induce anti-GM1 antibodies in mice in the absence of antibodies toward Campylobacter jejuni. This was also the case with seasonal influenza vaccines. The authors proposed that the individual immunogenic properties of various influenza vaccine strains could account for the variability in GBS incidence seen from one season to another. The immunogenic potential is likely a function of the influenza virus itself, rather than the preservatives or detergents used in the manufacturing process. The induction of anti-GQ1b antibodies by vaccines is unexplored and worthy of research. We present the third case of postvaccination MFS in the literature, and the first in association with the novel influenza A(H1N1) vaccine. In accordance with the World Health Organization's causality assessment criteria, it is “very likely” that, in our patient, disease was caused by the administration of vaccine. Postvaccination GBS, and MFS in particular, is a rare occurrence and should not deter at-risk populations from being vaccinated.

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Correspondence: Ashkan Shoamanesh, MD, Department of Medicine and Neurology, University of British Columbia, 1103-1068 W Broadway Ave, Vancouver, BC V6H 0A7, Canada (ashkan.sho@gmail.com).

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REFERENCES