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PRACTICAL PEARL

Acute Hemorrhagic Leukoencephalopathy Associated with Influenza A (H1N1) Virus

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Abstract
Background Acute hemorrhagic leukoencephalopathy (AHLE) is a rare condition associated with H1N1. In this condition the infection triggers an autoimmune response which results in perivascular demyelination and hemorrhage in the brain parenchyma.
Methods We report a case of a patient who developed brain edema and herniation as a result of AHLE.
Results A 27-year-old presented to a community hospital with fever, dyspnea, and malaise and was found to have H1N1-associated pneumonia. Despite treatment he progressed to acute respiratory distress syndrome and required mechanical ventilation. Due to failure on conventional ventilation, he was transferred to our hospital and was placed on high-frequency oscillatory ventilation. He was showing improvement until day 6 of transfer to our hospital when he was suddenly noted to have a rise in his blood pressure followed by hypotension. The following morning he was noted to have non-reactive pupils and was declared brain dead. Autopsy of the brain was consistent with AHLE.
Conclusions This case emphasizes the importance of awareness of this disease. The non-specific signs and symptoms, and the use of sedatives, make diagnosis challenging in the early stages of this disease. If suspected early, appropriate imaging can aid in the diagnosis. Treatment with immunosuppressive agents and plasmapheresis may prevent rapid progression and death. This is the first published case of AHLE in association with H1N1 that has been confirmed pathologically.

Keywords Influenza · H1N1 · Acute hemorrhagic leukoencephalopathy

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Introduction

Many neurological complications have been reported in association with the novel influenza A (H1N1) virus since the 2009 pandemic. The reported incidence of neurological complications in United States was around 4 % and was seen more commonly in the pediatric population and patients of Asian descent [1]. The most common complications reported were seizures and encephalopathy. The majority had complete neurological recovery, and very few deaths were reported [1–3]. However, there were more severe cases reported in Japan where patients presented with mild neurological symptoms and had rapid progression to brain edema and coma [4]. A form of neurological complication called acute necrotizing encephalopathy was also mostly reported in Asia and was associated with a high mortality [5]. Other rare conditions reported worldwide in association with H1N1 are the Guillain–Barré syndrome, acute disseminating encephalomyelitis (ADEM), posterior

reversible encephalopathy syndrome, and ischemic stroke [3, 6–8].

We report an unusual and frequently fatal neurological condition associated with H1N1 called acute hemorrhagic leukoencephalopathy (AHLE). AHLE is commonly considered a fulminant form of acute disseminated encephalomyelitis, a condition associated with diffuse perivascular demyelination. AHLE is also called Weston Hurst Syndrome because it was first described in 1941 by Dr. Weston Hurst [9]. Two cases of suspected AHLE were reported previously in the literature, but our case is the first in which the diagnosis was confirmed pathologically [10, 11]. The high morbidity and mortality associated with this disease necessitates physicians to be aware of this entity and consider it in their differential diagnosis.

Clinical Case

A twenty-seven year-old obese African American male initially presented to a community hospital with dyspnea, fever, and malaise for 2 days. He was hypoxemic (oxygen saturation 85 %) on admission and chest X-ray showed bilateral infiltrates. He was admitted for treatment of community-acquired pneumonia and was started on vancomycin, piperacillin–tazobactam, and levofloxacin. The next day he was also started on oseltamivir when H1N1 was detected from nasopharyngeal specimens by polymerase chain reaction (PCR). Despite treatment, his pneumonia progressed and resulted in worsening oxygenation requiring intubation on day 3. Due to difficulty with oxygenation using conventional ventilation, he was transferred to our academic center the same day for management with alternate modes of ventilation.

On arrival to our facility, he had a blood pressure of 140/78 mmHg, heart rate of 120 bpm, and a temperature of 102 °F. He was deeply sedated and paralyzed. On physical examination his pupils were equal and reactive to light. He had coarse breath sounds. An arterial blood gas obtained on fractional inspired oxygen (FiO_2) 100 % and positive end-expiratory pressure of 15 cmH_2O showed a PaO_2 of 66 (83–108 mmHg). Admission labs revealed a white blood count of 6.8×10^3 (4.0–10.0 cells/μL), hemoglobin 13 (13.5–17.5 g/dL), platelets 114×10^3 (150–399 cells/μL), creatinine 1.9 (0.75–1.20 mg/dL), AST 154 (3–44 international units per L), and ALT 50 (0–40 international U/L). Peripheral smear was negative for schistocytes. He was immediately placed on high-frequency oscillatory ventilation (HFOV). Paralysis was continued with cisatracurium, and he was sedated with propofol and lorazepam. The patient showed improvement in laboratory parameters and by day three of admission to our hospital the platelets, creatinine, and transaminases were within the normal reference range. The patient also showed continuous improvement on HFOV and by the sixth day was maintaining adequate oxygenation with mean airway pressure of 24 cmH_2O and FiO_2 of 40 %. The same day he was suddenly noted to have a transient elevation in systolic blood pressure (240 mmHg), followed by severe hypotension requiring multiple vasopressors.

The following morning the patient was noted to have non-reactive mid-sized pupils (5 mm). Evaluation after discontinuation of sedation and paralytics showed an absence of any neurological function. The patient remained on multiple pressors. Therefore, it was felt that he was unstable to be transported for brain imaging. Electroencephalography and somatosensory evoked potential performed after discontinuation of sedation for 48 h showed no brain activity. He was subsequently pronounced brain dead and ventilatory support was discontinued. Post-mortem examination of the brain revealed diffuse cerebral edema, multifocal punctate foci of hemorrhage and demyelination in the cerebral white matter and brainstem (Fig. 1a (pons)), a large hemorrhage in the right temporo-occipital lobe ($8 \times 4 \times 3.5$ cm^3) (Fig. 1b), with herniation of the right uncus (Fig. 1c). Histological examination revealed scattered small blood vessels (consistent with venules) with fibrinoid necrosis (predominantly neutrophils), petechial hemorrhages (Fig. 1d), and foci of perivascular demyelination (Fig. 1e) mostly in the white matter. No subcortical U fiber involvement was noted. These findings are consistent with the diagnosis of AHLE.

Discussion

We describe an adult who developed AHLE from H1N1 infection and had a fatal outcome despite clinical improvement of his pulmonary condition. AHLE has been associated with numerous infections such as influenza A, herpes simplex virus, varicella–zoster virus, Epstein–Barr virus, and human herpesvirus-6 [12]. A genetic predisposition is also suggested based on an association of particular HLA genes with the disease [13]. AHLE is considered an autoimmune condition in which an inflammatory response is triggered by these or other, unknown agents. The inflammatory response leads to vascular injury and perivascular demyelination, which presents as hemorrhage and necrosis surrounding small parenchymal vessels. These changes often lead to brain edema and herniation [13].

The early clinical signs and symptoms are fever, headache, neck stiffness, and seizures. These symptoms are very non-specific, being similar to other infectious and toxic insults to the brain [14]. Also, the use of sedation and neuromuscular blockade makes the recognition of these symptoms difficult. The diagnosis of this entity is also

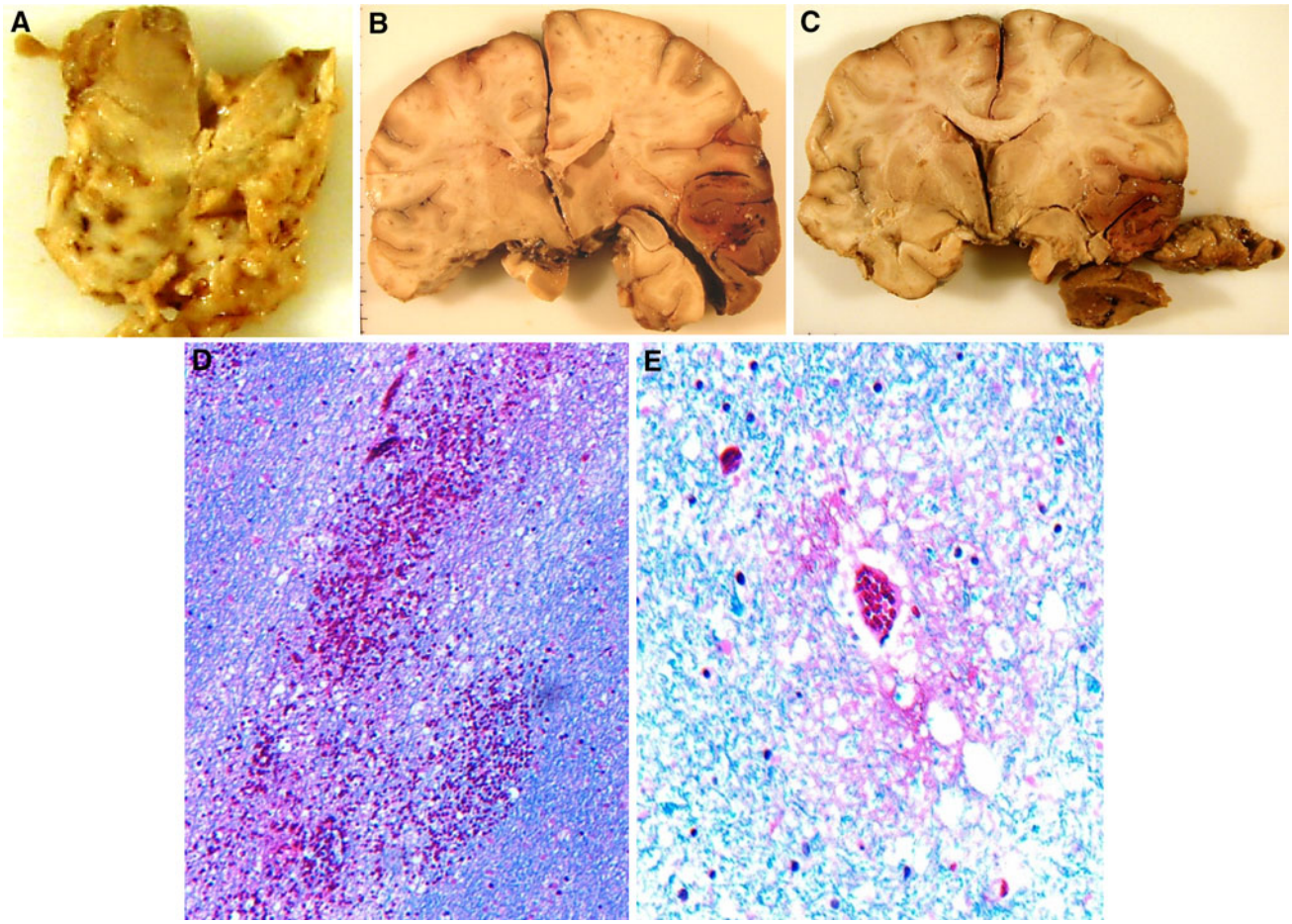

Fig. 1 **a** Pons with petechiae (*left* basis pontis) and necrosis (*right* basis pontis and tegmentum). **b** Cerebral hemispheres, coronal section demonstrates flattened gyri and obscured sulci (brain edema), foci of petechiae and pallor, gray/white matter blurring, and hemorrhage/necrosis in the right temporal lobe. **c** Cerebral hemispheres, coronal section demonstrate disruption and necrosis of the right uncus consistent with herniation. **d** Hematoxylin–eosin staining shows area of acute hemorrhage in the white matter (petechial hemorrhage). **e** Luxol fast blue stain (with hematoxylin–eosin counter stain) shows perivascular demyelination

challenging. The cerebrospinal fluid analysis typically shows increased levels of protein but PCR or cultures for viral organisms are often negative [14]. Computed tomography showing brain hypodensities, or magnetic resonance imaging demonstrating hyperintense lesions on T2/FLAIR images as well as sequences demonstrating hemorrhage can be confused with conditions such as vasculitis and thrombotic thrombocytopenic purpura; but if clinically suspected, the early use of imaging can help detect the development of cerebral edema. In the appropriate clinical setting, this can add support to the diagnosis [15]. Ultimately, the diagnosis can only be confirmed pathologically. On autopsy, the gross findings are diffuse cerebral edema, focal necrosis of both gray and white matter, and petechial hemorrhages. The histopathological findings include extensive perivascular demyelination, fibrinoid vascular necrosis, and hemorrhage [14]. The success rate of different treatment options is unknown due to the few reported cases of this entity. If signs of cerebral edema are detected early, craniectomy or ventriculostomy could be life saving. Treatment with high-dose intravenous steroids, intravenous immunoglobulin, and cyclophosphamide have been used with varying results [16]. Plasmapheresis has been used in a few cases with successful outcomes [17].

Our case demonstrates the dismal outcome often associated with AHLE. The failure to diagnose the early signs of neurological involvement and progression due to high doses of sedation and paralysis unfortunately resulted in cerebral herniation and brain death. The two previously published cases of AHLE suspected this diagnosis based on the neuroimaging findings. Our case is the first in which the diagnosis of AHLE is confirmed pathologically.

In conclusion, AHLE is a rare neurologic manifestation of H1N1, and is associated with high morbidity and mortality. Awareness of this condition among physicians will help in early diagnosis and consideration of immunosuppressive therapy or plasmapheresis, which may prevent rapid decline and death.

Conflict of interest Niranjan Jeganathan, Matthew Fox, Julie Schneider, David Gurka, and Thomas Bleck declare that they have no conflict of interest.

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