BRIEF REPORT

# Acute Necrotizing Encephalopathy Progressing to Brain Death in a Pediatric Patient with Novel Influenza A (H1N1) Infection

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**We report a case of encephalopathy progressing to brain death in a pediatric patient with confirmed infection with novel influenza H1N1. Although neurologic dysfunction associated with H1N1 has been described, we believe this to be the first published report of brain death associated with H1N1 infection.**

Neurologic complications of influenza have been well described in the literature and date back to the diagnosis of encephalitis lethargica during the 1918 influenza pandemic [1]. Neurologic manifestations of influenza are now known to include encephalitis, acute disseminated encephalomyelitis, Guillain-Barre syndrome, transverse myelitis, and acute necrotizing encephalopathy (ANE). Reports of ANE began surfacing from Japan during the influenza epidemics of the mid- and late 1990s [2–6]. Influenza-associated central nervous system (CNS) dysfunction has also been reported, although infrequently, in Europe and the United States [7–10]. Other infections associated with ANE include human herpesvirus–6 infection, measles, parainfluenza infection, and *Mycoplasma* infection [11].

According to studies from Japan, in the most severe cases of influenza-associated ANE, patients develop altered mental status with or without seizures and then rapidly progress to a comatose state within a mean of 24–72 hours from the onset of fever and upper respiratory symptoms [2, 3, 6]. Seizures are often resistant to antiepileptic medications [4]. Death, which occurs in roughly 30% of cases, results largely from cardiorespiratory compromise or complications from mechanical ventilation [2].

To our knowledge, encephalopathy associated with the novel H1N1 influenza strain was first reported in a case series of 4 pediatric patients in the United States in May 2009 [12]. All 4 patients had mild seizures and/or altered mental status, and all recovered fully without any neurological sequelae at discharge. Here, we report what we believe to be the first published case of H1N1 encephalopathy progressing to brain death in a pediatric patient in the United States.

***Case presentation.*** A 7-year-old, previously healthy, presumably immunocompetent female of Mandarin Chinese descent presented to a community emergency department with a 1-day history of fever (temperature, 39.4°C) and malaise but no upper respiratory symptoms. She had not been vaccinated for seasonal influenza, and she had not received the H1N1 vaccine. She was diagnosed with influenza A by rapid screen on nasal wash specimen and then discharged home with instructions for supportive care with oral fluids and ibuprofen. Approximately 4 hours after discharge from the first emergency department visit, she became confused, lethargic, unable to walk, and incontinent of bladder and bowel function. Approximately 7 hours after onset of these new symptoms at home, she presented again to the local emergency department. She was febrile (temperature, 40.8°C), she was obtunded, and she required emergent intubation for airway protection. A noncontrast head computed tomography scan revealed diffuse cerebral edema, infarcts of the basal ganglia bilaterally, and effacement of the fourth ventricle (Figure 1a). At this point, she was transferred to the pediatric intensive care unit at T. C. Thompson Children's Hospital in Chattanooga, Tennessee, for further care.

Upon arrival at the pediatric intensive care unit, she had a Glasgow Coma Score of 6T and an exam consistent with severe neurologic compromise. In the absence of neuromuscular blockade, she displayed no spontaneous movement and had minimal withdrawal to pain. Cough, gag, and corneal reflexes were all absent. Her pupils were 5 mm and nonreactive to light. She also demonstrated myoclonus. The family denied any toxic ingestion and denied use of salicylates. The only medication given at home was ibuprofen.

Initial laboratory abnormalities included aspartate aminotransferase level of 103, alanine aminotransferase level of 61, prothrombin time of 17.2, and international normalized ratio of 1.34. Her initial complete blood count and serum electrolytes were all normal.

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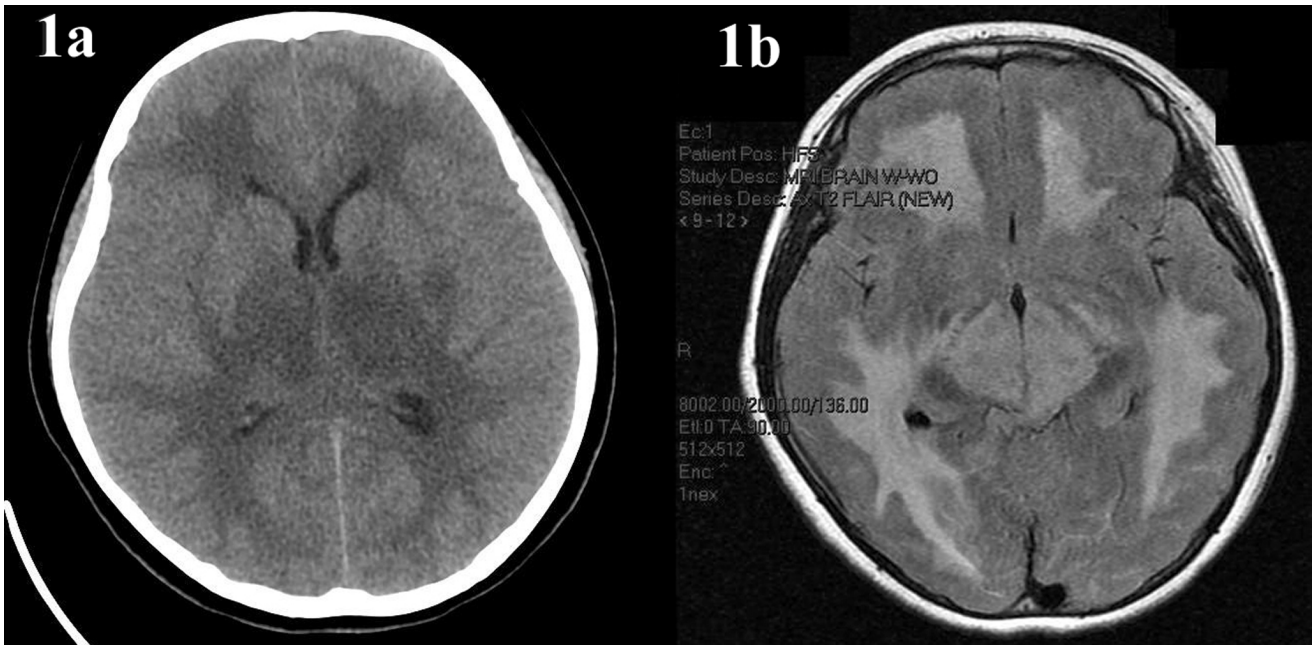


**Figure 1.** *a,* Noncontrast head computed tomography scan reveals extensive hypodensity in the white matter as well as the basal ganglia and thalami consistent with global insult. In addition, there is generalized cerebral edema. *b,* Magnetic resonance imaging of the brain (with fluid attenuation inversion recovery) demonstrates extensive and diffuse white matter and subcortical white matter signal abnormality that includes the bilateral thalami as well as increasing cerebral edema.

Initial management consisted of temperature control with a cooling blanket and rectal acetaminophen, elevation of the head of bed to 40°, mild hyperventilation, hypertonic saline, and mannitol because of signs of increased intracranial pressure. She was also empirically treated for bacterial meningitis with vancomycin and ceftriaxone as well as oseltamavir for influenza. Approximately 4 hours after admission, she demonstrated bradycardia and hypertension that were treated with boluses of mannitol and hypertonic saline. These signs of herniation syndrome were followed by severe hypotension that necessitated the use of fluid boluses and multiple vasopressive agents to maintain blood pressure. Neurosurgical consultation was obtained to determine if intracranial pressure monitoring and/or decompressive craniectomy were treatment options in this patient. The patient's parents refused consent for lumbar puncture.

Because of concern for stroke, magnetic resonance imaging (MRI) and magnetic resonance angiography of the brain were performed (Figure 1b). It was determined that she was not a candidate for intracranial pressure monitoring or decompressive craniectomy because of brainstem herniation. She quickly developed diabetes insipidus that required vasopressin infusion. On hospital day 3, she was pronounced brain dead following 2 brain death examinations performed by different physicians 24 hours apart, a nuclear medicine cerebral blood flow study that showed no cerebral perfusion, and an electroencephalograph consistent with electrical silence. Autopsy was refused by the family. By the time of death, we received notice that a polymerase chain reaction (PCR) assay performed by the Tennessee state laboratory was positive for H1N1 influenza infection.

***Discussion.*** To our knowledge, this is the first reported case of novel influenza A (H1N1)-associated ANE resulting in brain death in the United States. First described in Japan in 1979, ANE was formally characterized in 1995 and is defined as acute encephalopathy following a viral febrile illness with rapid deterioration of level of consciousness; multifocal, symmetric lesions seen on computed tomography or MRI in the thalamus, cerebral and cerebellar medullae, and brainstem; no cerebrospinal fluid pleocytosis; elevation of serum aminotransferases of variable degrees; and exclusion of resembling diseases [11]. The clinical course of ANE is rapidly progressive; patients present with fever and nonspecific symptoms, such as cough, emesis, and/or diarrhea, and quickly develop neurologic dysfunction. Approximately 18% of cases of ANE in Japan have been associated with influenza A infection [3]. The strain most frequently associated with ANE is influenza A, H3N2 subtype, although cases associated with H1N1 and influenza B have also been described [2, 7, 13–15]. The disease is associated with significant morbidity and mortality, and survivors usually exhibit at least short-term neurologic sequelae [6]. In addition to antiviral therapies such as oseltamavir, corticosteroids and intravenous immune globulin have been used to treat selected cases of ANE in Japan, with varying degrees of patient im-

provement [16]. Currently, there is no definitive treatment for ANE, and management of these patients centers upon supportive care for neurologic failure and treatment of increased intracranial pressure if present.

At present, it is unknown whether influenza virus physically enters the CNS or whether neurological dysfunction is secondary to other effects. On postmortem pathological examination, some authors have found evidence of petechial hemorrhages, congestion of intraparenchymal thalamic vessels, microthrombi, and vasogenic edema, suggesting that CNS dysfunction may result from vascular damage without evidence of direct penetration across the blood brain barrier [3]. Other authors describe high plasma concentrations of interleukin 6 and tumor necrosis factor–$\alpha$, suggesting that proinflammatory cytokines may be mediators of damage [1], although not all reports show elevation in inflammatory markers [4]. Very rarely do authors report direct evidence of influenza virus in the CNS [17]. In a survey of 94 Japanese hospitals over 9 influenza seasons, Togashi et al [2] reported that only 10% of cases had PCR detection of influenza in the cerebrospinal fluid. Fujimoto et al [18] showed PCR detection in 5 of 10 ANE patients.

It is unclear whether there are anatomical or biochemical differences that allow the virus entry into the CNS or that lead to remote effects on the brain or whether there are mutations in certain strains of the influenza virus that confer more neurotropic properties. Because the symptoms have such rapid onset and viral antigens have been found so rarely in brain tissue and cerebrospinal fluid, most authors have suggested that a cytokine-mediated process, rather than direct invasion of the CNS, is the pathophysiologic mechanism in this disease.

It appears that CNS sequelae of influenza occur with disproportionate frequency in patients of Asian descent, despite the fact that influenza itself is a very common winter febrile illness in all developed countries. Some authors suggest that the increased use of certain drugs, namely diclofenac sodium, mephenamate, and ephedrine, in Japan may play a role [4]. Per history, the patient described here had no exposure to diclofenac sodium, mephenamate, or ephedrine, although she had taken ibuprofen, another nonsteroidal anti-inflammatory drug.

During the time of this patient's presentation, the H1N1 pandemic was nearing its peak in the southeastern United States. Our institution treated a large number of children with confirmed H1N1 infection during this period, most of whom recovered fully. The patient we focus on in this report, although presumably exposed to the same strain of virus circulating in the community, was the only one with very rapid and fatal CNS dysfunction and happened to be of Asian descent. Therefore, it is unclear whether her Asian heritage was related to her illness.

In summary, we describe a pediatric patient with documented novel influenza A (H1N1) infection who presented with the well-described features of ANE and progressed to brain death. Although influenza is a relatively benign illness in the majority of healthy children, physicians who care for children in the United States should be aware of ANE and should maintain a high degree of clinical suspicion in any child presenting with acute mental status changes in the setting of influenza infection.

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