Neurological sequelae of pH1N1 influenza in children: A case series observed during a pandemic*

S. A. Baltagi, ——; M. Shoykhet, ——; K. Felmet, ——; P. M. Kochanek, ——; M. J. Bell, ——

Objective: To outline a series of cases demonstrating neurologic complications in children with Influenza infection. The ongoing 2009 influenza A pandemic (pH1N1) presents significant challenges to the field of pediatric critical care and requires increased awareness of new presentations and sequelae of infection. Since World Health Organization declared a pH1N1 pandemic, much attention has been focused on its respiratory manifestations of the illness, but limited information regarding neurologic complications has been reported.

Design: Case series.

Setting: Pediatric intensive care unit of a tertiary care medical facility.

Patients: Four children admitted to the pediatric intensive care unit between March and November 2009 at the Children’s Hospital of Pittsburgh with altered mental status and influenza infection.

Interventions: ————

The World Health Organization declared a pandemic of a novel virus, 2009 influenza A (pH1N1), on June 11, 2009. Although first recognized in Mexico, cases within the United States were first reported in spring 2009, culminating in a surge of new cases in the fall. At its peak, 48 states reported widespread flu activity with this virus. At the time of the writing of this manuscript, some 4000 deaths have been attributed to 2009 influenza A (pH1N1) infection in the United States. Several aspects of this emerging infection distinguish it from seasonal influenza. A syndrome of rapidly progressive hemorrhagic pneumonitis has been described in adults and children (1) as have anecdotal reports of the need for advanced hemodynamic support with extracorporeal membrane oxygenation (2). The populations at highest risk of mortality seem to be pregnant women and adults aged 25–49 yrs, substantially different from the at-risk population for seasonal flu. As we refine our understanding of this emerging infection and its differences from seasonal influenza, we must be alert to its unusual manifestations.

Infection with seasonal influenza virus (both type A and B) has been associated with a wide variety of neurologic complications, including seizures, Reye’s syndrome, encephalopathy/encephalitis, acute necrotizing encephalitis, acute hemorrhagic encephalopathy, and transverse myelitis (3–6). However, neurologic complications and encephalopathy/encephalitis attributed to 2009 influenza A (pH1N1) virus have rarely been described in the literature (7). For this manuscript, we have used standard nomenclature for influenza encephalitis or encephalopathy and all cases meet the definition of this disorder outlined previously (7). We describe a series of four children that have been admitted to our critical care unit between March and November 2009 with encephalopathy secondary to 2009 influenza A (pH1N1) virus infection (Tables 1 and 2).

Case Identification and Case Reports

The Institutional Review Board of the University of Pittsburgh reviewed this case series and determined that it did not meet the Federal definition of “human subjects research” (45 Code of Federal Regulations 46.102) (2), and hence did not require Institutional Review Board oversight. Within our institution, suspected influenza infection was investigated with a two-step process of generalized screening followed by confirmatory testing. In general, nasopharyngeal swabs (or other fluid specimens) were collected and initially processed by the QuickVue Influenza A+B Test kit (Quidel, San Diego, CA) in accordance with the manufacturer’s instructions. A swab was placed in an extraction solution whereby viral particles were released into the solution. Then, test strips (bound with mouse monoclonal anti-influenza A and anti-influenza B antibodies) were inserted and a colorimetric assay was performed. Samples from children with positive screening tests were then processed by real-
Thus, we included her case in this series, as the patient’s sputum tested positive for influenza A. In our laboratory, samples from the nasopharynx were batched for serotyping for epidemiologic purposes. At the time of this writing, our laboratory has failed to identify any influenza virus that is not 2009 influenza A (pH1N1) strain. Once it was evident that all influenza A (pH1N1) testing procedures evolved to confirm infection as outlined above. Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain were both normal, and electroencephalography (EEG) showed generalized background slowing without epileptiform activity. Routine cerebrospinal fluid (CSF) studies were within the normal range (red blood cell [RBC], 0/mL^3; white blood cell [WBC], 1/mL^3; glucose, 57 mg/dL; protein, 29 mg/dL; protein, 25 mg/dL), and CSF titers for influenza virus antibody (serotype A and B) were negative. Electrolytes, complete blood count, and liver function tests (aspartate transaminase, 14 IU/L; alanine aminotransferase, 27 IU/L; ammonia, 24 µmol/L; lactate, 0.8 mEq/L) were all within normal limits. CSF meningoencephalitis panel and polymerase chain reaction.

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age/Gender</th>
<th>Presentation</th>
<th>Examination on Admission</th>
<th>CSF Analysis</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10/M</td>
<td>Altered consciousness</td>
<td>Combative, no focal signs, GCS score of 7</td>
<td>WBC 1/mL^3, 5% PMN, 90% lymphocytes, RBC 0/mL^3, glucose 57 mg/dL, protein 29 mg/dL</td>
<td>Positive for influenza A by EIA -H1N1 confirmed by rRT-PCR</td>
</tr>
<tr>
<td>2</td>
<td>4/M</td>
<td>Progressive deterioration in mental status</td>
<td>Alert, no focal signs, GCS score of 9</td>
<td>WBC 0/mL^3, RBC 1/mL^3, glucose 148 mg/dL, protein 25 mg/dL</td>
<td>Positive for influenza A by EIA, -H1N1 confirmed by rRT-PCR</td>
</tr>
<tr>
<td>3</td>
<td>2/F</td>
<td>Seizures, altered consciousness, movement disorder</td>
<td>Drowsy, mute, no focal signs, GCS score of 7</td>
<td>WBC 1/mL^3, RBC 0/mL^3, glucose 49 mg/dL, protein 18 mg/dL</td>
<td>Positive for influenza A by EIA, -H1N1 confirmed by rRT-PCR</td>
</tr>
<tr>
<td>4</td>
<td>3/F</td>
<td>Coma, extensor Babinski and posturing</td>
<td>Extensor Babinski and posturing GCS score of 4</td>
<td>WBC 1/mL^3, RBC 2/mL^3, glucose 70 mg/dL, protein 77 mg/dL</td>
<td>Positive for influenza A by EIA</td>
</tr>
</tbody>
</table>

**Table 1. Clinical characteristics and laboratory findings of four children with 2009 influenza A (pH1N1) encephalitis**

**Patient 1**

A previously healthy, 10-yr-old boy was admitted to the pediatric intensive care unit for altered mental status. Parents found him unarousable after a 2-day history of high-grade fever to 39°C and he was brought to the emergency department for evaluation. Upon arrival, vital signs were unremarkable except for a fever of 38.9°C. General physical examination was unremarkable but repeat showed interval increase in the degree of volume loss. Subtle T2/FLAIR signal seen around frontal horns and occipital horns and restricted diffusion suggestive of necrosis. MRI showed marked swelling within the thalamus and restricted diffusion suggestive of necrosis. MRA/V were normal.

At discharge, GCS score = 6, nonverbal, CN VI and VII palsies, and swallowing difficulties. Five month after discharge, she is able to cruise and babble. CN VI palsy resolved and she has recovered her ability to swallow.

<table>
<thead>
<tr>
<th>Pt.</th>
<th>EEG</th>
<th>Neuroimaging</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diffuse slowing, no epileptiform activity noted</td>
<td>CT and MRI within normal limits</td>
<td>Back to normal baseline</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse slowing, no epileptiform activity noted</td>
<td>CT within normal limits</td>
<td>Back to normal baseline</td>
</tr>
<tr>
<td>3</td>
<td>Diffuse slowing, no epileptiform activity noted</td>
<td>Initial MRI was normal, but repeat showed interval increase in the degree of volume loss. Subtle T2/FLAIR signal seen around frontal horns and occipital horns</td>
<td>Poor truncal tone, choreoathetosis, increased awareness with environment, babbles few words</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse slowing, no epileptiform activity noted</td>
<td>MRI showed marked swelling within the thalamus and restricted diffusion suggestive of necrosis. MRA/V were normal</td>
<td>At discharge, GCS score = 6, nonverbal, CN VI and VII palsies, and swallowing difficulties. Five month after discharge, she is able to cruise and babble. CN VI palsy resolved and she has recovered her ability to swallow</td>
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**Table 2. Investigations and outcome of cases**

EEG, electroencephalogram; CT, computed tomography; MRI, magnetic resonance imaging; T2/FLAIR, FLAIR; MRA/V, magnetic resonance angiography/angiography; GCS, Glasgow Coma Scale; WBC, white blood cell; PMN, polymorphonuclear neutrophilic leukocyte; RBC, red blood cell; EIA, enzyme immunoassay; rRT-PCR, real-time reverse transcription-polymerase chain reaction.
merase chain reaction (PCR) for both herpes simplex virus and Epstein-Barr virus were negative. Urine and serum toxicology were negative. His clinical course improved rapidly, and he was extubated within 24 hrs with a GCS score of 11. He slowly improved back to his neurologic baseline. On day 5, he was discharged home with a normal neurologic examination.

**Patient 2**

A previously healthy, Caucasian 4-yr-old boy presented to our emergency department with fever, mild cough, rhinorrhea, decreased oral intake, and fatigue for 24 hrs to 48 hrs and a new onset rash over the axillae and neck. Additionally, parents reported that he exhibited unusual behaviors, such as voiding in inappropriate places, clearly abnormal for his level of development. His initial vital signs were significant for fever (39.5°C), tachycardia (176 beats/min), hypotension (79 mm Hg /35 mm Hg), and fluctuating level of consciousness. Physical examination was significant for a petechial rash over the upper torso. His neurologic examination was significant for a GCS score of 9, nonfocal motor examination, normal sensation to pain, normal deep tendon reflexes, and cranial nerves and flexor responses to the Babinski maneuver. Due to the hypotension and petechial rash, the initial working diagnosis was meningococcal sepsis. Hemodynamic instability was treated with volume expansion (approximately 100 mL/kg), inotropes (epinephrine up to 0.1 μg/kg/min at maximum), and hydrocortisone (2 mg/kg/day). The patient was intubated due to decreased level of consciousness and shock. Mircobiological cultures (blood, respiratory, urine) were obtained and remained sterile. Antibiotics/antivirals (ceftriaxone, vancomycin, oseltamivir) were administered. Nasopharyngeal swabs confirmed 2009 influenza A (pH1N1) infection. CT scan of the brain was normal and EEG demonstrated generalized background slowing without epileptiform activity. Lumbar puncture demonstrated an increased opening and closing pressure (30 cm H2O and 21 cm H2O, respectively), yet examination of the CSF was relatively unremarkable. Herpes simplex virus and enterovirus PCR were negative and influenza was not detected in CSF by real-time reverse transcription-polymerase chain reaction. Hematologic assessment demonstrated mild leukopenia (3.6 × 10⁹/L) with normal hemoglobin (13.3 g/dL), platelet count (217,000 × 10⁹/L), and coagulation profile (prothrombin time, 14.7 secs; partial thromboplastin time, 32 secs; international normalized ratio, 1.1). Again, serum electrolytes, glucose and liver function tests (aspartate transaminase, 44 IU/L; alanine aminotransferase, 27 IU/L) were normal. The child was extubated after 48 hrs and the neurologic examination was back to his baseline. On discharge, he was alert and had no apparent neurologic sequelae.

**Patient 3**

A 2-yr-old African American girl presented to our emergency department for changes in her mental status. Her mother reported that she had increasing upper respiratory symptoms over the past several days, fevers, and developed abnormal body movements and hallucinations manifested by waking up at night screaming. Within the past 10 days, she had been admitted to our facility with presumptive uncomplicated febrile seizures and subsequently discharged. Her admission vital signs were normal and physical examination was noncontributory. Her neurologic examination was significant for a nonverbal, agitated, confused child with normal strength, intact cranial nerves, and normal deep tendon reflexes. Her GCS score fluctuated between 7 and 9, and she maintained airway reflexes without difficulty. Diagnostic workup included a brain MRI, which was normal at the time of admission. Repeat imaging on day 10, however, demonstrated significant volume loss within the gray and white matter surrounding the frontal and occipital horns of the lateral ventricles (T2/FLAIR image, shown in Fig. 1). Magnetic resonance spectroscopy in the parietal region demonstrated a normal NAA peak without evidence of increased lactate. The 2009 influenza A (pH1N1) was isolated from her nasopharynx from her admission evaluation. Her initial management included fosphenytoin for seizure control, broad-spectrum antibiotics, and oseltamivir. Multiple EEGs failed to show epileptiform activity but had profound background slowing. She was treated with intravenous immunoglobulin and high-dose solumedrol in an attempt to mitigate brain injury from encephalitis. CSF examination demonstrated increased opening pressure (31 cm H2O) but was otherwise unremarkable (WBC, 1/mL; RBC, 0/mL; glucose, 49 mg/dL; protein, 18 mg/dL; culture sterile). Influenza was not isolated from her CSF. An
extensive workup was undertaken for causes of her neurologic symptoms including: serum lactate, serum pyruvate, urine organic acid, chromosomal study, urine amino acids, CSF amino acids, acylcarnitine profile, lyme titers, ASO, CSF PCR (both herpes simplex virus and Epstein-Barr virus), urine heavy metals, serum meningoencephalitis, and paraneoplastic panels. All of these tests were within the normal range. Her CSF did demonstrate N-methyl-D-aspartate (NMDA) receptor antibodies. Her hospital stay was eventful for periods of increased confusion followed by somnolence, fever, bizarre speech, truncal ataxia, and rhythmic movements of her extremities. Gradually, her level of consciousness improved, but her speech remained impaired. On hospital day 60, she was discharged to a rehabilitation facility with improving level of interaction with the environment but was dependent on a gastrostomy tube for feeding.

**Patient 4**

A 3-yr-old, previously healthy, Caucasian female was transferred to our facility for decreased level of consciousness. One day before admission, she developed flu-like symptoms consisting of low-grade fever and fatigue. The next day, her parents had difficulty in arousing her and she was taken to an outside facility for evaluation. She was found to be unresponsive to painful stimuli (GCS score of 4) and was emergently intubated for airway protection. Other therapies initiated include fosphenytoin for presumed seizures, and antibiotic therapy with vancomycin and ceftriaxone. She was transferred to our facility where admission vital signs were within normal limits and her temperature was 37.9°C. Physical examination demonstrated a flaccid, unconscious child with bilateral extensor plantar reflexes, flaccid deep tendon reflexes, and decerebrate posturing in response to painful stimuli. There was no obvious sensory level, CT of brain demonstrated hyperintense lesions in the thalamus bilaterally, and brain MRI showed marked swelling within the thalamus and restricted diffusion suggestive of necrosis (Fig. 2) with normal vasculature. EEG showed background slowing but no epileptiform discharges. Nasopharyngeal aspirate demonstrated influenza A (serotyping of the virus was not performed). Laboratory analysis revealed mild hyperglycemia (serum glucose, 195 mg/dL) but otherwise normal electrolytes, liver function tests, and hematologic parameters. CSF examination was normal except for slightly increased protein (WBC, 1/mL; RBC, 2/mL; glucose, 70 mg/dL; and protein, 77 mg/dL; culture sterile). CSF encephalitis panel failed to detect changes in acute concentrations of antibodies to >20 viruses, including influenza A. CSF PCR was negative for enterovirus, mycoplasma pneumonia, herpes simplex virus, and Epstein-Barr virus. She was treated with amantadine and oseltamivir for presumptive influenza necrotizing encephalopathy and intravenous immunoglobulin, and high-dose corticosteroids were administered for several days. Her respiratory failure slowly resolved and she was separated from mechanical support by the eighth day of hospitalization. After 19 days, she was discharged to a rehabilitation facility with minimal interactions with her environment, a GCS score of 6, cranial nerve VI and VII palsies, residual spasticity, and swallowing difficulties requiring gastrostomy tube placement. At her 5-month follow-up, she is able to cruise and babble a few words. Her examination shows complete resolution of cranial nerve VI palsy, partial resolution of cranial nerve VII palsy, and she has recovered her ability to swallow.

**DISCUSSION**

We describe several cases of 2009 influenza A (pH1N1) infection that predominantly manifested as neurologic conditions in children admitted to our facility during the recent global pandemic. During this period, 234 hospitalized children were diagnosed with 2009 influenza A (pH1N1) to our hospital, with 49 children admitted to the pediatric intensive care unit and four deaths. Commonalities within our cases are the presenting sign of abnormal mentation, EEG abnormalities consistent with an acute encephalopathy, and lack of concomitant lung or other organ dysfunction. We believe that children with acute changes in mentation and examinations consistent with encephalitis should undergo influenza testing as part of comprehensive assessment in their medical care.

Influenza viruses do not seem to have a predilection for the nervous system, although detection of virus within both the olfactory bulb and retina has been described in experimental models (8, 9). Although influenza virus infections predominantly cause respiratory illnesses, several neurologic complications can oc-
cur. Influenza A encephalopathy is the most common cause of encephalopathy in Japan with a prevalence of 7 of 100,000 child-years (10). Acute neurologic changes have been reported in patients with H5N1, another influenza virus with pandemic potential, and this pathogen has been recovered from the brain tissue of experimentally infected animals (11, 12). The pathophysiology of influenza-associated encephalopathy, from either pH1N1 or other strains, is still under investigation. Some (13, 14) have postulated that direct microglial or astrocyte responses (leading to apoptosis) or production of inflammatory cytokines could explain the neurologic findings. Others (15) have suggested that blood-brain barrier dysfunction may play a role. For example, matrix metalloproteinase-9 and tissue inhibitors of metalloproteinase 1 have been observed in serum of patients with influenza encephalitis, and the ratio between these proteins in serum has correlated with the severity of injury. We suspect that more information regarding the pathogenesis of influenza encephalitis will be elucidated as more cases are identified and studied.

Evidence of the patterns of illness occurring as a result of the current pandemic are just emerging. Kumar and colleagues (2) described the experience from the Canadian Critical Care Trials Group encompassing 118 adults and 50 children admitted to 36 critical care units. Although a wide range of pathology was described (including 81% requiring mechanical ventilation for respiratory failure, almost a third requiring vasoactive medications to improve cardiovascular performance and an observed mortality rate of 17.3% at 90 days), little information regarding either neurologic manifestations or sequelae were provided. Similarly, Louie and colleagues (1) recently summarized the experience of 2009 influenza A (pH1N1) infection in California over the first 16 wks of the pandemic, identifying 344 hospitalized children. Headache was reported in 14% of cases, yet neurologic sequelae seem to be much less prominent in these large series than cardiorespiratory effects of the infection.

Manifestations of permanent neurologic impairment in either adults or children after the 2009 influenza A (pH1N1) infection are relatively rare. In a review of six patients with encephalitis during the pH1N1 epidemic in Croatia in 2000, headache, hyperpyrexia, and fatigue were the main presenting features in infected adults (16). Seizures occurred in 50% of cases and brain edema was observed on imaging studies in 50% of patients, similar to our findings. All-cause mortality was 16.6% and one third of survivors suffered permanent neurologic sequelae, relatively similar to the 50% frequency in our small series.

Determining the overall prevalence of influenza encephalitis in children can be challenging, either in pandemic or seasonal outbreaks. In a series (17) of 311 children admitted with encephalitis, influenza encephalitis was diagnosed in 7% of cases. Physician’s clinical diagnosis of influenza (18, 19) has poor sensitivity and specificity, particularly in young children, but we believe our comprehensive testing procedures correctly identified the cases in this report. In this most recent pandemic, four cases of seizures—which may be a manifestation of influenza encephalitis—were observed in infected children in Dallas, TX (7). However, significant differences exist between these patients and those in our case series. First, whereas all children in our series had decreased levels of consciousness as initial manifestations of their illness, only two of the cases in Dallas demonstrated this finding. Importantly, all imaging studies performed in the Dallas group were normal, whereas two of our children demonstrated abnormalities on CT/MRI. Second, we observed only one child with seizures as a presenting sign, whereas the Dallas group described seizures in all cases. Third, two of our children had persistent neurologic sequelae by the time of hospital discharge, whereas all of the children from the Dallas series demonstrated apparent complete neurologic recovery. It is possible that age of the children may explain some of these differences (average age of our patients was 4.7 yrs, whereas those from the Dallas group were 11.3 yrs), as younger age has been associated with poorer neurologic outcome from seasonal influenza encephalitis (17, 20). Interestingly, in both series, none of the children demonstrated significant other organ dysfunction. This may indicate that genetic variations within the infecting virus predispose to neurologic or systemic complications from infection.

Other interesting findings of our data pertain to the diagnosis of acute necrotizing encephalitis (19) and the presence of NMDA receptor in CSF in our two most severe cases. Acute necrotizing encephalitis is a rare type of acute encephalopathy originally described in East Asia or in individuals of Asian descent that usually manifests itself after few days of viral prodrome (21–25). Diagnosis is usually made on the basis of CT and MRI findings of bilateral symmetric thalamic lesions (26) and is associated with a sudden onset of high fever, severe seizures, rapidly progressive coma, and death within days. Prognosis for neurologic recovery is generally poor, but our case demonstrates that long-term recovery can continue for some months. We also detected antibodies against the NMDA receptor within the CSF of patient 3. A new entity, anti-NMDA receptor encephalitis, has recently been postulated whereby antibody production against the NR1 subunit of the NMDA receptor causes seizures and encephalopathy (27–29). It has been associated with teratomas, infections (10% of patients have positive serology for Mycoplasma pneumoniae) but has not been associated with influenza A or pH1N1, to our knowledge.

Understanding the neurologic manifestations of 2009 influenza A (pH1N1) are a necessary first step toward developing therapeutic strategies to minimize acute and long-lasting neurologic injury. We treated all of our patients with oseltamivir, in accordance with guidelines published by the Centers for Disease Control and Prevention (http://www.cdc.gov/h1n1flu/recommendations.htm). We used corticosteroids and intravenous immunoglobulin in our two most severely affected children based on very sporadic reports of improvement from a variety of viral pathogens and clinical syndromes (30–32). However, we failed to observe a significant clinical improvement with any of these measures in our series. Any possible therapeutic effect of such therapies should be weighed against possible deleterious effects on immunologic function that has been observed after 2009 influenza A (pH1N1) infection. Obviously, a well-designed clinical trial would need to be performed to fully determine the benefits of such a strategy.

Our study has a number of limitations. Most obviously, our case series consists of a small number of children admitted to a single center. Obvious correlations with experience from other institutions will be required to fully define how 2009 influenza A (pH1N1) can affect neurologic conditions in childhood. Second, one of our cases failed to have definitive 2009 influenza A (pH1N1) testing performed. We believe that this case is likely pH1N1,
as the large majority of isolates of influenza A during the pandemic were of the pH1N1 serotype. However, it is possible that this case was simply a severe manifestation of seasonal influenza. Finally, determination of the severity of the neurologic injuries with 2009 influenza A (pH1N1) cannot be made at the present time because a sufficient amount of time has not elapsed from our first case. Because of this, it is impossible to fully evaluate the permanent nature of these injuries at this time.

In conclusion, neurologic complications from 2009 influenza A (pH1N1) infection occur and are often not associated with other organ injury. We strongly believe that clinicians should consider 2009 influenza A (pH1N1) as a potential cause of neurologic conditions, particularly autoimmune encephalitis associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection of mice within hours after intranasal infection. J Neurovirol 2007; 13:399 –409


12. Large pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. Proc Natl Acad Sci U S A 2009; 106: 14063–14068

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