

Pandemic influenza A (H1N1) 2009 with neurological manifestations, a case series

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Objectives Describe a series of atypical presentations of pandemic influenza A (H1N1) 2009.

Methods Description of case series using hospital records.

Results Six patients aged 1 to 65 years with confirmed pandemic influenza A (H1N1) 2009 infection presented with neurological complications within 2 to 5 days after the first signs of influenza-like illness. All six were admitted with seizures or altered mental status. No abnormalities were found in brain scans or cerebral

spinal fluid studies of any of the six. All were discharged without sequelae within days of admission.

Conclusions This is only the second report of pandemic influenza presenting with neurological manifestations. Clinicians caring for patients when pandemic influenza is prevalent in their communities should maintain a high level of awareness of the potential atypical presentations with which this disease can appear.

Keywords H1N1, influenza, neurologic, pandemic, seizure.

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Introduction

Since the first reports of human infection with 2009 pandemic influenza A (H1N1) in southern California in April 2009, more than 400 000 cases have been reported globally. As the pandemic has progressed, a clinical pattern of illness has begun to emerge that includes the entire spectrum of disease from mild self-limited infections to severe respiratory disease presenting as adult respiratory distress syndrome.^{1–3} While neurological complications have been reported in association with both type A and B seasonal influenza infections,^{4,5} information regarding their occurrence with 2009 pandemic influenza A (H1N1) is limited to one case series.⁶ In this paper, we describe a series of patients presenting to a large, private health care facility in Santiago, Chile with neurological symptoms as their presenting illness.

The Clínica Alemana de Santiago is a 400 bed multispecialty private not-for-profit health care facility associated with the Universidad del Desarrollo and located in the east side of Santiago. The clinic has in-house diagnostic laboratory capacity to perform up to 350 influenza tests per day using real time Reverse Transcriptase Polymerase Chain Reaction (rRT-PCR). The performance of the laboratory using rRT-PCR has been checked and validated in June 2009 by the national influenza center laboratory with a

concordance of 98% between the two laboratories. The first case of pandemic H1N1 was diagnosed in the emergency department of the facility on 25 May 2009, 8 days after the first reported case in Chile. By July 24th, 11 583 cases of influenza-like illness had been reported from Clínica Alemana, including 4604 confirmed cases due to pandemic H1N1 virus infection. As recommended by the Ministry of Health guidelines, all cases that met the case definition for pandemic influenza received treatment with oseltamivir.

Ninety-one pandemic influenza cases presenting to the clinic required admission, primarily for respiratory complaints. The average age of admitted cases was 34 years and 58% were female. Forty-one of the 91 admitted cases (45%) had a chronic medical condition known to be a risk factor for severe disease in seasonal influenza, most commonly chronic respiratory disease (12%), chronic heart disease (11%), and diabetes (7%). Six cases of the 91 presented with or developed neurological signs as part of the clinical presentation and are described below.

Case reports

Patient 1

A previously healthy 15-year-old male developed a mild cough, generalized muscle pain and fever of 38.5°C. On the

third day of his illness, a nasopharyngeal swab was collected and reported positive for 2009 pandemic influenza A (H1N1) by rRT-PCR. Treatment with oseltamivir at 75 mg twice per day was started the same day. Fever subsided on day 4 of his illness. On day 5, the patient developed confusion and agitation. He did not recognize relatives. On examination at the Emergency Room he had a temperature of 36.8°C and was disoriented, agitated but with no speech abnormalities. No focal neurological or meningeal signs were found. A non-contrast Computed Tomography (CT) and Magnetic Resonance Image (MRI) of the brain as well as cytochemical and bacteriological studies of cerebral spinal fluid (CSF) were all normal. An Electro Encephalogram (EEG) showed striking slowness of the left hemisphere with minor impairment of the activity on the right. Oseltamivir was discontinued and confusion improved within 12 hours without additional specific medical intervention. Rapid improvement of the EEG was observed.

Patient 2

A 53-year-old previously healthy male, developed cough and fever. On his fourth day of illness, he developed generalized tonic-clonic seizures, repeated 4 hours later and lasting about 2 minutes. These episodes were followed by a transient period of confusion. At the Emergency Room he had a third seizure, again lasting about 2 minutes. The patient was afebrile when examined in the emergency room but was noted to be disoriented. His mental state improved within 20 minutes. The neurological examination was otherwise normal. A rRT-PCR for pandemic influenza A (H1N1) 2009 from nasopharyngeal swab was positive. Magnetic Resonance Image of the brain, cytochemical and bacteriological studies of CSF and EEG taken a few hours after the seizures, were normal. Treatment with oseltamivir and phenytoin was started. The patient was discharged asymptomatic on phenytoin on the fifth day after the seizures. The phenytoin was stopped after 1 month and the patient was seizure free at a follow up visit 6 months later.

Patient 3

A 65-year-old female with early Alzheimer's disease manifested by recent onset of memory failure developed disorientation and agitation after 3 days of cough, fever above 38.5°C, and myalgia. She was admitted to hospital for further evaluation. Cytochemical study of CSF was normal, MRI showed brain atrophy, and EEG severe slowing of the basic rhythm with insertion of semi-rhythmic high voltage delta waves. Real time Reverse Transcriptase Polymerase Chain Reaction performed on a nasopharyngeal swab was positive for pandemic influenza A (H1N1) 2009, and oseltamivir was started at a dose of 75 mg twice per day. Two days after admission, she developed an interstitial pneumonia requiring admission to ICU for

5 days. Anticonvulsants were added empirically to the oseltamivir and she quickly improved. She was discharged asymptomatic after 13 days having returned to her baseline mental status.

Patient 4

A previously healthy 16-year-old female was found unconscious in her bathroom after complaining of 24 hours of abdominal pain, without diarrhea or vomiting. On examination she had no focal neurological deficits, and no signs of head trauma. Toxicological study, cytochemical study of CSF, MRI of the brain and the first EEG performed were normal. Her consciousness was impaired for 4 hours, after which she made a full recovery. The next day she was noted to have temperature of 37.8°C and cough. A rRT-PCR performed on a nasopharyngeal swab was positive for 2009 pandemic influenza A (H1N1). A second EEG showed epileptiform activity in the right anterior and medial temporal lobe. She was started on anticonvulsants and oseltamivir, and was discharged asymptomatic after 5 days. No follow up information is available.

Patient 5

A 38-year-old previously healthy female was started on empiric therapy with oseltamivir 75 mg twice daily because of a 24-hour history of malaise, headache, and sore throat. After 1 day of treatment she developed severe myalgias, fever above 38.5°C and dry cough. She went to the emergency room where she was found to be confused, somnolent and disorientated; and was admitted to the hospital for further study. The rRT-PCR from a nasopharyngeal swab was positive for pandemic influenza A (H1N1) 2009. An Electro Encephalogram and cytochemical study of CSF was normal, and CT of the head with contrast showed no structural abnormalities. She was continued on her oseltamivir treatment at the same dose, and was discharged asymptomatic after 3 days.

Patient 6

A previously healthy 1-year-old female was brought to the emergency room after a tonic-clonic seizure. On initial evaluation, her temperature was 39.3°C, she was awake and alert and had no focal neurological deficits. A nasopharyngeal swab was collected and tested positive for 2009 pandemic influenza A (H1N1). Treatment with oseltamivir at 30 mg twice per day was started the same day and her fever resolved on the first day of treatment. An EEG was unremarkable as was her subsequent hospital course. She was discharged on the second day after admission with a diagnosis of febrile seizure and pandemic influenza. No anticonvulsant medications were used and the patient was in good condition with no sequelae when seen at follow up 6 months after admission.

Discussion

This case series represents the second report on neurological complications associated with 2009 pandemic influenza A (H1N1) and the first to report on neurological complications in adult patients. All six had neurological complaints as their primary cause of admission for pandemic influenza H1N1. All had influenza-like symptoms in addition to their neurological syndromes, although for patient number four, these manifested after the neurological complaints. One patient (case 1) was unique in that his neurological symptoms presented somewhat late in the course of his illness while he was already taking oseltamivir and resolved shortly after discontinuation of the drug. This may represent an adverse event related to oseltamivir rather than a complication of the influenza infection itself. All made an uneventful recovery. This represents an unusual incidence of neurological manifestations of influenza in the experience of this clinic. In a typical year, the Clinica Alemana will have 0–2 admissions for influenza with neurological manifestations. However, as the actual incidence of influenza in the community is undefined, it is unclear whether this represents an unusually high proportion of total influenza cases. The profile of other influenza admissions is similar to that reported by other institutions with respiratory

difficulties being the most common cause of admission in 42% of cases followed by severe influenza disease unspecified (27%), Gastrointestinal complaints (6%), pregnancy (4%), cardiovascular complications (3.3%), and septic shock (3.3%).

Central nervous system (CNS) impairment during an infection with influenza viruses has been described since the influenza pandemic of 1918–1920,⁷ most frequently in children. Previously described neurological complications associated with influenza include Reye's syndrome, convulsions, impairment of consciousness, encephalitis, and encephalopathy. Reports in recent years from Japan, Canada, and the United States have described significant mortality and rates of neurological sequelae associated with neurological complications of influenza, occurring primarily in children under the age of 15 years.^{4–8} Other reports have communicated isolated cases of CNS complications in adults.^{9–11} Our series is unusual in that three of the six are adults and only one was under 15 years. Neuropsychiatric events associated with oseltamivir use have also been reported with increasing frequency in recent years, predominantly in Japan, prompting the manufacturer and the United States Food and Drug Administration to both review the issue.^{12,13} While the clinical syndrome manifested by case 1 is consistent with those of previous reports of

Table 1. Clinical, laboratory, electroencephalographic, and radiological features of six patients with pandemic influenza A (H1N1) 2009 associated neurological symptoms

Age in years	Sex	Chronic illnesses	Time from onset of influenza symptoms to start of neurological symptoms	Neurological finding	CSF finding	EEG	Imaging studies	Outcome
15	Male	No	5 day	Delirium	Normal	Slowness in left hemisphere	MRI normal	Recovered
53	Female	No	4 day	Grand mal seizures, Confusion	Normal	Normal	MRI normal	Recovered
65	Female	Early Alzheimer's disease	3 day	Delirium	Normal	Severe slowness	MRI with brain atrophy	Recovered to pre-existing state
16	Female	No	2 day	Unconsciousness	Normal	Epileptiform discharges	MRI normal	Recovered
38	Female	No	2 day	Confusion, disorientation, decreased level of consciousness	Normal	Normal	CT scan normal	Recovered
1	Female	No	1 day	Grand mal seizure	Not done	Normal	Not done	Recovered

CSF, cerebral spinal fluid; CT, computed tomography; EEG, electro encephalogram; MRI, magnetic resonance image.

oseltamivir-related neuropsychiatric events, the causal link between the two is as yet unproven.

2009 pandemic influenza H1N1 has demonstrated the ability to cause severe respiratory disease in previously healthy adults. Our report contributes to defining the clinical spectrum of infection from pandemic influenza H1N1 by describing a series of adult patients presenting with unusual neurological complaints. Clinicians caring for patients when pandemic influenza is prevalent in their communities should maintain a high level of awareness of the potential atypical presentations with which this disease can appear.

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