Neurologic Complications Associated with Influenza Vaccination: Two Adult Cases

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Abstract

We describe two adult cases of neurologic complications occurring after influenza vaccination. The first case was a 62-year-old man who experienced convulsions 5 days after vaccination, and the second case was a 70-year-old man who exhibited paraplegia 7 days after vaccination. Diagnoses of acute disseminated encephalomyelitis and transverse myelitis with acute motor axonal neuropathy were made, respectively, and steroid pulse therapy and intravenous gamma globulin therapy alleviated the patients' symptoms. Although the efficacy and cost benefit of influenza vaccination have been widely accepted, such neurologic complications might occur in the elderly or even in adults.

Key words: acute disseminated encephalomyelitis, myelitis, acute motor axonal neuropathy, influenza vaccination, adult onset, side effect

Case Reports

Patient 1 was a 62-year-old man who had been diagnosed with type-C liver cirrhosis, for which he had been admitted to our hospital once or twice per year for treatment. Five days after an influenza vaccination (HA type, 22-7-B) administered by a home doctor on November 20, 2001, generalized convulsion occurred and the patient was admitted to our hospital. He was intubated transiently in the emergency room because of respiratory failure. Myoclonic movement was found on the left side of his face when he was transferred to a neurological ward. There was no apparent paresis. His reflexes were generally hyperactive, and pseudobulbar palsy and dysuria were noted. Laboratory analyses revealed liver dysfunction and a serum ammonium concentration of 237 µl/dl. There was no significant inflammatory reaction and antibodies for the influenza virus in paired sera were not significantly elevated. A lumbar tap revealed a pressure of 140 mmH2O, and cerebrospinal fluid examination revealed a protein concentration of 280 mg/dl, five cells per microliter, and an IgG concentration of 101 µg/ml. MR diffusion- and T2-weighted images exhibited high signal intensities in midbrain, bilateral occipital cortices, right insular cortex, temporal operculum, inferior frontal gyms, and left frontal white matter (Fig. 1). Although MR images obtained 3 weeks after admission showed no abnormalities in the spinal cord, the patient presented bladder dysfunction and thus we diagnosed him as having ADEM. The left facial myoclonus disappeared after daily intravenous administration of 1,000 mg methylprednisolone for 3 days. The same dosage was administered again one week later, and the pseudobulbar palsy was ameliorated. One month later the dysuria also was alleviated. At that time the abnormal-intensity lesion in MRI disappeared. Serum ammonium level decreased to around 150 µl/dl by administration of branched amino acid and he was discharged without any sequelae.

Patient 2 was a 70-year-old man with a history of rheu-
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Figure 1. Cranial MR imaging at admission in case 1. A. Diffusion-weighted image exhibiting high signal intensities in bilateral occipital cortices, right insular cortex, and right thalamus. B. T2-weighted image also exhibiting high signal intensities, but these are less prominent than in the diffusion-weighted image.

Asthmatic arthritis and diabetes mellitus. His home doctor had controlled both diseases and the severity was mild. Backache followed by dysuria and paraplegia appeared 7 days after an influenza vaccination administered by his home doctor on November 4, 2000. The cranial nerves were normal, but right lower-dominant paraplegia and distal upper-limb motor pareses were noted. The right patella tendon reflex was hyperactive, but other reflexes were reduced. Below the nipple level all sensation modalities were suppressed. Laboratory analyses revealed an increased lymphocyte CD4/CD8 ratio, and anti-GM1 antibodies were detected in his serum. An antibody titer for the influenza virus was unremarkable for paired sera. An antinuclear antibody was negative. RA measured 503 IU/ml. The serum HbA1c concentration was 7.3%. Although there was neither pleocytosis nor elevated protein concentration in the cerebrospinal fluid, the amplitude and, to a lesser extent, the velocity of the muscle compound action potentials were reduced (Table 1), which suggested acute motor axonal neuropathy. Follow-up data obtained 1 month later showed only partial recovery in the amplitude of muscle compound action potentials. Sensory evoked potentials induced by median nerve stimulation were almost normal, but tibial nerve stimulation did not evoke a response. A spinal MR T2-weighted image exhibited a high signal intensity in C6-T3 vertebral level (Fig. 2A). Brain MRI showed only lacunar infarction. A daily dose of 1,000-mg methylprednisolone was administered for 3 days, followed by 60 mg of prednisolone per day, which was gradually reduced.

Because of poor response to steroid therapy and symptom similarity to Guillain-Barré-type neuropathy, plasma exchange was performed but was not effective. A high dose of gamma globulin (0.5g/kg body weight) was administered.

Table 1. Nerve-conduction Data for Case 2

<table>
<thead>
<tr>
<th>Nerve</th>
<th>MCV (m/s)</th>
<th>Amplitude (mV)</th>
<th>SCV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>47.0/50.0 (NE/52.0)*</td>
<td>0.1/2.5 (0.0/4.0)</td>
<td>54.0/59.0 (62.0/60.0)</td>
</tr>
<tr>
<td>Ulnar</td>
<td>39.0/34.0 (43.0/46.0)</td>
<td>1.9/3.0 (3.5/4.5)</td>
<td>–</td>
</tr>
<tr>
<td>Tibial</td>
<td>39.0/40.0 (34.0/43.0)</td>
<td>6.0/7.0 (4.0/6.5)</td>
<td>–</td>
</tr>
<tr>
<td>Sural</td>
<td>–</td>
<td>–</td>
<td>38.0/49.0 (32.0/45.0)</td>
</tr>
</tbody>
</table>

*right/left: measured at admission (one month later). MCV: Motor nerve conduction velocity, SCV: Sensory nerve conduction velocity, NE: Not evoked.
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Figure 2. Spinal cord MR T2-weighted imaging in case 2. A. Image exhibiting a high signal intensity in C6-T3 vertebral level at admission. B. Image obtained 4 months after demonstrates the reduction of the lesion.

We did not find any case report in the literature where the patient had both transverse myelitis and motor axonal neuropathy associated with vaccination. There have been twice in 5 days with 5 weeks interval and the first administration showed some efficacy. A follow-up spinal MR image 4 months after showed a reduction of the lesion (Fig. 2B), but although the patient showed partial recovery, he was still unable to walk unaided after 10 months. The serum HbA1c concentration was reduced to 6.4% by diet when he was discharged.

Discussion

In our case 1, hyperammonium was present but such focal lesions were usually not found in the central nervous system—we therefore concluded that the lesions were caused by ADEM. The cerebrospinal fluid was not reanalyzed at the follow-up because of rapid reduction of symptoms. In case 2 the CSF findings were normal at admission, perhaps because of the examination being performed too early, and unfortunately there was no follow-up data. Although the patient had diabetes mellitus, its severity was too mild to cause polyneuropathy. Spinal MRI findings, the nerve-conduction study, and the presence of anti-GM1 antibodies in the patient’s serum strongly suggested acute myeloneuropathy caused by an allergic reaction.

The occurrence of complications following influenza vaccination decreased after the introduction of the HA type of influenza vaccine in 1972 in Japan, but up to 1996 around 70 cases with neurologic complications had been reported (3). ADEM and myelitis constituted eight and two of these cases, respectively, and all were children. GBS was reported in 16 cases, but all of the cases may not have been related to the vaccination because some cases had prodromal infection. The present report is important because both cases were adults (i.e., early-elderly subjects). Epidemiologic evidence from the US has indicated that many cases of GBS occurring after receiving an A/New Jersey (swine) influenza vaccination in 1976 were related to the vaccination itself (1). A surveillance program concluded that the causative “trigger agent” in the vaccine administered in 1976 has not been present in subsequent influenza vaccines (4). Up to 2001 only a small number of GBS cases following vaccination had been reported in Japan. Antony et al reported a case of Brown-Séquard syndrome following the administration of trivalent influenza vaccine, describing it as the first case to be reported in the literature (2). Bakshi and Mazziotta reported MRI findings in acute transverse myelitis after influenza vaccination—the patient had a complete long-term recovery of neurological function with a good response to steroids (5).
reports of an axonal-type GBS with anti-GM1 antibodies in the patient’s serum, but these had not occurred after vaccination. We think that both myelitis and GBS-type polyneuropathy might occur after vaccination. A possible immunological cross-reaction between the antigen of *Campylobacter jejuni* and GM1 ganglioside has been reported (6, 7), so that after *C. jejuni* infection such an allergic reaction might occur. The presence of anti-GM1 antibodies in the sera of the present patients is rather unusual because there is no such prodromal *C. jejuni* infection. Determining the risk of neurologic complications is of course difficult, but the cases presented here were associated with underlying disease (such as type-C liver cirrhosis and rheumatic arthritis), and so there might have been an underlying immunological status that produced such an allergic neurologic reaction.

Concerning the treatment, steroid pulse therapy was effective in patient 1 whereas neither steroid treatment nor plasma exchanges were effective in patient 2, but intravenous gamma globulin showed mild efficacy in the latter patient. Because of the rarity of this disease with only a few cases reported in the literature, no treatment regimen has been established.

In patients with multiple sclerosis the exacerbation rate following influenza illness is significantly higher than that after vaccination, and hence an annual influenza vaccination should be offered routinely to all patients with relapsing multiple sclerosis (8). Govaert et al reported the efficacy of influenza vaccination in elderly individuals in a randomized double-blind placebo-controlled trial (9), and Nichol et al proved the efficacy and cost effectiveness of vaccination in multiple sclerosis. Therefore, the rare occurrence of the complications and the possibility of neurologic complications after influenza infection should not discourage us against vaccination. Even though adult cases with ADEM or myelitis after influenza vaccination are rare, if a person shows some neurologic signs after the vaccination the home doctor should still refer the patient to a neurologist as soon as possible. Further epidemiological surveillance for complications and the effectiveness of influenza vaccinations might be worthwhile in Japan.

**Acknowledgements:** We thank Dr. S. Kusunuki for his help in measuring anti-GM1 antibodies in the patient’s sera.

**References**


