Objective: To describe the first adult with neurologic complications associated with H1N1 influenza virus infection.

Design: Case report.

Patient: A 40-year-old man with severe H1N1 influenza infection with prolonged hypoxia and critical illness who remained comatose after withdrawal of sedatives and paralytics.

Interventions: Clinical examination and magnetic resonance imaging.

Results: Brain imaging revealed multifocal T2 hyperintense lesions, edema, and hemorrhages consistent with acute hemorrhagic leukoencephalitis (AHL) and restricted diffusion in the basal ganglia consistent with hypoxic brain injury. The patient remained in a severely disabled state following treatment with plasma exchange and high-dose corticosteroids.

Conclusions: This is the first study of neurologic complications associated with H1N1 influenza infection in adults. Severe brain injury can occur by 2 distinct mechanisms: a fulminant autoimmune demyelinating insult (AHL) and hypoxic brain injury. Clinicians should be aware of these potential complications so that appropriate imaging and treatment can be considered.

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A novel influenza A (H1N1) virus discovered in 2009 has caused the first influenza pandemic in more than 30 years. Although neurologic complications of seasonal influenza have been described, their frequency in association with H1N1 influenza remains unknown. To date, there have been no reports of neurologic manifestations of H1N1 influenza infection in adults. In children there are reports of seizures and encephalopathy1 and 1 case of fatal acute necrotizing encephalopathy.2

Acute hemorrhagic leukoencephalitis (AHL) is a rare fulminant form of acute disseminated encephalomyelitis, initially described by Hurst.3 The mortality rate in this demyelinating disease may be as high as 70%.4 Clinical features of AHL typically follow a respiratory infection and include headache, seizures, focal neurologic signs, and encephalopathy, which may rapidly progress to coma. Brain magnetic resonance imaging reveals multifocal T2 white matter hyperintensities with marked edema and areas of hemorrhage.5 Although usually fatal, there have been favorable recoveries described in patients treated with immunosuppressive therapy and plasma exchange.6,7 We describe a patient with AHL in addition to hypoxic ischemic brain injury associated with severe H1N1 infection.

REPORT OF A CASE

A previously healthy 40-year-old man presented to a local emergency department with subacute malaise, fever, and dyspnea. His oxygen saturation was 68% with room air, and he was admitted to the hospital with suspected community-acquired pneumonia. His condition deteriorated overnight; he was intubated for hypoxic respiratory failure and transferred to a larger institution. His temperature was 38.4°C, heart rate, 122 beats per minute; blood pressure, 141/78 mm Hg; and oxygen saturation, 88% while mechanically ventilated with fraction of inspired oxygen (FiO2) of 100%, with positive end expiratory pressure of 12 cm of water. To facilitate low tidal volume ventilation, he was paralyzed and sedated with intravenous infusions of cisatracurium and propofol. Chest computed tomography

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We describe the first adult with neurologic complications associated with the 2009 H1N1 influenza virus. This case illustrates the severe brain injury that can occur by 2 different mechanisms in this setting: a postinfectious autoimmune demyelinating insult (AHL) and hypoxic injury resulting from severe acute respiratory distress syndrome (ARDS). There are compelling arguments for 2 disease processes in this case rather than combining the laboratory and radiographic findings. The marked restricted diffusion involving the striata and globi pallidi strongly indicates a major hypoxic insult. The progressive white matter involvement, together with CSF findings of elevated IgG index, synthesis rate, and protein are all consistent with AHL. However, we acknowledge that basal ganglia involvement can occur with acute disseminated encephalomyelitis and that diffusion-weighted imaging abnormalities have been described in AHL.

Acute encephalopathies have been described in association with seasonal influenza, mostly in children. Hurst disease, or AHL, is the most severe form and is commonly fatal. We present here the first case of Hurst disease described after severe H1N1 influenza infection. Though there was no definitive diagnosis by brain biopsy and pathologic review, we believe that the imaging findings of deep white matter involvement with edema and hemorrhage in addition to the CSF findings are consistent with AHL. The absence of pleocytosis is compatible with the diagnosis, as up to 50% of patients with acute disseminated encephalomyelitis have been reported to have completely normal CSF findings, and several cases with a diagnosis of AHL have had normal CSF cell

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**COMMENT**

showed extensive bilateral consolidations and ground glass opacities (Figure). Broncho-alveolar lavage was performed, and tracheal secretions tested positive for influenza A via testing with reverse transcriptase polymerase chain reaction performed at the Minnesota Department of Health laboratory. Additional testing for influenza (eg, serum serology) was not performed. The patient was treated with oseltamivir for 5 days.

The patient remained intubated, mechanically ventilated, paralyzed, and sedated while developing progressive bilateral alveolar infiltrates and refractory hypoxemia. On arterial blood gas, his pH ranged from 7.02 to 7.25 for nearly 1 month, with Po2 between 50 and 60 mm Hg, PCO2, 80 to 100 mm Hg; and oxygen saturation, 70% to 80% while receiving FiO2 of 85% to 100%. A bispectral index monitor was placed to monitor cerebral activity. One month into his critical illness, an acute drop on the bispectral index monitor to nearly 0 was noted while the patient was still paralyzed. Head computed tomography showed bilateral subcortical hypodensities with a small amount of hemorrhage. Episodes of intermittent tachypnea and eye deviation prompted treatment with intravenous valproic acid but there was no evidence of electrographic seizures on serial electroencephalograms (EEGs). A brain magnetic resonance image showed multiple lesions in both cerebral hemispheres associated with edema and multifocal petechial hemorrhages. The patient remained comatose after withdrawal of paralysis and sedation. Repeated magnetic resonance imaging 6 days later showed progression of the lesions, and he was transferred to our institution.

On arrival the patient was comatose, with preserved brain stem reflexes, left gaze deviation, and absent motor response to noxious stimuli. Continuous electroencephalographic monitoring showed independent multifocal sharp waves but no electrographic seizures. He was treated with 7 sessions of plasma exchange and 10 days of high-dose intravenous methylprednisolone without significant clinical improvement. Repeated magnetic resonance imaging showed little change in the multifocal supratentorial white matter lesions but revealed symmetric areas of restricted diffusion in the globus pallidi and caudate nuclei, consistent with anoxic brain injury (Figure). Testing of cerebrospinal fluid (CSF) revealed increased protein (0.244 g/dL; to convert to grams per liter, multiply by 10.0), 1 total nucleated cell, 157 erythrocytes, elevated IgG synthesis rate (33 mg/d), elevated IgG index (0.89), and no oligoclonal bands. Two months after onset of symptoms, he remained in a severely disabled state.

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**Figure.** Radiographic images of severe H1N1 infection. A, Chest computed tomography in H1N1 influenza and acute respiratory distress syndrome shows extensive opacities. Brain magnetic resonance imaging reveals subcortical hyperintensities (B and C), with hemorrhages on gradient echo sequence (D). E and F, Diffusion-weighted imaging and apparent diffusion coefficient images show restricted diffusion in the basal ganglia consistent with hypoxic brain injury.
We can expect hypoxic brain injury in comatose survivors of treatment for major lung injury resulting in poor gas exchange. However, the magnitude of this potential problem is unknown. There is debate regarding permissive hypoxemia and optimal oxygen administration in patients with ARDS secondary to H1N1 influenza. This is based on findings that interventions in ARDS that improve hypoxemia (eg, nitric oxide, high-frequency oscillatory ventilation, prone ventilation) have not translated to survival benefit\textsuperscript{12-14} and that most patients with ARDS die of multisystem organ failure rather than hypoxemia.\textsuperscript{15} Our case may illustrate the potential for devastating neurologic injury resulting from a prolonged period of hypoxemia. Although it is entirely unknown whether more aggressive oxygen administration may improve oxygen delivery in patients with massive intrapulmonary shunts, permissive hypoxemia in H1N1 influenza associated with ARDS may not be permitted by the brain.

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REFERENCES


Announcement

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