Acute Transverse Myelitis and Acute Motor Axonal Neuropathy Developed after Vaccinations against Seasonal and 2009 A/H1N1 Influenza

Nozomu Sato¹,², Kosuke Watanabe¹, Kiyobumi Ohta¹,² and Hiroaki Tanaka¹

Abstract

Acute transverse myelitis (ATM) has been described as an uncommon complication of vaccinations and is rarely accompanied by inflammatory peripheral neuropathy. We report a case of a 77-year-old woman who developed ATM and acute motor axonal neuropathy (AMAN) following vaccinations against seasonal and 2009 A/H1N1 influenza. She manifested ophthalmoplegia, quadriplegia and sensory impairment. MR imaging showed a longitudinally-extensive spinal cord lesion, and nerve conduction study revealed motor axonal polyneuropathy. Despite prompt treatment, her symptoms poorly recovered. While concurrent ATM and AMAN may suggest the presence of a common antigen, their scarcity indicates the importance of other factors causing immunologic disruptions.

Key words: acute transverse myelitis, acute motor axonal neuropathy, post-vaccination, influenza, 2009 A/ H1N1 influenza and interleukin-6

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Introduction

Acute transverse myelitis (ATM) is an inflammatory disorder of the spinal cord that can develop as a manifestation of multiple sclerosis, neuromyelitis optica and systemic disorders, such as systemic lupus erythematosus, Sjögren’s syndrome and sarcoidosis (1). Alternatively, it can be an isolated illness, and is often described in association with preceding infections or vaccinations (2). Simultaneous development of inflammatory disorders of the central nervous system (CNS) and the peripheral nervous system (PNS) is generally considered to be uncommon, and there have been an extremely limited number of cases of concurrent ATM and inflammatory peripheral neuropathy.

Here we report a case of ATM accompanied by acute motor axonal neuropathy (AMAN) that left severe disabilities following vaccinations against seasonal and 2009 A/H1N1 influenza viruses. To our knowledge, this is the third published report of an adult case of concurrent ATM and AMAN (3, 4), and the second report of ATM in temporal association with 2009 A/H1N1 flu vaccines (5).

Case Report

A 77-year-old woman with a history of successfully resected rectal cancer received vaccinations against seasonal influenza (trivalent, unadjuvanted, inactivated, split-virus vaccine) and, a month later, against 2009 A/H1N1 flu (monovalent, unadjuvanted, inactivated, split-virus vaccine derived from A/California/7/2009 virus). One day after the second vaccination, she woke up with a chest pain. An hour later, tingling feelings in her hands developed, and weakness of her arms and legs appeared and rapidly deteriorated over the next 24 hours. She had no signs or symptoms suggesting preceding infections.

On presentation, she manifested restricted eye movements, complete tetraplegia, impaired sensation of all modalities below the C5 level and urinary retention. Tendon reflexes were persistently diminished throughout the course and the plan-
tar reflexes were bilaterally extensor. Respiratory insufficiency became apparent and she needed ventilator support.

MR imaging revealed a longitudinally extensive spinal cord lesion from the C2 to the upper thoracic level (Fig. 1A). The lesion extended over the whole transaxial section of the cervical spinal cord (Fig. 1B) and slight enhancement with gadolinium was observed (Fig. 1C). No lesion was seen below the T7 level (Fig. 1D). Brain MRI only detected small ischemic lesions in the cerebral white matter and the brainstem was intact.

Cerebrospinal fluid (CSF) analyses (Table 1) showed a normal cell count (2/mm³), normal protein level (0.36 g/L)

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**Table 1.** Data Obtained by Cerebrospinal Fluid Analyses

<table>
<thead>
<tr>
<th>Days after admission</th>
<th>0</th>
<th>14</th>
<th>49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell count / 3 mm³</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mon / 3 mm³</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Poly / 3 mm³</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Protein / g/L</td>
<td>0.36</td>
<td>0.36</td>
<td>0.19</td>
</tr>
<tr>
<td>IgG index</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBP / g/L</td>
<td>159 x 10⁻⁹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCB</td>
<td>N. D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6 / g/L</td>
<td>559 x 10⁻⁹</td>
<td>3.2 x 10⁻⁹</td>
<td>3.2 x 10⁻⁹</td>
</tr>
<tr>
<td>HSV-DNA PCR</td>
<td>N. D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VZV-DNA PCR</td>
<td>N. D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV-DNA PCR</td>
<td>N. D.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Mon, mononuclear cells; Poly, polymorphonuclear cells; MBP, myelin basic protein; OCB, oligoclonal band; IL-6, interleukin-6; HSV, herpes simplex virus; VZV, varicella-zoster virus; EBV, Epstein-Barr virus; N. D., not detected.
concentration (usually $< 4.3 \times 10^{-7}$ g/L) concentration and normal IgG index (0.52), but the interleukin-6 (IL-6) concentration (usually $< 4.3 \times 10^{-7}$ g/L) was markedly increased ($5.59 \times 10^{-7}$ g/L). HSV, VZV and EBV were not detected by PCR from the CSF. Serum anti-AQP-4, anti-DNA, anti-GM1, anti-GD1a, anti-GD1b and anti-GQ1b antibodies, were not detected. Serum angiotensin-converting enzyme and IgE levels were normal. Serum CEA and soluble interleukin-2 receptor were not elevated, and thoracic and abdominal CT scans revealed no abnormal findings suggestive of malignancy.

Because of ophthalmoplegia and persistently diminished tendon reflexes, concurrent involvement of peripheral nerves was suspected. Nerve conduction study (NCS) conducted on admission day (one day after the onset of the symptoms) revealed increased motor stimulation thresholds and absent F-waves responses in every tested nerve. Subsequent NCS conducted three days later (Table 2) showed decreased compound-muscle-action-potential (CMAP) amplitudes in bilateral median and ulnar nerves, and those of the bilateral posterior tibial nerves were initially normal, but they also decreased to less than half of the original values on the follow-up NCS (Fig. 2). Sensory nerve conduction study detected mild abnormalities only at common entrapment sites. There were no signs of demyelination; severely reduced nerve conduction velocities, temporal dispersions or conduction blocks were not observed. Serum anti-ganglioside antibodies, including anti-GM1, anti-GD1a, anti-GalNac-GD1a, anti-GD1b and anti-GQ1b antibodies, were not detected. *Campylobacter jejuni* was not isolated from her stool culture.

A diagnosis of ATM and suspected Guillain-Barré syndrome (GBS), the latter of which was subsequently changed to AMAN based on the NCS findings, was made on admission day, and she was treated with intravenous high-dose immunoglobulin (0.4 g/kg body weight/day for 5 days) and methylprednisolone pulse therapy (1 g/day for 3 days) followed by prednisolone administration, which started at 60 mg/day and was gradually tapered off. Her eye movements improved and the CSF IL-6 level normalized within the following two weeks (Table 1). The swelling of the spinal cord had subsided in the follow-up MR imaging (Fig. 1E). Her muscle tonus, initially flaccid, started to increase within two months. However, her weakness and impaired sensations made little recovery, and she remained bed-ridden and ventilator-dependent at discharge from the hospital, eight

**Table 2. Findings of the Nerve Conduction Study within the First Four Days of Admission**

<table>
<thead>
<tr>
<th>Nerve</th>
<th>CMAP Amp. / mV</th>
<th>MCV / m/sec</th>
<th>TL / msec (Dist. / mm)</th>
<th>F waves</th>
<th>SNAP Amp. / µV</th>
<th>SCV / m/sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Lt</td>
<td>2.0 / 2.0 / 1.9</td>
<td>54.4 / 44.1</td>
<td>4.1 (75)</td>
<td>N. R.</td>
<td>19.6* / 10.5*</td>
<td>53.5* / 56.6*</td>
</tr>
<tr>
<td>Median Rt</td>
<td>2.0 / 1.4 / 1.6</td>
<td>49.8 / 46.5</td>
<td>3.8 (70)</td>
<td>N. R.</td>
<td>15.0 / 8.7</td>
<td>42.9 / 58.2</td>
</tr>
<tr>
<td>Ulnar Lt</td>
<td>2.7 / 2.8 / 2.6</td>
<td>50.8 / 55.3</td>
<td>3.0 (55)</td>
<td>N. R.</td>
<td>8.5* / 5.8* / 4.0*</td>
<td>48.3* / 71.0* / 53.7*</td>
</tr>
<tr>
<td>Ulnar Rt</td>
<td>2.1 / 2.1 / 2.1</td>
<td>62.1 / 36.4</td>
<td>2.9 (66)</td>
<td>N. R.</td>
<td>16.5 / 5.3 / 4.9</td>
<td>51.8 / 64.6 / 52.9</td>
</tr>
<tr>
<td>Posterior tibial Lt</td>
<td>16.2* / 11.8*</td>
<td>47.6*</td>
<td>5.8* / 80*</td>
<td>N. R.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior tibial Rt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sural Rt</td>
<td>14.8 / 9.1</td>
<td>36.0</td>
<td>3.4 / 78</td>
<td>N. R.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The data shown in the table were taken three days after the admission except for the MCS and F-wave analysis of the left posterior tibial nerve and SCS of the left median and ulnar nerves, which were not examined on that day. For these, the data on the admission day were shown instead (shown with asterisks). Although the CMAP amplitudes of the bilateral posterior tibial nerves were initially normal, their motor stimulation thresholds were markedly increased. For example, stimulations of 81 mA for the right posterior tibial nerve and 53 mA for the left were needed to obtain the supramaximal stimulations at the ankles, where no edema was seen.

Abbreviations: MCS, motor nerve conduction study; SCS, sensory nerve conduction study; CMAP, compound muscle action potential; Amp., amplitude; MCV, motor conduction velocity; TL, terminal latency; Dist., distance; SNAP, sensory nerve action potential; SCV, sensory conduction velocity; Lt, left; Rt, right; N. R., no response.

**Figure 2.** Serial nerve conduction studies on the left posterior tibial nerve. Initially, the CMAP amplitude was normal (16.2 mV) when the nerve was stimulated at the ankle (A), but a month later, it was reduced to 7.9 mV (B). No significant reduction was observed in the motor conduction velocity.

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months after the development of the disease.

**Discussion**

The present case developed severe ATM with accompanying AMAN following immunizations against seasonal and 2009 A/H1N1 flu, whereas the presence of systemic autoimmune disease, malignancy or viral infection was unlikely. Although the CSF cell count, protein level and IgG index were not elevated, the clinical manifestations and the MRI findings fulfilled the proposed diagnostic criteria of idiopathic ATM (6).

Despite the prompt treatment, she poorly recovered from her neurological deficits. Recently, IL-6 has been shown to be selectively elevated in CSF in transverse myelitis with its concentration being correlated with clinical long-term outcome (7). Markedly elevated CSF IL-6 in the present case might suggest that the cytokine cascade involving IL-6 could be a candidate for the target of therapy.

Since the spinal cord lesion could not explain impaired eye movement or continuously diminished tendon reflexes of the lower extremities, and there were no other lesions visible on MRI to explain these findings, simultaneous involvement of the PNS was suspected. Having started treating with intravenous immunoglobulin, we reserved our diagnosis at the time of the second NCS (Table 2). Diminished F-wave responses and decreased motor neuron excitability are known to be signs of spinal shock (8), and decreased CMAP amplitudes in the upper extremities might have been just reflecting Wallerian degeneration due to the cervical spinal cord lesion. Reduced CMAP amplitudes have been documented in some patients as early as four days after acute spinal cord injury (SCI) (9), although another article insisted that it would not be observed until one week after acute SCI (10). Having confirmed the results of the follow-up NCS, which showed reduced CMAP amplitudes of the posterior tibial nerves (Fig. 2), and of the spinal MR imaging, which revealed no lesion to explain persistently diminished patella and Achilles tendon reflexes, we reached the conclusion that concurrent AMAN was the likely diagnosis, though anti-ganglioside antibodies were not detected. While myelitis left severe neurological deficits, complete recovery of ophthalmoplegia was obtained in the present case, indicating the importance of proper diagnosis and treatment of peripheral nerve involvement, which is often overlooked in patients with fulminant CNS impairment.

Although being rare, various inflammatory neurological disorders, such as acute demyelinating encephalomyelitis (ADEM), ATM and GBS, have been described in association with flu vaccinations (3, 11, 12). Their causative relationships are uncertain, except for one instance: a clear epidemiological link was observed between the 1976 swine flu vaccination and the subsequent increase in the incidence of GBS (12). The exact component of the 1976 vaccine that triggered GBS, however, is still unknown. The causal association between the vaccinations and ATM and AMAN in the present case is also obscure. As the year 2009 witnessed a global outbreak of a new strain of A/H1N1 influenza virus, people at higher risk were recommended to receive vaccines (13). Health authorities have been monitoring adverse events out of caution, and, to date, there have been no data suggesting their inferior safety (14).

Inflammatory disorders overtly affecting both the CNS and PNS are generally considered to be uncommon, but simultaneous impairment of peripheral nerves has been documented in a few cases of ATM associated with influenza vaccination (3, 11). ATM accompanied by AMAN is even rarer and, to our knowledge, there have been only two adult cases reported so far (3, 4).

The mechanism of molecular mimicry has been proposed and vigorously investigated for AMAN that develops following Campylobacter jejuni infection. The lipopolysaccharide components of C. jejuni include ganglioside-like structures (15) and have been shown to induce production of anti-GMI IgG antibodies (16), which are characteristic, and may or may not be directly causative (17, 18), antibodies in AMAN. Interestingly enough, there have been a couple of cases of ATM that followed C. jejuni enteritis (19, 20), in one of which serum anti-GM1 IgG and IgM were elevated (20). Moreover, a few cases of ADEM after C. jejuni infection have been reported, and in one case concurrent AMAN was documented (21). Indeed, gangliosides are abundantly found not only in the PNS but also in the CNS (22), and immunohistochemistry analysis showed broad distribution of GM1 across the spinal cord, especially in the grey matter (23). Based on these findings, we speculate that the presence of a common antigen may underlie simultaneous development of ATM and AMAN. On the other hand, we could not find any data directly suggesting molecular mimicry between the nervous tissue and influenza vaccines. The latent period of less than 24 hours between the second vaccination and the disease onset may also argue against the possibility that 2009 A/H1N1 flu vaccination might have resulted in cross-reactive immune responses to the nervous system.

The fact that concurrent ATM and AMAN are extremely rare indicates that the presence of a common epitope alone cannot explain the pathogenesis of the present case. In addition to molecular mimicry, inflammatory neurological disorders can be triggered by vaccines through other mechanisms, such as epitope spreading and activation of heterogeneous lymphocytes through cytokine productions (2, 24). The markedly elevated CSF IL-6 level might suggest the latter possibility, and in this respect, one cannot rule out the potential causal effect of either of the preceding vaccinations. Indeed, a similar effect of vaccination can be postulated as part of the pathogenesis of myelitis that developed only two days after immunization against influenza in a man with a history of bilateral optic neuritis (25). The benefits of immunizations against influenza virus have been established, but we should bear in mind that, in extremely rare occasions, severe inflammatory neurological disorders are ob-
served in temporal relationship with vaccinations.

The authors state that they have no Conflict of Interest (COI).

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References