Simultaneous Development of Acute Disseminated Encephalomyelitis and Guillain-Barré Syndrome Associated with H1N1 09 Influenza Vaccination

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Abstract

A 36-year-old man was admitted to our hospital because of urinary retention and muscle weakness affecting all 4 limbs after receiving a H1N1 09 influenza vaccination. Magnetic resonance imaging demonstrated multiple lesions in his brain and spinal cord. Furthermore, nerve conduction study showed acute sensorimotor neuropathy, and anti-GM2 antibodies were detected in his serum. Based on the temporal association and exclusion of alternative etiologies, we made a diagnosis of acute disseminated encephalomyelitis (ADEM) and Guillain-Barré syndrome (GBS). To our knowledge, this is the first case of co-morbid ADEM and GBS after influenza vaccination with positive anti-ganglioside antibodies.

Key words: acute disseminated encephalomyelitis, anti-ganglioside antibody, GM2 ganglioside, Guillain-Barré syndrome, influenza vaccination


Introduction

Acute disseminated encephalomyelitis (ADEM) and Guillain-Barré syndrome (GBS) are neuroinflammatory disorders associated with antecedent infection, immunization or vaccination, typically affecting the central nervous system (CNS) and peripheral nervous system (PNS), respectively (1, 2). Molecular mimicry and cross-reactive immune response is considered to play a crucial part in their pathogenesis (1, 2). Concurrent neuroimmunological disorders of the CNS and PNS are uncommon, and few cases presenting with the simultaneous development of ADEM and GBS have been described to date.

Case Report

A previously healthy 36-year-old man of third-generation Brazilian of Japanese descent developed acute urinary retention 10 days after receiving a H1N1 09 influenza vaccination (monovalent, unadjuvanted, inactivated, split-virus vaccine derived from A/California/7/2009 virus). He consulted the urology department in our hospital, and started intermittent self-catheterization. Further examination performed in the neurology department showed no evident abnormalities in the cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) of the brain, cervical, thoracic, and lumbar spine. A week later, he noticed weakness and numbness affecting all 4 limbs. These symptoms progressed for 3 days, and he thereafter developed difficulty walking. He was admitted to our hospital on the 21st day after vaccination. On admission, his axillary temperature was 38.2°C, and he had nuchal rigidity. A neurological examination showed tetraparesis, numbness, and impaired sensation of all modalities below the C5 level. The tendon reflexes were diminished in the upper extremities and lost in the lower extremities, and plantar responses were bilaterally extensor. Routine laboratory tests showed no abnormalities. Serum antibodies against glycolipid antigens, including anti-GM2 IgM antibodies were measured by enzyme-linked immunoabsorbent assay as described elsewhere (3). The specific optical density (OD) values were corrected by subtracting the OD of a control.
well, and a serum was considered positive if the specific OD was more than 0.1 for anti-GM2 IgM antibodies. Anti-GM2 antibodies were positive (specific OD, 0.312) with the IgM class, while other types of anti-glycolipid antibodies, including anti-GM1, GM3, GD1a, GD1b, GQ1b, GA1 (asialo GM1), and galactocerebroside (GalC) antibodies were not detected in his serum. CSF contained 69 lymphocytes/mm³ and 57 mg/dL protein. Intrathecal IgG production was not increased, and isoelectric focusing for oligoclonal bands was negative. Bacterial and viral infections including *Campylobacter jejuni*, *Mycoplasma*, herpes-genus viruses, including cytomegalovirus, and human immunodeficiency virus were extensively screened in stool, serum or CSF, however, all results were negative. MRI on the 22nd day after vaccination showed multiple T2-weighted and FLAIR high signal lesions in the white matter, brainstem and cervical spine, and slight enhancement after administration of gadolinium was observed (Fig. 1). Nerve conduction study (NCS) indicated sensory-motor neuropathy with the abnormal median-normal sural (AMNS) response pattern, that is, he had reduced median amplitudes compared with sural amplitudes (Table 1). The sensory nerve action potential (SNAP) was not elicited in bilateral median and right ulnar nerves. Visual evoked potentials were unremarkable.

ADEM with peripheral neuropathy of unknown cause was suspected at the time of hospitalization, and we started administering intravenous methylprednisolone 1 g/day for 3 days. His symptoms, including urinary retention, were markedly improved, thus we added one more course of the same treatment after an interval of one week. He became able to walk again without assistance by the 35th day, and stopped self-catheterization on the 40th day after vaccination. Subsequently, his anti-GM2 antibody titer was found to be positive, and GBS was diagnosed. MRI of the brain and cervical spine on the 41st day was unremarkable, and NCS on the 42nd day after vaccination showed elicited SNAP in bilateral median and ulnar nerves with decreased amplitudes. Although he could independently perform the activities of daily living, mild weakness and numbness of the distal extremities persisted, and he was transferred to a rehabilitation center on the 55th day after vaccination. There has been no recurrence or worsening of symptoms for more than 3 months from the onset.

**Discussion**

A 36-year-old man simultaneously developed ADEM and GBS. He had no symptoms indicating prior infection. The temporal association and exclusion of alternative etiologies raised the possibility of neuroinflammatory disorders related to the antecedent influenza vaccination. To the best of our knowledge, this is the first case of co-morbid ADEM and...
GBS after influenza vaccination with positive anti-ganglioside antibodies.

ADEM is a monophasic syndrome occurring in the context of an infection, immunization, or vaccination. It typically follows a prodromal phase of 1-4 weeks, then multifocal lesions of the CNS appear (1). Acute urinary retention is common in ADEM (4). Successful use of high-dose steroids has been widely reported to provide marked improvement of the symptoms in ADEM patients (5).

GBS is an acute polynuropathy typically characterized by progressive muscle weakness and areflexia. In addition to ADEM, immune-mediated mechanisms due to molecular mimicry are considered to be responsible for the pathogenesis of GBS. In about half of patients with GBS, serum antibodies to various gangliosides are identified in the human PNS (2). Anti-GM2 antibodies, which were positive in the present case, are frequently found in GBS associated with cytomegalovirus infection (6). The NCS of our case showed acute sensory-motor neuropathy with the AMNS pattern in sensory conduction, which is often seen in GBS (7).

ADEM and GBS associated with conventional influenza vaccination seem to be rare; 3 cases of ADEM and 9 GBS patients per 38 million vaccine recipients were reported, respectively, in the post-marketing surveillance from 1994 to 2004 in Japan (8). With the exception of the 1976 swine influenza vaccination (A/New Jersey/76 H1N1), causative relationships between vaccination and neuroimmunological disorders have been uncertain, and H1N1 vaccination has also been shown not to be significantly associated with such adverse events (9). Some cases of simultaneous ADEM and GBS have been reported, particularly in the pediatric population, although no case related to influenza vaccination has been described. Huber et al. reported a case of combined ADEM and acute motor axonal neuropathy (AMAN) after hepatitis A vaccination and *Campylobacter jejuni* infection (10). Anti-GM1 antibodies were positive in that patient, and the partial effectiveness of steroid therapy was described. Sato et al. reported a case of acute transverse myelitis and AMAN after H1N1 influenza vaccination, with negative anti-ganglioside antibodies (11). They performed high-dose immunoglobulin and steroid treatment, however, the patient did not experience a significant recovery. In the present case, we did not treat the patient with immunoglobulin therapy or plasmapheresis, since steroid pulse therapy had already been noted to be effective, and the neurological symptoms had markedly improved.

Although the pathogenesis of both ADEM and GBS are thought to be due to autoimmunity to myelin protein antigens, cross-reactivity with the influenza vaccine has not been established. Gangliosides, including GM2, are abundantly found not only in the PNS, but also in the CNS (12). Although anti-GM2 antibodies are frequently detected in cytomegalovirus-associated GBS (6), the localization of GM2 in human neural tissues is unclear. With regard to anti-GQ1b antibodies, Odaka et al. investigated 194 patients with anti-GQ1b IgG antibodies and proposed that Bickerstaff brainstem encephalitis (BBE), GBS and Miller Fisher syndrome (MFS) are all part of a continuous clinical spectrum, which is an antibody-mediated “anti-GQ1b antibody syndrome (13).” Furthermore, Yuki clarified that, according to the clinical, etiological and immunological examination, BBE and MFS are the same type of entity mediated by a common autoantibody (14). He proposed the term “Fisher-Bickerstaff syndrome”, thus representing the concept of the single autoimmune disease involving both the PNS and CNS. The role of anti-ganglioside antibodies in the pathophysiology of GBS is now well established, but it remains to be elucidated if they play a similar role in the pathogenesis of CNS inflammation diseases like ADEM or multiple sclerosis (MS). Kanter et al. reported that the application of lipid microarrays identified antibody response to the gangliosides GM1 and asialo-GM1 in the cerebrospinal fluid of

| Table 1. Findings of the Nerve Conduction Study on the 22nd Day after Vaccination |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | DL (ms)         | MCV (m/sec)     | CMAP amp (mV)   | SCV (m/sec)     | SNAP amp (µV)   |
| Median          | Lt 6.8          | 52              | 8 / 7.6         | -               | n.e.            |
|                 | Rt 7.5          | 47              | 11.6 / 11.6     | -               | n.e.            |
| Ulnar           | Lt 2.2          | 61              | 14.3 / 10.6     | 56              | 9.4             |
|                 | Rt 3            | 37              | 11 / 9          | -               | n.e.            |
| Peroneal        | Lt 4.3          | 51              | 7.4 / 6.5       | -               | n.e.            |
|                 | Rt 4.5          | 51              | 10.2 / 9.0      | -               | n.e.            |
| Tibial          | Lt 6.7          | 46              | 23.8 / 20.1     | -               | n.e.            |
|                 | Rt 6            | 56              | 13.3 / 13.6     | -               | n.e.            |
| Sural           | Lt              | 56              | 43              |                 |                 |
|                 | Rt              | 51              | 31              |                 |                 |

DL indicates distal latency; MCV, motor conduction velocity; CMAP amp, compound muscle action potential amplitude; SCV, sensory conduction velocity; SNAP amp, sensory nerve action potential; n.e., not elicited.
patients with MS (15). Similarly, GalC is known to be one of the major components of CNS myelin, and experimental studies have shown that GalC-specific antibodies can mediate demyelination (16, 17). Furthermore, these antibodies also bind to the surface of a human oligodendrocytoma cell line, indicating that they recognize a biologically relevant epitope (18). Antibodies to GalC also have been observed in postinfectious encephalitis subsequent to mycoplasma infection (19). The clinical significance of the anti-ganglioside response in CNS inflammation diseases is still obscure. However, based on these reports, the simultaneous occurrence of ADEM and GBS associated with influenza vaccination might also be explained by a shared epitope among the influenza vaccine, PNS and CNS myelin, and the GM2 ganglioside.

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

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References