

Transverse Myelitis Activation Post-H1N1 Immunization: A Case of Adjuvant Induction?

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Innovations in vaccination technology have helped eradicate many diseases throughout the Western and developed worlds. During the last 50 years vaccines have diminished the incidence of once commonplace pediatric and adult diseases. Although vaccine technology is safe, non-specific reactions following the administration of immunizations sometimes occur, which typically include site-reaction transient flu-like symptoms. However, recent evidence has spotlighted the development of autoimmune phenomena post-vaccination in sporadic cases [1]. These adverse reactions are thought to be due to associated adjuvants and foreign antigens. Recently, the autoimmune syndrome induced by adjuvants (ASIA) was defined, which includes related diseases such as the Gulf War syndrome, macrophage myofasciitis syndrome, siliconosis, and post-vaccination phenomena [2].

The current understanding is that vaccine adjuvants play an essential role in the pathogenesis of autoimmunity in these patients. They typically consist of aluminum salts, which are added to help enhance the response of the host innate and adaptive immune system [2]. In a minority of patients, the adjuvants stimulate the creation of autoantibodies as well as the appearance of clinical symptoms such

as myalgia, myositis, arthralgia, chronic fatigue, sleep disturbances, neurological manifestations and cognitive impairment. The increasing number of cases in the literature linking vaccine adjuvants and autoimmunity has helped substantiate this relationship [3]. For instance, there is evidence demonstrating a connection between various defined rheumatologic illnesses with immunizations, such as systemic lupus erythematosus developing after the hepatitis B virus (HBV) and human papillomavirus vaccinations. Furthermore, a possible association between various autoimmune syndromes and the varicella and measles-mumps-rubella vaccinations has also been documented [4].

In the general population, autoimmune manifestations of a neurological nature following immunization have also been reported. These post-vaccination neurological complaints consist predominately of neuropathy, encephalitis, vasculitis and demyelination. A literature review showed that neuromuscular conditions, such as Guillain-Barre syndrome (GBS), myasthenia gravis, optic neuritis and inflammatory myopathies, have a temporal relationship with the HBV and hepatitis A vaccines as well as numerous other vaccines. It has also been reported that cases of multiple sclerosis have been triggered by the administration of the HBV vaccine. Additionally, there is a correlation between the cellular *Bordetella pertussis* portion of the diphtheria-tetanus-pertussis vaccine and increased risk of seizure. However, since many of these neuromuscular autoimmune illnesses are rare in themselves, a direct relationship cannot be confirmed.

During the spring of 2009, an eruption of new influenza cases was quickly denoted “the swine flu.” The H1N1 vaccination was created for four influenza A viruses and its efficacy led to a reduction in H1N1 infectivity rates and hospital admissions. While some H1N1 vaccines were associated with flu-like symptoms typically 4 to 7 days post-administration, a very small population of patients developed more severe side effects, including autoimmune and neuroimmune phenomena.

Although the etiology of transverse myelitis, a rare inflammatory spinal-cord condition, is largely unknown, there is growing evidence in the literature that an autoimmune syndrome induced by the adjuvant phenomenon is responsible in some cases for the disease pathogenesis [4]. According to a recent multi-analysis conducted by our research team, 37 cases of transverse myelitis developed within one month post-vaccination that used various common immunizations [5]. Similar to the immune reaction of infectious diseases, vaccine adjuvants cause autoimmunity in a similar manner, including molecular mimicry, epitope spreading, up-regulation of cytokines, and polyclonal activation of B and T lymphocytes [5].

In this report, we will attempt to further the discussion by illustrating a case of transverse myelitis 2 months post-vaccination with the influenza A (H1N1) immunization.

PATIENT DESCRIPTION

A 41 year old man presented to our department with headache, leg paresthesia and

sensory loss of 2 months duration. The patient had been diagnosed with psoriasis 9 years earlier and was initially prescribed only a topical medication to treat the skin lesions. His disease history is significant for one exacerbation 5 years after his original diagnosis, which manifested as an abrupt eruption of psoriatic lesions in the scalp and nails. The patient also developed arthritis of the hands and left foot dactylitis shortly thereafter. He was then treated with prednisone 5 mg/day and methotrexate 20 mg/week, and has been in complete remission without any medication for the past 2 years.

The patient's vaccination history was significant for both the influenza A (H1N1) and yellow fever immunizations. The yellow fever vaccine was administered 16 months before onset of the initial neurological symptoms. He reported myalgia, arthralgia, fatigue, xerostomia and non-bilious non-blooding emesis for a period of 8 days post-vaccination. Two months before the appearance of neurological symptoms, he had received the influenza A (H1N1) vaccination and no acute adverse reaction occurred. Two months later, the patient consulted with a family physician due to the gradual appearance of an occipital headache and generalized fatigue. He was sent for magnetic resonance imaging (MRI), which demonstrated a mild disk protrusion at the level of C5-C6 without spinal cord compromise. Cervicobrachialgia was suspected for which analgesics and anti-inflammatory medications were prescribed, resulting in slight amelioration of his symptoms.

Owing to the persistence of his neurological complaints, the patient was admitted to our department for further workup. Upon admission, he complained of continued occipital-located headache, which persisted throughout the day and night. He also complained of xerostomia without signs of xerophthalmia. He reported paresthesia of both legs with any movement of his neck. He denied recent trauma, visual disturbances, nausea, vomiting or recent fever. On physical examination, he appeared well and in no acute distress. His

vital signs and cardiovascular and respiratory systems were unremarkable. His abdomen was soft and non-tender. Neurological examination was significant only for a loss of transient vibratory sensation in his thighs bilaterally. He denied neck stiffness and displayed no meningeal signs.

His blood cell count and liver and muscle enzymes were within normal limits. Protein electrophoresis, electrophoresis of immunoglobulins and complement were within the normal reference range. Furthermore, serological testing was negative for rheumatoid factor, antinuclear antibodies (including specific testing for anti-RNP, Sm, Ro, La), anti-DNA, anticardiolipin antibodies (immunoglobulins G and M), lupus anticoagulant, and perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies (p-ANCA and c-ANCA). Tests for *Mycobacterium tuberculosis*, including the purified protein derivative test and polymerase chain reaction, were normal. Enzyme-linked immunosorbent assay (ELISA) for anti-aquaporin 4 antibodies was also negative. A lumbar puncture was performed and cerebral spinal fluid (CSF) demonstrated normal appearance, cytology and biochemistry. CSF testing for VDRL, parasitic and viral serologies were negative, and electrophoresis gamma was 18% (7–14%) with absent monoclonal bands.

A spinal cord MRI highlighted three medullar hyperintense lesions on T2 that enhanced after gadolinium use: two appeared at D1 and D5, which were at the left paramedian region, and did not exceed 0.5 cm in diameter, and one was at the level of D7, reaching 1 cm in diameter, also left paramedian. A brain MRI demonstrated no abnormalities. Further neurological evaluation was normal, including electroneuromyography of all four limbs and visual evoked potential.

The patient was diagnosed with transverse myelitis based on clinical symptoms and the MRI findings. He was treated initially with three pulses of intravenous methylprednisolone 1000 mg. Additionally, oral corticosteroids and azathioprine were administered as maintenance therapy. Approximately 3 months after admission,

he experienced a total remission of all neurological symptoms. At follow-up 7 months after admission to our department, the patient's brain and spinal cord MRIs demonstrated no signs of demyelinating lesions.

COMMENT

We describe a 41 year old man who experienced leg paresthesia and sensory loss 2 months after immunization with the influenza A H1N1 vaccination. The clinical laboratory and imaging results were compatible with the diagnosis of transverse myelitis, while a direct etiology was not defined. The patient was successfully treated with corticosteroids and azathioprine. The fact that the symptoms appeared 2 months after the vaccination suggests an immune mediated reaction to the immunization, or ASIA syndrome [5]. The patient's background of psoriatic arthritis, together with a history of inflammatory reaction following yellow fever immunization, may suggest an autoimmune tendency.

The seasonal influenza virus may cause neurological symptoms; the incidence of encephalopathy and delirium during infection is as high as 1:100,000 especially among children. Nevertheless, a small minority of patients may suffer from neurologic-autoimmune phenomenon following the H1N1 vaccination. The most notable example of an influenza vaccine causing an autoimmune process is that of Guillain-Barre syndrome after the induction of the Influenza A/New Jersey vaccination in 1976. The incidence of GBS was significantly higher in the population receiving the vaccination. A recent meta-analysis of the relation between GBS and the influenza A (H1N1) 2009 monovalent inactivated vaccine showed a slightly increased risk of the condition developing.

In a large Swedish cohort of one million patients receiving the Pandemrix Influenza A (H1N1) monovalent-adjuvanted vaccine, there was an increase in the risk of Bell's palsy and various paresthesias. Since the 2009 H1N1 pandemic, there has also been a reported spike in the incidence of narcolepsy in Europe that may be associ-

ated with the swine-influenza vaccination. This finding reinforces the view of some researchers in the field of sleep disorders that the impairment of orexin-producing neurons in the brains is associated with an autoimmune process.

Additionally, there are at least three case reports in the literature that describe episodes of transverse myelitis that occurred after H1N1 immunization. In one report, a 44 year old man suffered from fever and various neurological symptoms, including right leg paresthesia, one month after receiving the influenza A (H1N1) vaccine. The patient demonstrated hyperdense MRI lesions at the level of C6 and C7 and was diagnosed with TM. In South America, a second report chronicled a 52 year old woman who developed a thoracic intra-

medullary lesion one week after immunization with a H1N1-trivalent vaccine without evidence of other causes of the episode. A third case of transverse myelitis was described after the administration of the monovalent A (H1N1) nasal influenza vaccine in a 27 year old woman.

In conclusion, the induction of transverse myelitis post-immunization is plausible in view of the increasing frequency of case reports in the medical literature demonstrating this phenomenon as well as the growing biological evidence of a post-vaccination autoimmune pathogenesis.

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References

1. Blank M, Israeli E, Shoenfeld Y. When APS (Hughes syndrome) met the autoimmune/inflammatory syndrome induced by adjuvants (ASIA). *Lupus* 2012; 21: 711-14.
2. Shoenfeld Y, Agmon-Levin N. ASIA-autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun* 2011; 36: 4-8.
3. Zafir Y, Agmon-Levin N, Paz Z, Shilton T, Shoenfeld Y. Autoimmunity following Hepatitis B vaccine as part of the spectrum of 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants' (ASIA): analysis of 93 cases. *Lupus* 2012; 21: 146-52.
4. Schattner A. Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines. *Vaccine* 2005; 23: 3876-86.
5. Agmon-Levin N, Kivity S, Szyper-Kravitz M, Shoenfeld Y. Transverse myelitis and vaccines: a multi-analysis. *Lupus* 2009; 18: 1198.