

The Neurological Manifestations of H1N1 Influenza Infection; Diagnostic Challenges and Recommendations

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Abstract

Background: World Health Organization declared pandemic phase of human infection with novel influenza A (H1N1) in April 2009. There are very few reports about the neurological complications of H1N1 virus infection in the literature. Occasionally, these complications are severe and even fatal in some individuals. The aims of this study were to report neurological complaints and/or complications associated with H1N1 virus infection.

Methods: The medical files of all patients with H1N1 influenza infection admitted to a specified hospital in the city of Shiraz, Iran from October through November 2009 were reviewed. More information about the patients were obtained by phone calls to the patients or their care givers. All patients had confirmed H1N1 virus infection with real-time PCR assay.

Results: Fifty-five patients with H1N1 infection were studied. Twenty-three patients had neurological signs and/or symptoms. Mild neurological complaints may be reported in up to 42% of patients infected by H1N1 virus. Severe neurological complications occurred in 9% of the patients. The most common neurological manifestations were headache, numbness and paresthesia, drowsiness and coma. One patient had a Guillain-Barre syndrome-like illness, and died in a few days. Another patient had focal status epilepticus and encephalopathy.

Conclusions: The H1N1 infection seems to have been quite mild with a self-limited course in much of the world, yet there appears to be a subset, which is severely affected. We recommend performing diagnostic tests for H1N1 influenza virus in all patients with respiratory illness and neurological signs/symptoms. We also recommend initiating treatment with appropriate antiviral drugs as soon as possible in those with any significant neurological presentation accompanied with respiratory illness and flu-like symptoms.

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Keywords • Influenza A (H1N1) • neurological • seizure • coma

Introduction

The seasonal influenza virus infection has been associated with various neurological complications.¹ Influenza has been

accompanied with many cases of encephalitis and encephalopathy.^{2,3} Human infection with novel influenza A (H1N1) was first detected in Mexico,⁴ and then the virus spread rapidly to the other countries.⁵ World Health Organization (WHO) declared pandemic phase of the disease in April 2009. The majority of infected patients live in highly populated areas. Most of the patients develop mild to moderate respiratory symptoms.⁶ The main clinical manifestations of the infection are fever, cough and sore throat. Other complaints such as myalgia, headache and diarrhea have been reported, and others could be expected.⁷ There are very few reports about the neurological complications of influenza A (H1N1) virus in the literature,⁸ and the prevalence of these complications has not been evaluated yet. The objectives of this study were to report the neurological complaints and complications associated with influenza A (H1N1) virus infection.

Materials and Methods

The study was approved by the Ethics Committee, Shiraz University of Medical Sciences. The study is a retrospective analysis of medical records of all patients with H1N1 influenza infection from October through November 2009. Routinely, patients with H1N1 influenza infection who had severe symptoms (e.g., high grade fever, dyspnea, decreased level of consciousness, or any unusual symptoms) were admitted to Ali-Asghar Hospital, Shiraz University of Medical Sciences, Shiraz, Iran. These patients and others, who were admitted to other hospitals affiliated with Shiraz University of Medical Sciences during this period and were diagnosed as having H1N1 infection were studied. All patients had confirmed H1N1 virus infection with real-time PCR assay. We collected all available clinical data by reviewing patients' charts, and direct phone calls to them or their care-givers. All data were kept confidential through codes. We considered headache, numbness and paresthesia, vertigo, ataxia, and drowsiness and weakness as mild, and coma, seizure, encephalitis, meningitis and paralysis (e.g. due to Guillian-Barre syndrome or myelitis) as significant complaints and/or complications of the disease.

Categorical data are expressed as absolute frequencies and percentages where appropriate. The parametric data are presented using descriptive statistics (mean±standard deviation).

Results

Totally, 55 patients with H1N1 infection were

studied. Twenty-eight (50.9%) patients were males and 27 (49.1%) were females. Patients' age ranged from 1 to 70 years with a mean of 23.1 and a standard deviation of 14.3 years. Ten (17.5%) patients had an underlying medical condition including asthma, diabetes mellitus, seizure disorder or renal failure. Two (3.6%) patients were pregnant. Overall, 23 (41.8%) patients developed neurological signs or symptoms while were ill with influenza. The most common neurological symptom was headache, which was reported in 19 (34.5%) of patients. This was followed by numbness and paresthesia in 10 (18.2%), drowsiness in five (9.1%), and coma in five (9.1%). Other symptoms were focal weakness in four (7.3%), generalized weakness in one (1.8%), vertigo in four (7.3%), ataxia in two (2.6%), myoclonus in one (1.8%) and seizure in one (1.8%) patients. Among patients who developed coma, four patients died, and one recovered. The following two case histories illustrate severe neurological complications of the illness.

Patient 1

A 16-year-old boy was admitted in neurology ward due to fever and two generalized tonic-clonic seizures. The patient had flu-like symptoms for 10 days prior to his admission. His cerebrospinal fluid analysis was normal (no cells, and normal protein and sugar). His electroencephalogram (EEG) showed diffuse cerebral dysfunction (slowing) and multifocal spikes. He was discharged, with instructions to take oral sodium valproate. He was admitted again with fever, clonus in his left lower extremity, left sided weakness and a generalized tonic-clonic seizure seven days after he was discharged from the hospital. While hospitalized, he developed *epilepsia partialis continua* with clonic movements restricted to his left side, without impairment of consciousness. His EEG showed repeated T4 (right mid-temporal) sharp waves and moderate diffuse cerebral dysfunction (excess theta / delta activity in wakefulness). Brain MRI revealed multiple subcortical white matter lesions, with increased T2 signal and no signal changes in the T1 weighted images. He was treated with phenytoin. He subsequently developed respiratory distress and decreased level of consciousness. The H1N1 PCR was positive, and he started receiving oseltamivir. After the initiation of antiviral treatment, his condition improved and he was discharged one week later. He did not report any recurrence of seizure in the follow-up visits during four months after being discharged. However, his follow-up EEG at one

month after the discharge showed T4 (right mid-temporal) sharp waves with a normal background.

There is another case report published recently.⁹ The authors described a 17-year-old male with encephalitis and seizure. The seizure occurred on the second day of respiratory symptoms with a fever. He was confirmed with the H1N1 virus infection. He took oseltamivir (75 mg twice a day) for five days and oxcarbazepine (300 mg twice a day). He was discharged without a recurrence of seizure attacks.

Patient 2

A 22-year-old woman had visited her local physician because of flu-like symptoms and mild weakness in her lower extremities. She had received oral antibiotics and dexamethasone. Three days later she was admitted to the hospital with paraplegia and leg pain. Her lower extremity deep tendon reflexes were absent in physical examination. Her cranial nerves were intact. Two days later, she developed quadriplegia and decreased level of consciousness (coma). She rapidly developed severe respiratory difficulty and expired due to cardio-respiratory arrest. Her H1N1 PCR assay was positive.

Discussion

The H1N1 infection seems to have been quite mild with a self-limited course in much of the world, yet there appears to be a subset, which is severely affected. In our study, mild and/or severe neurological complaints/complications were reported in 42% of the patients infected by H1N1 virus. In our patients, the most common neurological complaints were rather mild. These included headache, numbness and paresthesia, vertigo, drowsiness and weakness. Severe neurological complications occurred in about 9% of the patients. These same complications have also been associated with seasonal influenza infection. Influenza virus infection (A and B) are associated with seizures,² acute inflammatory demyelinating polyneuropathy, acute disseminated encephalomyelitis, transverse myelitis,¹⁰ and alterations in the level of consciousness ranging from lethargy to coma.¹¹ The H1N1 influenza virus infection was also associated with encephalitis and fulminant cerebellitis.^{9,12,13} In another study, a higher proportion of patients complained of headache (about 62% vs. 35% in the present study) and vertigo (40% vs. 7% in this study); however, the prevalence of decreased levels of consciousness (8.2%) was

almost similar to our study (9.1%).¹⁴ According to a previous study,¹⁵ headache has been reported to occur less frequently (20%) in children with swine flu. It should be mentioned that headache is often a mild and non-specific symptom observed in many neurological and non-neurological disorders, either infectious or non-infectious.

Conclusion

We recommend performing diagnostic tests for H1N1 influenza virus in all patients with symptoms of respiratory illness and neurological signs/symptoms. Given the potential for severe complications in patients with positive H1N1 PCR test who have any moderate to severe neurological symptoms, we recommend to initiate treatment with appropriate antiviral drugs as soon as possible. The favorable response of one patient to oseltamivir provides some support for this recommendation, though more systematic studies are required.

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Conflict of Interest: None declared

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