



Case Report

Influenza-associated seizures in healthy adults: Report of 3 cases[☆]

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ABSTRACT

To describe seizures occurring in 3 healthy adults with influenza infection. Seizures associated to influenza infection are rare in adults without encephalitis. Clinical observations of 3 healthy adult patients with influenza A and B infection and seizures. We present here 3 healthy adult patients with seizures related to influenza A or B infection without evidence encephalitis, encephalopathy or any other cause for seizures. Prognosis was excellent. Seizures can occur in healthy adults with influenza infection without evidence of encephalitis, a possibility to be borne in mind to avoid potentially harmful therapeutic and diagnostic procedures.

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1. Introduction

Influenza is an acute infectious respiratory disease with great public health impact because of its worldwide distribution and morbidity. Although most influenza complications are pulmonary, extrapulmonary complications can occur, including neurological disturbances. Encephalopathy, followed by seizures or status epilepticus are the main neurological complications, occurring more frequently in children during natural influenza infection [1]. Other, less common complications include acute disseminated encephalomyelitis, Reye's syndrome, Guillain-Barre syndrome, post-viral parkinsonism, cerebellitis, and acute necrotizing encephalitis [1]. They can occur during infection, where most fatal and severe cases are observed, or after vaccination, which usually conveys a more favorable prognosis.

We present here 3 previously healthy adult patients who developed seizures related to well-established influenza A and B infection without evidence of concomitant encephalitis.

2. Patient description

2.1. Patient 1

A 51-year-old healthy male presented a sudden episode, witnessed by his wife, of diffuse jerky movements during sleep which ceased in a few minutes, rendering the patient confuse, with amnesia of the episode, and evidence of tongue biting. Transferred to the Emergency

Department, he had 3 additional, convulsive episodes that were treated with benzodiazepines. He had sustained fever for 3 days prior to admission. A nasopharyngeal swab test using isothermal nucleic acid amplification technology (Alere™ i Influenza A & B) confirmed influenza A infection. This episode coincided with an influenza outbreak. General and neurological examinations were normal. Complete blood counts and blood chemistries were within the normal range. He had no history of prior seizures, febrile seizures, head trauma, stroke, or family history of seizures.

EEG, CSF and neuroimaging findings are described on Table 1. He was discharged on therapy with phenytoin and levetiracetam, both withdrawn after one month. He became afebrile in a week and seizures have not recurred in 18 months.

2.2. Patient 2

A 50-year-old healthy male was brought to the Emergency Department because of a tonic-clonic seizure of about 1–2 minutes, witnessed by his wife, with subsequent confusion for 15 minutes. He had had fever and expectoration for two days before the convulsive event and was being treated with amoxicillin. Examination revealed a tongue bite and was otherwise normal. A nasopharyngeal swab test (Alere™ i Influenza A & B) confirmed influenza A infection, consistent with an ongoing influenza outbreak. EEG, CSF and neuroimaging findings are described on Table 1. Complete blood counts and blood chemistries were within the normal range except for an increased serum C reactive protein value of 32.9 mg/L (normal <5 mg/L). He was discharged the following day without antiseizure antiepileptic medication and seizures have not recurred in 18 months. There was no history of prior seizures, febrile seizures, head trauma, stroke, or family history of seizures.

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Table 1
Characteristics of patients with influenza infection and seizures.

	Patient 1	Patient 2	Patient 3
Influenza virus, type	A	A	B
Month of presentation	December	February	February
Age (years)	51	50	19
Gender	Male	Male	Female
Personal history of seizures	No	No	No
Fever (maximum)	40 °C	39.5 °C	39 °C
Other symptoms	Malaise, chills, myalgias, mild headache	Cough, expectoration, dizziness, mild headache	Myalgias, asthenia, malaise
Type of seizures	Generalized tonic–clonic	Generalized tonic–clonic	Generalized tonic - clonic
Number of seizures	4 seizures in 48 h	One seizure	One seizure
Therapy for seizures	Phenytoin and levetiracetam for one month	None	None
Basal EEG	Diffuse slowing without epileptiform discharges; 1 week later, normal	Normal	Normal
Sleep deprivation EEG	Normal	Normal	Normal
Neuroimaging	Brain MRI (normal)	Brain CT scan and MRI (normal)	Brain MRI (normal)
Cerebrospinal fluid findings	Acellular, normal protein and glucose values	2 cells/ μ L, normal protein and glucose values	4 cells/ μ L, normal protein and glucose values

2.3. Patient 3

A 19-year-old female in prior good health was brought to the Emergency Department because of a tonic–clonic seizure of about 2–3 minutes followed by confusion for 15 minutes. A throat swab test confirmed influenza B infection, also consistent with an ongoing influenza outbreak. Physical exam was normal. Results of EEG, CSF and neuroimaging are described in Table 1. Complete blood counts and blood chemistries were within the normal range except for an increased serum C reactive protein value of 17.4 mg/L (normal <5 mg/L). She was discharged without medication and seizures did not recur in 18 months. She denied prior seizures, febrile seizures, head trauma, stroke, or family history of seizures.

3. Discussion

The 3 patients here described suffered generalized tonic–clonic seizures in the context of influenza viral (A and B) infection. All of them were healthy adults without comorbidities or history of seizures, and occurred in the first days of influenza infection, which coincided with ongoing community outbreaks. The infection was confirmed by a rapid, highly sensitive and specific method based on nucleic acid amplification in nasopharyngeal samples.

None of these patients showed any abnormalities on brain MRI, CSF analysis and EEG. Thus, a diagnosis of encephalitis was reasonably ruled out, despite the presence of seizures and fever. They all made a complete recovery without antiviral medication, and did not have seizure recurrence after antiseizure drugs had been withdrawn.

A recent review on the neurological complications after influenza A found that encephalopathy, encephalitis, and seizures were the most common neurological complications [1], and that they occurred mainly in children. Five subtypes of influenza-associated encephalopathy have been described, and all of them can be associated with seizures: a) mild encephalopathy with reversible splenic lesion; b) hemorrhagic shock and encephalopathy syndrome; c) acute encephalopathy with seizures and late restricted diffusion; d) acute necrotizing encephalopathy; and e) encephalopathy with malignant brain edema. Seizures are usually generalized tonic–clonic, either single, in clusters or as status epilepticus. Oftentimes, they are refractory to anti-seizure medications. There was no evidence of encephalopathy in our patients.

There is scant literature in influenza-related seizures in adults. In a population-based study in California on the neurological complications associated with severe and fatal influenza A infection, seizures were reported in 44 patients, only 6 of whom were adults, all of them with accompanying neurologic or metabolic disorders facilitating the seizures [2]. A 21-year-old Nepalese male with severe generalized convulsive status epilepticus who died from septic shock has also been reported

[3]. Another adult patient was reported with adult H1N1 infection and focal status epilepticus followed by complete recovery in 48 h [4]. A 49-year-old Japanese male with seizures and influenza infection A was reported, but he had a diagnosis of Gitelman's syndrome and cholesteryl ester transfer protein deficiency [5]. Of note, none of the previously reported patients had influenza B, as did third patient. In this regard, 2 adults previously manifest seizures in the context of influenza B encephalopathy [6].

In contrast to the aforementioned patients, our patients did not have evidence of encephalopathy or encephalitis, did not have concomitant conditions or metabolic disturbances predisposing to seizures, and showed a benign prognosis without the need for prolonged antiseizure medication and with no seizure recurrence. These findings expand the spectrum of neurological complications of influenza A and B infection in adults.

The pathogenic mechanisms underlying the central nervous system complications of influenza infection are unknown. While pulmonary inflammation is a direct consequence of infection of bronchial and alveolar cells and macrophages, the contribution of viral replication in brain tissues remains unclear. While viral RNA in the CSF has been detected in a few cases, most reported cases lacked CSF pleocytosis, and the viral PCR tested negative in our patients, thus suggesting an indirect inflammatory process. It has also been suggested that both vaccination and infection might promote blood–brain barrier dysfunction, resulting in neural tissue inflammation and dysfunction. In this regard, children with an immature blood–brain barrier may be prone to virus invasion due to the size of influenza viral particles [1].

In conclusion, the possibility of isolated seizures occurring in healthy adults with influenza infection without evidence of encephalitis should be borne in mind to avoid potentially harmful therapeutic and diagnostic procedures.

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