

Acute Disseminated Encephalomyelitis After Influenza Vaccination: A Case Report

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Acute disseminated encephalomyelitis is an inflammatory demyelinating disease of the central nervous system that has been associated with influenza immunization, but only a few cases related to vaccination for influenza have been reported. Acute disseminated encephalomyelitis developed in a 42-year-old woman within 3 weeks of receiving the seasonal influenza vaccine. She had 80% recovery after 3 months of treatment with methylprednisolone. Although cases of acute disseminated encephalomyelitis after vaccination for influenza are rare, enough of them have occurred that critical care nurses should be aware of the possibility. Early treatment can prevent serious residual signs and symptoms; therefore, correct and quick diagnosis is important. Medical history obtained from patients with central nervous system problems should include history of recent vaccinations. (*Critical Care Nurse*. 2016;36[3]:e1-e6)

Acute disseminated encephalomyelitis (ADEM) is a rare inflammatory demyelinating monophasic disease of the central nervous system.¹ The estimated occurrence of the disease is 1 case per million persons per year.² ADEM after vaccination is associated with several different vaccines, including those for rabies, diphtheria-tetanus-polio, smallpox, measles-mumps-rubella, Japanese B encephalitis, pertussis, influenza, hepatitis B, and swine fever.³ The most likely neurological phenomena triggered by vaccines are Guillain-Barré syndrome, seizures, cranial neuropathy, and ADEM.⁴ However, a recent study⁵ also indicated that general vaccination did not increase the overall occurrence of nervous system demyelinating syndromes.

The highest incidence of ADEM occurs during childhood⁶; however, cases have occurred in young adults, adults, and the elderly.⁷ Most cases occur after bacterial or viral infections, and, among these, 5% are diagnosed after vaccination (with either inactivated or live vaccine). All the patients with ADEM sought care within 30 days of the onset of signs and symptoms.⁸ Adult patients with ADEM may have any or all of the following: fever, mental distortion, pyramidal dysfunction, cerebellar ataxia, optic neuritis, myelitis, and

CASE REPORT

A 42-year-old woman with moderate glaucoma and hypertension received an injection of quadrivalent inactivated influenza vaccine (Fluarix, GlaxoSmithKline, lot 5EE73) in the fall of 2013. The vaccine contained the influenza A-H1N1 virus, the influenza A-H3N2 virus, the influenza B/Yamagata lineage virus, and the influenza B/Victoria-lineage virus.²

In the United States, the Centers for Disease Control and Prevention and the Healthcare Infection Control Practices Advisory Committee have recommended that all health care workers get vaccinated annually against influenza.¹⁵ As a nurse, the patient had received an annual influenza vaccination each of the previous 20 years and had had no adverse reactions to any of those vaccinations. However, 7 days after the 2013 vaccination, she experienced numbness in both lower extremities. She reported this symptom to the chiropractor she was seeing for lower back pain. The chiropractor told her that the numbness was evidence that the chiropractic treatment was working. The patient also experienced abdominal skin tenderness and reported that her skin was unusually warm to the touch, although no rash or skin change was visible. She also said that she had fatigue; however, she thought that the fatigue might be due to the stress of caring for 2 young children or to stress related to her work. The lower-extremity numbness continued intermittently during the next several days. The patient then went on a business trip.

Clinical Findings

Twenty-five days after the trip, the numbness had ascended to the patient's abdomen and right hand. She then sought help from orthopedists and had a spinal radiograph, spinal computed tomography, and needle electromyography on both hands. The test results were unremarkable. Twenty-nine days later, the patient was referred to a neurology clinic. Because she had the Babinski sign and hyperreflexia of tendon reflexes in

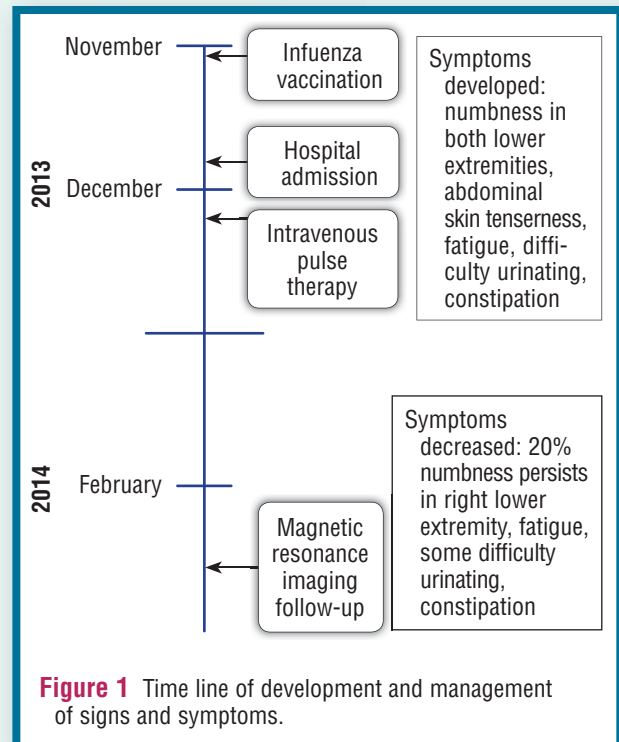


Figure 1 Time line of development and management of signs and symptoms.

the limbs (3+ to 4+), she was referred to the emergency department for cervical magnetic resonance imaging (MRI). The pinprick test indicated impairment below the right C3 and left T2 levels. The patient experienced difficulty urinating and passing stools. A urinary catheter was inserted and drained more than 1000 mL of yellow urine. Figure 1 provides a time line of these events.

Diagnostic Focus and Assessment

After admission, the patient's numbness ascended to the chest, causing difficulty breathing. In addition, she had hyperesthesia in the right part of the scalp, the skin behind the right ear, the right upper extremity, and both lower extremities, and the numbness became more severe. She could walk with assistance; however, tandem gait and jumping on one leg were difficult. The Lhermitte sign was positive, so a lumbar puncture was performed.

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Analysis of the cerebrospinal fluid yielded the following results: pressure 165/125 mm H₂O, with 47 white blood cells and 22 red blood cells per high-power field, protein level 58 mg/dL, and glucose level 63 mg/dL. The immunoglobulin G index was 0.39.

MRI of the cervical spine revealed mild hyperintense spinal cord lesions at C2-C3 and T1-T3, and a crescent-shaped lesion outside the dual sac, which corresponded to the hyperintense lesions. Brain MRI before and after injection of contrast material showed small lesions in the subcortical white matter of the left high parietal and left dorsal aspects of the pons, and the left middle part of the cerebellar peduncle had a high signal on T2-weighted images, consistent with a demyelinating process. Also, a focus of enhancement in the left middle cerebellar peduncle indicated a relatively active lesion. The cervical spine MRI showed multiple intramedullary high-signal lesions on a T2-weighted sagittal view from C3 to C4, C5 to C6, and the dorsal aspect of the pons, with mild enhancement (Figure 2).

An autoimmune profile survey was done, and possible metabolic causes related to myelopathy were checked, including syphilis and HIV disease; all test results were within the reference range. Blood cell counts, hepatic and renal function, electrolyte levels, blood glucose level, and lipid levels were all within the reference range.

Therapeutic Focus and Assessment

At this point, ADEM was diagnosed because the patient's signs and symptoms occurred after she had received a vaccination for influenza. Differential diagnoses included multiple sclerosis, neuromyelitis optica, and spinal vascular lesion. The option of steroid treatment was discussed with the patient, and a 5-day methylprednisolone pulse therapy was started, with a dose of 1 g/d via intravenous infusion. The patient's signs and symptoms improved. After the therapy, her only symptoms

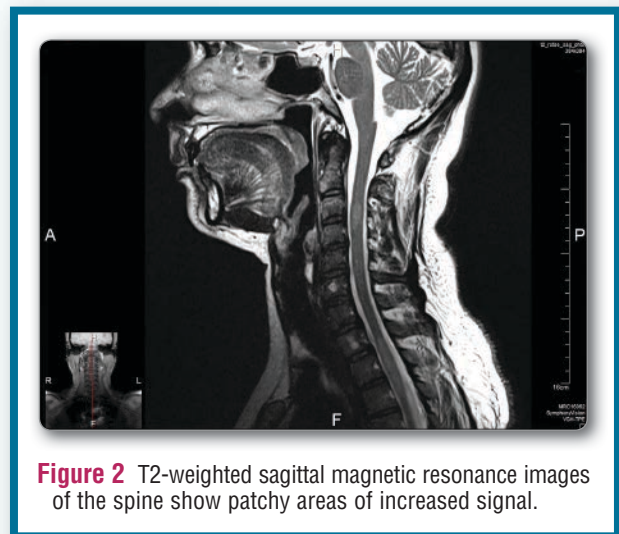


Figure 2 T2-weighted sagittal magnetic resonance images of the spine show patchy areas of increased signal.

were tingling in the lower extremity and numbness in the toes. The patient was discharged after 10 days of hospitalization. Oral steroids were prescribed, with a tapering off in dose during a 4-week period.

Follow-up and Outcomes

The patient's numbness and swelling were limited to the sole and toes of the right foot after the first 5 days of the pulse therapy. However, during the first week after initiation of oral steroid therapy, she reported that numbness and swelling were returning to her right knee. After 2 weeks of oral steroids, the numbness in the right knee was gone, and the only numbness remaining was in the sole of the right foot. However, when the dose of oral steroids was decreased again, the area of numbness expanded back to the right calf. No new symptoms developed during the first 6 months; however, the patient returned to her urologist and gastroenterologist for a follow-up on the constipation. She was encouraged to use a laxative containing polyethylene glycol (MiraLax) to return her bowels to normal functioning. In addition, she was told to maintain as active a life as possible.

extrapyramidal syndromes.^{4,9,10} Only a few patients had these signs and symptoms specifically associated with vaccination for influenza and ADEM,¹¹⁻¹⁴ and thus far formal reporting of the association has been limited.³

Limited adverse reactions to influenza vaccine include headache, local pain, swelling, and myalgia. Most of these reactions are mild and of short duration and usually

disappear within 1 to 2 days without medical treatment.⁷ Influenza vaccination is considered unlikely to be associated with adverse neurological effects¹⁵; therefore, clinicians should report any adverse neurological event (eg, ADEM) that may be associated with a vaccination.

Between October 1, 2009, and March 31, 2010, influenza vaccine was associated with 212 neurological adverse

events according to the Vaccine Adverse Event Reporting System of the Centers for Disease Control and Prevention.¹⁶ A total of 75% of the adverse events were associated with inactivated influenza vaccine, and 10% were associated with live-attenuated vaccine; in 15%, the vaccine type was not reported.¹⁶

In this article, we present a case study of a woman with sudden weakness in her extremities and describe how ADEM was diagnosed and subsequently treated.

Discussion

In this report, we describe a case of ADEM induced by influenza vaccine. Onset of signs and symptoms was 7 days after vaccination. Most patients with ADEM experience fever, mental distortion, pyramidal dysfunction, cerebellar ataxia, optic neuritis, myelitis, and extrapyramidal syndromes. The woman whose case is reported had solely myelitis-related signs and symptoms. The MRI results, clinical manifestations, and laboratory findings fulfilled the criteria of the Brighton Collaborations Encephalitis Working Group for level 1 diagnostic

ADEM will progress markedly if left untreated or if treatment is delayed. Beginning treatment early slows the rate of progression.

certainty for ADEM.¹⁰ The patient required almost 3 months from the day of the vaccination to

achieve 80% recovery from all the signs and symptoms. Thus, compared with patients in other reported cases,^{7,13,17} this patient had a positive outcome. Her only current signs and symptoms most likely related to ADEM are some tingling and numbness in her right foot, constipation, and difficulty in urination.

Because of the limited number of cases of ADEM worldwide, no large studies on the occurrence of the disease after influenza vaccination have been reported.⁷ Despite the scarcity of data, a reasonable conclusion is that fast and effective treatment and management can decrease the severity of the neurological signs and symptoms of ADEM, even when the signs and symptoms are not reversible.⁴ ADEM will progress markedly if left untreated or if treatment is delayed. Beginning treatment early slows the rate of progression, a finding that supports beginning treatment at the time of diagnosis.⁷

ADEM after vaccination might be related not only to the viral component of the vaccine but also to contamination of the preparation.³ According to the causality

assessment of the World Health Organization, the probability of a causal relationship between our patient's vaccination and ADEM would be categorized as very likely. The very likely determination applies to cases in which the "clinical event [has a] plausible time relationship to vaccine administration [that] cannot be explained by concurrent disease or other drugs or chemicals."¹⁸ With ADEM, full recovery is expected in most cases (75%-90%),³ and early treatment is especially useful for preventing severe residual signs and symptoms.¹² Therefore, early diagnosis and treatment are important.

Nursing Interventions

Generally, our patient had minimum complications and limited ADEM-related signs and symptoms. Many patients with ADEM have an altered state of consciousness, focal deficits, loss of bladder control, and bowel problems, which are often misdiagnosed. In our case, the patient experienced a painful bandlike sensation that extended horizontally through the abdomen and back area at the level of inflammation in the spinal cord. Because the inflammation developed in a focal area, a series of sensory and motor-related signs and symptoms was to be expected.¹⁹ In addition, ADEM patients often have paresthesias such as numbness and tingling. Any changes in these sensory-motor signs and symptoms should be documented on each nursing shift.¹⁹

Whenever a patient has neurological weakness or signs and symptoms related to sensory, motor, and autonomic nerves, an evaluation for ADEM should be considered. First, does the patient have numbness and/or weakness in a lower extremity or paraparesis? If so, what is the patient's state of consciousness? Second, does MRI show a lesion or enhancement solely in the spinal cord or also in the brain? Does the patient have any sensory loss or pain? Third, does the patient experience any urinary retention or loss of bowel control?²⁰ (Many patients with ADEM have difficulties in elimination.) Fourth, laboratory studies should include analysis of cerebrospinal fluid and blood to evaluate oligoclonal bands and levels of aquaporin-4 antibodies, and other blood analysis as needed to test for other potential immunosuppression-related diseases such as systemic lupus erythematosus or Guillain-Barré syndrome.²¹ Because several diseases involving myelin have manifestations similar to those of ADEM, aquaporin-4 antibodies and oligoclonal bands should be assessed to differentiate

multiple sclerosis or neuromyelitis optica.²² Last, pain assessment is important. Neuropathic pain can occur as a result of sensitization of the nerves. Even an act as delicate as touching the patient or adjusting the bed linen can cause the patient excruciating pain. This symptom might be relieved with certain medications.

While our patient was in the emergency department and critical care unit, nurses played an important role in managing her signs and symptoms. During the course of high-dose steroids, for example, nurses monitored the patient's blood pressure to ensure that her hypertension was not unduly elevated by the steroids. (In our case, blood pressure actually decreased, possibly due to prolonged bed rest.) Pulse therapy was effective for our patient; however, not all ADEM patients respond to high-dose steroid treatment.²³ If the pulse therapy had been unsuccessful, the next line of treatment would have been plasma exchange⁴ to remove the inflammatory factors from the blood.²⁴ A critical care nurse would be expected to prepare and administer intravenous steroids and/or set up the plasma exchange by placing a catheter into a vein in each arm or other suitable places and then prepare the patient for the treatment. Nurses should be aware of the potential side effects of treatment and should educate patients and patients' family members about what to expect.²³

MRI follow-up 3 to 6 months after the episode of ADEM to evaluate the lesions revealed in the baseline MRI in subcortical white matter is recommended, as are repeat blood studies to measure levels of aquaporin-4 antibodies.⁴ If the neurological signs and symptoms return, patients should check with a neurologist as soon as possible; the return might indicate a relapse of the ADEM or even the onset of multiple sclerosis or neuromyelitis optica.⁴ After a patient's condition has stabilized from the manifestations of the first episode of ADEM, nurses should discuss indications of a possible relapse. Nurses might also suggest consultation with an ophthalmologist or immunologist to help with other potential differential diagnosis, such as optic neuritis or Lyme disease. Social resources and assessment of caregiver issues need to be touched upon also.²⁵

Conclusion

Influenza vaccine is considered safe.²⁶ However, adverse events do occur, and the possibility of these events (and what to do when they occur) is currently not routinely discussed by clinicians giving influenza vaccinations,

except that recipients are asked about allergy to eggs, a history of Guillian-Barré syndrome, or some other indicator that an adverse event could occur.² Therefore, a study of our case and of other similar cases in which a patient experienced ADEM after receiving a vaccine is useful. After 3 months of treatment, our patient had an approximately 80% recovery. Cases in which vaccines are suspected of inducing serious autoimmune illnesses are rare, but they do exist, and health care providers should be aware of the possibility. Vaccination records and patients' histories should be evaluated immediately for any patient who has signs and symptoms related to diseases of the central nervous system soon after receiving a vaccination for influenza. **CCN**

Financial Disclosures
None reported.

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References

1. Tomonari A, Tojo A, Adachi D, et al. Acute disseminated encephalomyelitis (ADEM) after allogeneic bone marrow transplantation for acute myeloid leukemia. *Ann Hematol.* 2003;82(1):37-40.
2. The Transverse Myelitis Association. Acute disseminated encephalomyelitis (ADEM). 2016. <https://myelitis.org/living-with-myelitis/disease-information/#adem>. Accessed March 29, 2016.
3. Huynh W, Cordato DJ, Kehdi E, Masters LT, Dedousis C. Post-vaccination encephalomyelitis: literature review and illustrative case. *J Clin Neurosci.* 2008;15(12):1315-1322.
4. Alexander M, Murthy JM. Acute disseminated encephalomyelitis: treatment guidelines. *Ann Indian Acad Neurol.* 2011;14(suppl 1):S60-S64.
5. Langer-Gould A, Qian L, Tartof SY, et al. Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseases. *JAMA Neurol.* 2014;71(12):1506-1513.
6. Wijnans L, de Bie S, Dieleman J, Bonhoeffer J, Sturkenboom M. Safety of pandemic H1N1 vaccines in children and adolescents. *Vaccine.* 2011;29(43):7559-7571.
7. Alicino C, Infante MT, Gandoglia I, et al. Acute disseminated encephalomyelitis with severe neurological outcomes following virosomal seasonal influenza vaccine. *Hum Vaccin Immunother.* 2014;10(7):1969-1973.
8. Pellegrino P, Carnovale C, Perrone V, et al. Acute disseminated encephalomyelitis onset: evaluation based on vaccine adverse events reporting systems [published correction appears in *PLoS One.* 2013;8(12)]. *PLoS One.* 2013;8(10):e77766.
9. Adamec I, Klepac N, Kolenc D, Ozretic D, Habek M. Isolated and persistent cognitive dysfunction in a patient with acute disseminated encephalomyelitis. *Cogn Behav Neurol.* 2013;26(1):30-35.
10. Sejvar JJ, Kohl KS, Bilynsky R, et al. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine.* 2007;25(31):5771-5792.
11. Lee ST, Choe YJ, Moon WJ, Choi JW, Lee R. An adverse event following 2009 H1N1 influenza vaccination: a case of acute disseminated encephalomyelitis. *Korean J Pediatr.* 2011;54(10):422-424.
12. Machicado JD, Bhagya-Rao B, Davogusto G, McKelvy BJ. Acute disseminated encephalomyelitis following seasonal influenza vaccination in an elderly patient. *Clin Vaccine Immunol.* 2013;20(9):1485-1486.
13. Maeda K, Idehara R. Acute disseminated encephalomyelitis following 2009 H1N1 influenza vaccination. *Intern Med.* 2012;51(14):1931-1933.
14. Shoamanesh A, Traboulee A. Acute disseminated encephalomyelitis following influenza vaccination. *Vaccine.* 2011;29(46):8182-8185.

15. Centers for Disease Control and Prevention. Summary recommendations: prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP) United States, 2013-14. <http://www.cdc.gov/flu/professionals/acip/2013-summary-recommendations.htm>. Accessed March 16, 2016.
16. Williams SE, Pahud BA, Vellozzi C, et al. Causality assessment of serious neurologic adverse events following 2009 H1N1 vaccination. *Vaccine*. 2011;29(46):8302-8308.
17. Denholm JT, Neal A, Yan B, et al. Acute encephalomyelitis syndromes associated with H1N1 09 influenza vaccination. *Neurology*. 2010;75(24):2246-2248.
18. Williams SE, Klein NP, Halsey N, et al. Overview of the Clinical Consult Case Review of adverse events following immunization: Clinical Immunization Safety Assessment (CISA) network 2004-2009. *Vaccine*. 2011; 29(40):6920-6927.
19. Tuppeny M. Viral meningitis and encephalitis. *Crit Care Nurs Clin North Am*. 2013;25(3):363-380.
20. Waldrup BC. Identifying transverse myelitis in the emergency care arena. *Adv Emerg Nurs J*. 2009;31(2):131-139.
21. Ordonez L, Skromne E, Ontaneda D, Rivera VM. Multiphasic disseminated encephalomyelitis, systemic lupus erythematosus and antiphospholipid syndrome. *Clin Neurol Neurosurg*. 2007;109(1):102-105.
22. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189.
23. Harris C, Lee K. Acute disseminated encephalomyelitis. *J Neurosci Nurs*. 2007;39(4):208-212.
24. Atkinson SB, Carr RL, Maybee P, Haynes D. The challenges of managing and treating Guillain-Barré syndrome during the acute phase. *Dimens Crit Care Nurs*. 2006;25(6):256-263.
25. Cheng EM, Crandall CJ, Bever CT Jr, et al. Quality indicators for multiple sclerosis. *Mult Scler*. 2010;16(8):970-980.
26. Centers for Disease Control and Prevention. Influenza vaccination information for health care workers. <http://www.cdc.gov/flu/healthcareworkers.htm>. Accessed March 16, 2016.