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Brief report

Acute disseminated encephalomyelitis following influenza vaccination

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ABSTRACT

Introduction: Approximately 5% of cases of acute disseminated encephalomyelitis are preceded by vaccination within 1 month prior to symptom onset. This occurs rarely following influenza immunization.
Methods: Case presentation and literature review.
Results: A 75-year-old woman developed acute disseminated encephalomyelitis within 3 weeks of receiving the seasonal influenza vaccine. The patient subsequently passed away, despite treatment with methylprednisolone and plasma exchange therapy.
Conclusions: The literature on post-influenza vaccination encephalomyelitis is limited. The majority of published cases had favourable outcomes following treatment with intravenous methylprednisolone. Given the limited number of cases, no incidence estimates have been published.

1. Introduction

It has been previously reported that approximately 5% of cases of acute disseminated encephalomyelitis (ADEM) are preceded by vaccination within 1 month prior to symptom onset [1]. Vaccines that have been repeatedly reported in association with ADEM include: the live measles/mumps/rubella, diptheria/pertussis/tetanus, Japanese B encephalitis, and smallpox vaccine [2–4]. However, the only epidemiologically and pathologically proven association is with the Semple form of the rabies vaccine [5,6]. Although post-influenza infection ADEM is well established, there is little within the literature regarding post-influenza vaccination ADEM. We present a case of ADEM following seasonal influenza vaccination, as well as a review of the literature.

2. Method

Published cases of ADEM associated with the receipt of the influenza vaccine were obtained via a MEDLINE search, with no date limitations, using the broad search terms: influenza or post-influenza; vaccine or vaccination or immunization; and encephalomyelitis or ADEM. In addition, the references of the resulting articles and review articles on post-vaccination neurological complications or autoimmunity were checked for additional studies.

3. Case presentation

A 75-year-old south Asian woman presented in November of 2008 with a 20 day history of headache, malaise, fatigue, intractable hiccups, nausea and vomiting. Symptoms began evolving 2 days following receipt of the inactivated seasonal influenza vaccine. The patient developed left hemiparesis 20 days post-immunization (PI) and by 29 days PI had progressed to hemiplegia and hemianesthesia of the left side. She then became encephalopathic and developed brainstem involvement with a left abducens palsy, dysarthria, right hemiparesis, and incontinence. Her neurological exam demonstrated bilateral spastic tone, brisk reflexes and extensor plantar responses.

Her past medical history included non-insulin dependent diabetes mellitus type 2, dyslipidemia, hypertension, hypothyroidism and a seronegative arthropathy. She had no other recent illness, history of tuberculosis, or travel history in the preceding 24 months. She had previously received the seasonal influenza vaccine annually between 2003 and 2006. Magnetic resonance imaging (MRI) of the brain and spine demonstrated a long segment of T2 hyperintensy extending from the caudal medulla down the entire length of the cervical cord terminating at T6. Spinal cord expansion was present throughout this segment, maximal at C5/C6 (Fig. 1). Skip lesions were also present through the rest of the spinal cord down

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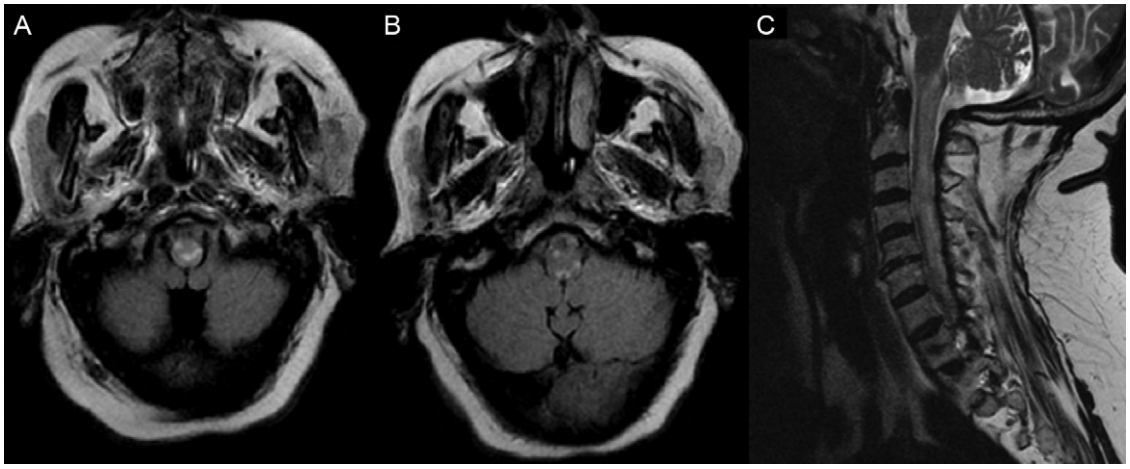

Fig. 1. Axial T2 FLAIR MRI images (A and B) through medulla demonstrating patchy areas of increased signal. Sagittal T2-weighted image (C) demonstrating diffuse hyperintensity throughout the length of the cervical cord with associated spinal cord expansion.

into the conus medullaris. Patchy enhancement was present on post-gadolinium sequences throughout. The remainder of the brain MRI was within normal limits for her age (non-specific white matter changes).

Her cerebrospinal fluid (CSF) demonstrated lymphocytic pleocytosis (white blood cell count of 208/μL), comprised 56% neutrophils, 29% lymphocytes and 15% monocytes, and elevated protein of 911 mg/L. A comprehensive parainfectious workup and rheumatologic panel were negative apart from an elevated CRP of 37.4 mg/L. CSF cytology was negative for malignant cells. Her clinical and radiologic findings fulfilled published criteria for ADEM [7].

Despite treatment with broad-spectrum antibiotics, acyclovir, methylprednisolone and plasma exchange therapy (7 treatments in 14 days), the patient continued to deteriorate to quadriplegia and required intubation secondary to hypercapneic respiratory failure. She developed pneumonia and passed away 70 days PI.

4. Discussion

The earliest reports of neurological complications following vaccination were likely the 'neuroparalytic accidents' stemming from Jenner's discovery during the 19th century [8]. It was not long until the term was also applied to the neurological complications resulting from Pasteur's rabies vaccine. The Semple rabies vaccine, derived from animal nervous tissue, has been particularly associated with a relatively high incidence of ADEM ranging from 1/300 to 1/7000 [5]. Accordingly, the sera and CSF of these patients have demonstrated significant levels of antibody to myelin basic protein [5,6]. The association of ADEM with other vaccines has yet to be validated.

Our patient began developing symptoms 2 days following seasonal influenza vaccination, developed focal neurological signs by roughly 3 weeks and displayed significant brainstem involvement. Her clinical presentation and neuroimaging are consistent with a diagnosis of ADEM according to the Brighton Collaboration Encephalitis Working Group [7]. Seeing as the patient passed away 70 days PI and did not attain the minimum 3 months follow-up duration required to document a monophasic pattern of illness and fulfill a level 1 of diagnostic certainty, her case meets a level 2 of diagnostic certainty for ADEM. Although CSF findings are not included in the abovementioned diagnostic definition of ADEM, the CSF pleocytosis and elevated protein in our patient are useful indicators of central nervous system inflammation. Unfortunately, aquaporin-4-antibodies were not tested in this patient and had she survived, it is conceivable that she may have developed optic neuritis in time and met a diagnosis of neuromyelitis optica.

A review of 12 cases of post-influenza vaccine encephalopathy published up to 1982 found that patients typically presented within 3 weeks of vaccination and that most patients had a complete recovery, apart from those with brainstem dysfunction who had unfavourable outcomes [2]. Only 4 of these 12 patients had clear focal neurological findings, and given the lack of available imaging modalities of the time, it is uncertain how many of these cases would truly meet a diagnosis of ADEM.

We were able to find 15 cases reported as either encephalomyelitis or ADEM following influenza vaccination published since 1982, 10 of which provided clinical information (Table 1) [8–18]. Men comprised 72.7% of these cases. In keeping with the previous series, neurological symptoms typically developed within 3 weeks of vaccination and patients generally had a good recovery (6/11 with complete recovery). Our patient is only the 2nd patient of the reported cases [2] who died as a result of her disease sequelae. On the contrary, Türkoglu and Tüzün recently published case, which also had significant brainstem involvement, had a complete clinical recovery 6 months following treatment with high dose methylprednisolone. Their patient was, however, younger than ours and suffered from less neurological deficit at his clinical nadir [16].

Interestingly, Ravaglia et al. presented a patient who was previously diagnosed with post-infectious ADEM, who then suffered a relapse after influenza vaccination. They also presented a similar patient where influenza vaccination led to relapsing transverse myelitis [12]. This observation would suggest a common pathogenic mechanism amongst post-vaccinial and post-infectious cases. The influenza virus has been shown to contain 14 antigens that display cross-reactivity with myelin basic protein [19]. The influenza vaccine contains killed or live attenuated virus that can retain their natural occurring antigens. Thus, these antigens could potentially serve as epitopes, eliciting autoimmunity, much in the same manner proposed in post-infectious ADEM.

Given the limited number of cases, no incidence estimates have been published. However, extrapolating from the data collected during a survey performed at the Japanese Kitasato Institute, one

Table 1
Reported cases of post-influenza vaccination encephalomyeltis/ADEM since 1982.

Author, year	Age/gender	Vaccine	Time to symptom onset	Investigations	Rx	Outcome
Lapphra et al. [18]	2/M	H1N1 influenza (2009–2010)	4 d – unsteady gait 6 d – dysconjugate gaze 11 d – optic neuritis	**MRI:** diffuse high intensity in the cerebellum, left basal ganglia and optic nerves **CSF:** normal	IV MP	Complete recovery at 6 m
Turkoglu and Tuzun [16]	44/M	Seasonal influenza	9 d – hemiparesis, urinary incontinence	**MRI:** Continuous T2-weighted hyperintense lesion from pons to midbrain and caudal diencephalon with post-gadolinium enhancement **CSF:** normal	IV MP	Complete recovery at 6 m
Kavadas et al. [17]	3/M	Seasonal influenza (Fluviral®Shire, 2003)	12 d – fever 14 d – irritability, decreased LOC, weakness, impaired gaze	**MRI:** small asymmetric areas of hyperintensity **CSF:** WBC 16, protein 0.38	NA	Complete recovery
Kavadas et al. [17]	5/M	Seasonal influenza (Fluviral®Shire, 2003)	12 d – fever, vomiting, aphasia, decreased LOC, seizures	**MRI:** Multifocal patchy hyperintensities in frontoparietal area **CSF:** WBC 82, protein 0.3	NA	Complete recovery
Huynh et al. [8]	61/M	Seasonal influenza (Fluvax, 2005)	3 w – bilateral visual blurring and pain on eye movement 2 m – fluctuating LOC	**MRI:** relatively symmetric FLAIR hyperintensities involving the pons, globus pallidus and thalami **CSF:** WBC 24, protein: 0.71	IV MP	Complete recovery apart for a mild decrease in visual acuity
Izurieta et al. [13]	14/M	Seasonal influenza	2 d – confusion, hyperreflexia, meningismus	**MRI:** noted to be consistent with ADEM	CS	Improved within 24 h
Ravaglia et al. [12]	60/F	Seasonal influenza	10 d – acute paraparesis	**MRI:** multifocal T2-weighted hyperintense lesions of the spinal cord, with enhancement post-gadolinium **CSF:** WBC 12, protein 0.70	IV MP	Almost complete recovery
Nakamura et al. [11]	62/M	Seasonal influenza (2001–2002)	5 d – seizures, left facial myoclonus	**MRI:** T2-weighted hyperintensities in the midbrain, bilateral occipital lobes, right insular cortex, temporal operculum, inferior frontal gyrus and left frontal white matter **CSF:** WBC 5, protein: 2.8	IV MP	Complete recovery at 1 m
Vilain et al. [10]	64/M	Seasonal influenza (1996–1997)	5 d – headache, arthralgias 33 d – optic neuritis	**MRI**: normal **CSF:** protein 0.3	IV MP	Almost complete recovery at 9 m
Antony et al. [9]	57/F	Seasonal influenza	10 d – right leg parasthesia, left leg weakness, urinary retention	**MRI:** increased signal with edema of the spine from C3-T5 and adjacent to the frontal horns **CSF:** WBC 15, protein: 0.3, glucose: 78	IV MP	Persistent sensory deficit of right flank and T9 level Improved weakness

Abbreviations: F = female, M = male, d = days, w = weeks, m = months, LOC = level of consciousness, MRI = magnetic resonance imaging, FLAIR = fluid attenuated inversion recovery, CSF = cerebrospinal fluid, WBC = white blood cell count, Rx = treatment, NA = information was not provided, IV = intravenous, MP = methylprednisolone and CS = corticosteroids.

could estimate the incidence of post-influenza vaccination ADEM to be approximately 1 in 10 million [14].

5. Conclusions

Although a rare occurrence, the indication that certain vaccines can trigger serious autoimmune conditions should be recognized. Physicians should be aware of these novel presentations, include a vaccination history when assessing such patients, and report cases when applicable.

We present the second case of post-influenza vaccination ADEM leading to death within the literature. As this is the exception, with most reported cases displaying complete recovery, brainstem dysfunction may serve as a poor prognostic indicator. When assessing post-vaccination adverse events it is always difficult to separate causality from a temporal coincidence, however, in accordance with the World Health Organization's causality assessment criteria [20] it is 'very likely' that in our case disease was caused by the administration of vaccine.

Appendix A.

World Health Organization causality assessment criteria (Table A1).

Table A1
World Health Organization causality assessment criteria [20].

Very likely/certain	Clinical event with a plausible time relationship to vaccine administration, and which cannot be explained by concurrent disease or other drugs or chemicals
Probable	Clinical event with a reasonable time relationship to vaccine administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals
Possible	Clinical event with a reasonable time relationship to vaccine administration, but which could also be explained by concurrent disease or other drugs or chemicals
Unlikely	Clinical event whose time relationship to vaccine administration makes a causal connection improbable, but which could plausibly be explained by underlying disease or other drugs or chemicals
Unrelated	Clinical event with an incompatible time relationship to vaccine administration, and which could be explained by underlying disease or other drugs or chemicals
Unclassifiable	Clinical event with insufficient information to permit assessment and identification of the cause

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