Influenza Vaccine-Induced CNS Demyelination in a 50-Year-Old Male

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Conflict of interest: None declared

Patient: Male, 50
Final Diagnosis: Acute post-vaccination CNS demyelinating disorder
Symptoms: Blurred vision • hemiparesis • hemiplegia • hypertonia • itching • paresthesia
Medication: —
Clinical Procedure: MRI
Specialty: Neurology
Objective: Rare disease

Background: There are several categories of primary inflammatory demyelinating disorders, which comprise clinically similar neurologic sequelae. Of interest, clinically isolated syndrome (CIS) and acute disseminated encephalomyelitis (ADEM) are 2 demyelinating conditions of the central nervous system (CNS), whose clinical similarity pose a significant challenge to definitive diagnosis. Yet, both remain important clinical considerations in patients with neurologic signs and symptoms in the context of recent vaccination.

Case Report: We report a case of a 50-year-old Caucasian male with a course of progressive, focal, neurologic deficits within 24 h after receiving the influenza vaccine. Subsequent work-up revealed the possibility of an acute central nervous system (CNS) demyelinating episode secondary to the influenza vaccine, best described as either CIS or ADEM.

Conclusions: Case reports of CNS demyelination following vaccinations have been previously noted, most often occurring in the context of recent influenza vaccination. This report serves to document a case of CNS demyelination occurring 24 h after influenza vaccination in a middle-aged patient, and will describe some salient features regarding the differential diagnosis of CIS and ADEM, as well as their potential management.

MeSH Keywords: Activities of Daily Living • Demyelinating Diseases • Encephalomyelitis, Acute Disseminated • Influenza Vaccines

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Background

Primary inflammatory demyelinating disorders of the central nervous system (CNS) are comprised of several disease categories, all of which may demonstrate a clinically similar neurologic presentation. Of interest, clinically isolated syndrome (CIS) and acute disseminated encephalomyelitis (ADEM) are 2 demyelinating conditions whose clinical similarity poses a significant challenge to definitive diagnosis. ADEM describes an inflammatory demyelinating disease of the CNS that may occur following viral illnesses or vaccinations. This definition is similar for CIS, while also being synonymous with the “first attack” of multiple sclerosis (MS). While rare, these entities remain important clinical considerations in patients with neurologic signs and symptoms in the context of recent vaccination. This is especially relevant with the wide contingent of influenza-vaccinated patients. The Centers for Disease Control (CDC) reports an estimated 139.8 million people vaccinated against season flu during the 2011–2012 campaign, with a similar number of doses of flu vaccine distributed during the 2012–2013 flu season [1]. Thus, encounters with post-vaccination acute demyelinating syndromes may be experienced at both the in-patient and primary care level. Prompt medical management and plans for comprehensive and focused rehabilitation can produce favorable clinical outcomes in these patients, but the optimal management of such cases has yet to be defined.

Case Report

A 50-year-old Caucasian male presented to the emergency department in our facility following complaints of left-sided weakness and blurred vision. The patient had a medical history significant for hypothyroidism, hyperlipidemia, gastroesophageal reflux disease, psoriasis, attention deficit hyperactivity disorder, depression, and a right-sided supraclavicular phrenic nerve lipoma, which was removed in 2007.

On the day before admission, the patient noted left arm numbness and weakness, which resolved for a few hours. Overnight, there was increasing left leg weakness with full left arm paresthesia, and at work the following day, our patient reported an “itchy” sensation over the entire left face and blurred vision in the left eye. No discrete blurred spots were reported in the left eye and vision in the right eye remained unchanged. With increasing symptom severity, the patient arrived to the emergency department for further evaluation.

Notably, the patient had received an influenza vaccination (H1N1, H3N2, B/Yamagata and B/Victoria) 1 day prior to symptom onset. His surgical history included hernia repair, appendectomy, knee arthroscopy, tonsillectomy, and excision of the aforementioned lipoma. Family history revealed hypertension and heart disease within the maternal lineage, and a sister with anemia. The patient was a former smoker of 1 pack per day for 3 years, successfully quitting in 1983. The patient also reported occasional alcohol intake and no recreational drug use. An allergy to penicillin was noted. The patient had a current medication regimen including levothyroxine, dexlansoprazole, clotrimazole/betamethasone cream, methylphenidate, and alprazolam.

A full review of systems proved unremarkable, including the denial of any trauma. On arrival at the emergency department, the patient was afebrile and vital signs were stable.

Physical examination demonstrated no significant findings, except for definitive left-sided weakness, with no expressive or receptive aphasia evident. Moreover, the neurologic examination also revealed slight facial asymmetry on tests for cranial nerves 5 and 7. The remaining cranial nerves were grossly normal. Motor testing showed arm and leg weakness at 3/5 and left-sided drift. Tone was increased on the left, and coordination was slightly diminished on the left compared to the right with rapidly alternating movement. No tremor or ataxia was noted. Sensation to pain, temperature, and vibration was intact. Reflexes were 3+ on the left, and 2+ on the right, with down-going toes bilaterally.

Investigations

Results of a comprehensive metabolic panel, coagulation studies, and complete blood count were all within normal limits. LDL and triglycerides were elevated at 106 mg/dL and 193 mg/dL, respectively.

The full evaluative course of this patient was extensive and initially focused on a working diagnosis of acute stroke. A chest X-ray, performed on admission, was unremarkable. Computed tomography (CT) of the head without contrast did not reveal any space-occupying lesion, no intracranial hemorrhage, hydrocephalus, or shifting of the ventricles. Evidence of cerebral infarction or edema was non-existent. Similarly, CT angiography of the head and neck was unremarkable. Bilateral carotid duplex studies demonstrated carotid stenosis less than 40% on the right and the left.

On the second day of hospitalization, magnetic resonance imaging (MRI) of the brain and full spinal cord with- and without contrast were obtained during further work-up. MRI of the brain showed no distinct intra-axial hemorrhage, mass, mass effect, or enhancing lesion, or evidence of acute stroke. Scattered foci of bright T2 FLAIR signal changes were seen in the peri- and non-periventricular region, deep hemispheric centrum, peririgonal, and cortical/subcortical regions, indicative...
of a demyelinating disease (Figure 1A–1D). MRI of the cervical spine proved benign, and MRI of the lumbar and thoracic spine were unremarkable and without evidence of herniated disc pulposus or spinal stenosis.

A cerebrospinal fluid (CSF) sample was obtained by lumbar puncture, which proved to be completely normal by laboratory evaluation, and gram stain was negative with no growth on culture after 7 days. Additionally, cytological analysis of the

**Figure 1.** Brain MRI of post-vaccination CNS demyelination disorder in a 50-year-old male. (A, B) Axial FLAIR MRI images, demonstrating multiple, bilateral, asymmetric hyperintense lesions, as marked. (C, D) Axial T1 MRI images, retrieved during the same MRI acquisition as A & B and displayed in the same plane for comparison to A & B, respectively, demonstrating the inconspicuous nature of the lesions by this modality.
spinal fluid showed no evidence of malignancy. Testing for oligoclonal bands within the CSF was also negative.

Cardiology work-up was also performed. This included an EKG, which showed normal sinus rhythm, and an echocardiogram revealed mild left atrial dilation and a left ventricular ejection fraction of 60%.

**Differential diagnosis**

Over the initial course of hospitalization, an etiological explanation for the left-sided symptoms had yet to be concluded. Our attention shifted to the possibility of an acute demyelinating episode secondary to the influenza vaccine received on the day prior to symptom manifestation. We propose that this patient experienced a post-vaccination acute demyelinating disorder, best described as CIS or ADEM.

We wondered if this presentation could be consistent with CIS. The typical CIS presentation is described as a single episode of CNS dysfunction, followed by partial resolution. Its diagnosis is typically characterized by at least a 24-h episode in the absence of fever or infection, and without clinically evident encephalopathy [2], all of which were appreciated in this case. Notably, related to the blurred vision in the left eye, there may have been questionable optic neuritis, either unilateral or developing bilaterally, associated with CIS, but subsequent work-up for this clinical finding was not pursued. As described in our case, motor system involvement, more commonly as weakness in the legs than the arms, and coordination deficits are also common clinical findings associated with CIS. Additionally, our patient did demonstrate possible sensory symptoms associated with first-attack MS. These include numbness and paresthesia, and an intense itching sensation commonly experienced in the cervical dermatomes, and often occurring unilaterally, such as the facial presentation in our patient. It should be noted that the patient’s symptoms and MRI results did not fulfill the McDonald criteria for MS [3]. Additionally, the CSF sample did not reveal oligoclonal bands, as would be expected with CIS.

Secondly, we believe the patient’s presentation may resemble aspects of ADEM. While a set of consensus criteria does not exist for the differentiation of ADEM from first-attack MS, a retrospective study in 54 patients has proposed criteria to be used to distinguish patients with ADEM from those with first-attack MS [4]. This suggested criteria includes 2 of the following 3 findings: 1) the presence of symptoms atypical for MS, including 1 more of the following: conscious alteration, hypersomnia, seizures, cognitive impairment, hemiplegia, tetraplegia, aphasia, or bilateral optic neuritis, 2) gray matter involvement on brain MRI, and finally 3) the absence of oligoclonal bands in a drawn CSF sample [4]. With our patient presenting with left-sided hemiplegia, grey matter involvement on imaging, and a lack of oligoclonal bands, ADEM may also have encompassed this patient’s clinical picture.

A follow-up MRI was not performed in this patient. As such, temporal changes and the resolution of brain lesions could not be obtained, which assist a more definitive diagnosis of ADEM. While this case remained clinically monophasic in nature without a course of relapse, the insufficient follow-up time needed to document the absence of relapse on brain MRI may reduce the diagnostic certainty of ADEM. Additionally, our patient had no reliable report of altered mental status or behavioral changes, suggestive of encephalopathy. Because encephalopathy is seen in 74% of patients with ADEM, its clinical presence is considered mandatory for a definitive diagnosis [5]. For this reason, CIS remains as favorable alternative diagnosis.

Given the objective examination and clinical coordination with MRI results, consideration was also given to demyelinating disease, as seen with either Lyme disease or hypertension. While serologic testing for Lyme disease was not performed, our patient had a low probability of tick exposure and produced a normal CSF sample. Our patient had no history of hypertension.

**Treatment course**

Medically, with a proposed diagnosis of post-vaccination CNS demyelination secondary to influenza vaccination, a 5-day course of twice-daily intravenous methylprednisolone (500 mg) was prescribed, followed by a 12-day tapered course of once-daily oral prednisone (20 mg). Additionally, the patient was referred for comprehensive in-patient rehabilitation.

Upon presentation to the in-patient rehabilitation unit (IPR), the patient was alert and oriented to person, place, and time. He exhibited no cranial nerve abnormalities. He had significant left hemiparesis, with both upper and lower extremity strength graded as 1/5. Our patient demonstrated mild balance deficits in the seated position and severe balance deficits in the standing position. Sensation was diminished to light touch, pain, and proprioception in the left arm and leg. He required maximal physical assistance with all activities of daily living (ADL) and mobility, including bed mobility, transfers, and ambulation up to 40 feet. Severe knee hyperextension during standing and walking was noticed. Additionally, significant hypertonicity and coordination deficits in the left arm and leg were demonstrated. His admission functional independence measure (FIM) score was 74.

Rehabilitation treatment consisted of intense ADL, gait, and transfer training, as well as strengthening exercises. Body-weight supported gait training was implemented using treadmill and over-ground tracking systems. Upper extremity exercises were facilitated using Bioness (Bioness Inc, Valencia, CA) and Reo-Go...
(Patterson Medical, Warrenville, IL) devices. His IPR stay lasted 12 days. He was given 3 hours of daily therapy, combined physical and occupational therapy, during his 12-day stay, with 1 day of rest. After a successful rehabilitation program, he was discharged home. He was able to perform all ADLs at either an independent or standby-assist level, with the exception of tube transfers, which required minimal physical assist. Our patient was able to walk 150 feet, transfer, and climb a flight of stairs with modified independence. His discharge FIM score was 106.

Discussion

Both CIS and ADEM belong to a class of CNS demyelinating syndromes. For ADEM, it is known that 75% of cases arise from post-infectious and post-immunization events. Most often, ADEM occurs in children of 6.5 years median age of onset, with annual incidence rates ranging from 0.4 to 0.8 per 100 000 [6]. In cases of CIS, the usual age of presentation is between 20 and 40 years old, with a mean age of 30 years [2].

No large population studies are available to estimate incidence rates of post-vaccination acute demyelinating syndrome following influenza vaccination. A literature review reported that over a 34-year period, beginning in 1979, 71 cases of inflammatory CNS diseases following vaccination have been documented [5]. Among these, the influenza vaccine was the most common association [5]. The present report demonstrates another documented case of a rare clinical encounter in a middle-aged patient.

While reports of post-vaccination CNS demyelinating syndromes have been associated with the influenza vaccine, there have been occurrences with other vaccines as well. These include rabies, diphtheria, smallpox, and Hepatitis B [6]. In addition, there have been cases of ADEM specifically among adolescent females following vaccination with quadrivalent Human Papilloma Virus [5,7–9]. Despite concern about CNS demyelinating disorders as a serious adverse event following vaccination, it should be noted that one of the most common vaccinations associated with ADEM, live measles, demonstrates an incidence rate of a mere 1–2 per million [6]. Thus, despite rare reported adverse events like CIS and ADEM, vaccines remain a safe and effective strategy for disease prevention and patients should not be discouraged from receiving vaccinations. Additionally, while CNS demyelinating syndromes may be encountered after infections and vaccinations, the causal association has not been proven.

Literature reports have noted that the onset of CIS and ADEM symptoms, post-vaccination, vary between 1 and 20 days. While CIS is known to occur within 24 h from time of vaccination, the onset of ADEM may be delayed compared to CIS, at days to weeks from vaccination exposure [10]. Such initial symptoms may include obtundation, headaches, and ataxia, which are often rapid in onset, progressing over hours and peaking within days [11]. Additional physical findings may include visual field defects, focal motor weakness, focal cortical signs, sensory abnormalities, altered deep tendon reflexes, and further cerebellar dysfunction. Both CIS and ADEM are often monophasic in nature [2,6,10]. Given the clinical similarities, differentiation between CIS and ADEM remains the most challenging aspect in diagnosis. As related to this case, for example, in favor of ADEM over CIS, remains the lack of oligoclonal bands on CSF, and, conversely, in favor of CIS over ADEM, the lack of clinical signs of encephalopathy [2].

While no concrete explanation for post-vaccination CNS demyelination in humans is acknowledged, reports consistently hypothesize that molecular mimicry may be central to the pathogenesis. Antigenic epitopes similar to both the inoculated vaccine components and host CNS protein may induce auto-reactive T and B-cells [6,10]. Subsequently, upon entering the CNS, these immune players induce an autoimmune demyelinating process in the CNS, resulting in the upper motor neuron symptoms observed. These molecular sequelae are further supported by the treatment strategy focused on immunosuppression and immunomodulation.

Clinical outcomes largely depend on the duration and severity of inflammation within the brain and the extent of neuronal and axonal damage [10]. Treatment strategies for CIS and ADEM are largely similar, based on empirical and observational evidence. Given the inflammatory etiology, high-dose intravenous methylprednisolone has been suggested for both diseases [2,6]. IVIG and plasma exchange provide alternative therapeutic approaches. For CIS specifically, recombinant human interferon-beta and glatiramer acetate may delay time to next relapse and potential conversion to MS, with the latter intervention evidenced in a randomized, double-blind, placebo-controlled trial in 481 patients [5,12].

For ADEM specifically, a full recovery within 1–6 months is expected in up to 90% of patients [6]. Similarly with CIS, most episodes are mild and resolve without any medical intervention [2]. However, an important clinical consideration with regards to CIS remains its potential for conversion to MS. Reports have suggested that with CIS optic neuritis, CIS spinal cord involvement, or CIS brainstem involvement up to 85%, 61%, and 60%, respectively, of patients may convert to clinically definite MS, with those respective CIS lesions. In contrast, a study has suggested that an MS conversion rate of 35% over 38 months may be seen in patients with ADEM, characterized by new lesions in time and space [13].

With regards to the use of neuroimaging in post-vaccination CNS demyelination disorders, MRI is noted to be the superior method for disease prevention and patients should not be discouraged from receiving vaccinations. Additionally, while CNS demyelinating syndromes may be encountered after infections and vaccinations, the causal association has not been proven.

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strategy. For CIS, on T2-weighted MRI, 50–70% of adults show white matter brain lesions, suggesting demyelination [2]. The McDonald criteria used for the diagnosis of MS applies to typically presenting cases of CIS, yet its utility in atypical presentations has not been determined [3, 14]. It has been reported that in a patient with suspected CIS, the presence of abnormal lesions on a T2-weighted MRI may predict a long-term 60–80% risk for clinically definite MS [2]. For ADEM, from the onset of clinical signs, it is common to see a 5–14 day delay in the appearance of lesions on imaging [11]. Thus, the full extent of lesions may not be appreciated if an MRI is obtained early in the patient’s clinical course. Additionally, while it is acknowledged that MRI is usually abnormal in ADEM, there have been reports of normal MRI in adults with ADEM, even after multiple imaging [15]. MRI features of ADEM are typically bilateral, poorly margined, and often asymmetrical [16]. T2-weighted and FLAIR sequences typically illustrate hyperintense lesions, which are indistinct on unenhanced T1-weighted sequences [17–19]. The case described here demonstrated such MRI features.

Conclusions and Learning Points

This case report illustrates the rare clinical occurrence of a CNS demyelinating disorder associated with influenza vaccination.

Together, CIS and ADEM belong to a class of CNS demyelinating syndromes.

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