CASE REPORT

A 20 year old female with type I diabetes mellitus presented in March 2011 with one week of malaise and fatigue. On initial exam, her blood pressure was 106/66 mmHg, pulse 114 beats per minute, temperature 101.9 °F, respirations 51 per minute, and pulse oximeter oxygen saturation measured 92%. Arterial blood gas pO2 was 68 mmHg (75-90 mmHg), pCO2 was 24 mmHg (35-45 mmHg), glucose 193 mg/dL (70-99 mg/dL), and creatinine 2.82 mg/dL (0.6-1 mg/dL). Chest X-ray showed bilateral patchy infiltrates. Real time PCR sampled from pharyngeal mucosa tested positive for H1N1 influenza.

She was admitted to the ICU and given IV fluids, piperacillin/tazobactam, azithromycin and oseltamivir. For respiratory distress, she was intubated, sedated with midazolam and fentanyl, and required an oscillator for seven days with traditional ventilation for an additional ten days. Her creatinine normalized. Blood cultures showed no growth. She developed a hospital-acquired fungal UTI treated with fluconazole but remained normotensive and hemodynamically stable throughout the hospitalization.

On hospital day 17, she was extubated. Once she was able to verbalize, she stated that she could not see. Initial neurologic examination revealed hand

motion vision, mild agitation and irritability, normal pupil reaction, a normal external and fundus examination, and was otherwise non-focal. She was noted to have oral herpes labilis and was started on intravenous acyclovir.

Brain MRI performed on hospital day 18 showed symmetric T2 signal hyperintensities with associated restricted diffusion bilaterally involving the thalami, posterior parietal, and occipital cortex (Figure 1a). These areas of restricted diffusion were dark on ADC mapping. There was mild patchy enhancement in regions of signal abnormality and no hemorrhage on gradient echo, nor evidence of venous thrombosis on T1-weighted imaging.

EEG showed periodic lateralizing epileptiform discharges from the right hemisphere. CSF showed no white or red blood cells, glucose was 78 mg/dL (40-70 mg/dL), and protein was 110 mg/dL (12-60 mg/dL). CSF HSV PCR, cryptococcal screen, gram stain, and bacterial culture were all negative. Acyclovir was discontinued. She became drowsy and agitated, and on hospital day 20 she required re-intubation for worsening respiratory function. Brain MRI repeated on day 28 showed less restricted diffusion but more prominent FLAIR abnormalities in the occipital cortex (Figure 1b).

She was again extubated on day 27, and on the following day, she was alert. Examination revealed best corrected visual acuity of J5 in both eyes with normal pupil function and fundus exam, without disc edema. She had no further

respiratory decompensation, but maintained a persistently flat affect. On hospital day 36, her neuro-psychologic examination showed moderately reduced general cognitive function. Simple auditory attention was preserved. However, on tasks requiring visual attention and speed, her performance was moderately to severely impaired. Abstract visual construction was also decreased.

Discussion

There are three types of Influenza virus: A,B and C. Influenza A is an enveloped RNA virus of multiple strains, and is named for which subtypes of hemagglutinin and neurominidase antigen are on its surface. These subtypes include H1N1, H1N2, H3N1, H3N2, and H2N3 (1). Episodically, influenza A H1N1 strains have caused human disease outbreaks. For example, the 1918 Spanish flu epidemic implicated in encephalitis lethargica was triggered by an H1N1 strain (1). In 2009, a novel genetically distinct strain of H1N1 influenza A became pandemic. This 2009 strain clinically manifested mainly with respiratory problems, especially in young people.

Neurologic sequelae of the 2009 H1N1 strain are mainly described in children and result in seizures and encephalopathy (2,3). Focal neurologic problems caused from H1N1 are less commonly reported, and include hemisensory loss (4). Exacerbations of neurologic conditions like myasthenia gravis or the concomitant development of new neurologic conditions like stroke may also

occur (5). CSF serology and cell counts in H1N1 patients are often normal (6). Indeed, virion RNA is rarely found with any viral associated encephalopathy (7,8,9). In one case report by Sandoval, H1N1 was isolated from the CSF, but this is the exception (10). The elevated protein and normal WBC in our patient are consistent with the CSF profile from other H1N1 patients (6,11).

Radiographic CNS abnormalities from Influenza A encephalitis may occur due to several mechanisms. Hypoxic or anoxic damage as a result of the respiratory dysfunction could potentially cause CNS ischemia or infarction (11). Alternatively, CNS damage could be due to direct or parainfectious processes related to the H1N1 virus. Mainly described in children, these parainfectious hyperimmune syndromes range from acute demyelinating encephalomyelitis (ADEM), to more hyperacute states such as acute hemorrhagic leukoencephalopathy (4). Probably related, acute necrotizing encephalopathy (ANE) is a syndrome mainly described in East Asian children, resulting in seizures, fever, and coma, and appearing radiographically as bilaterally symmetric lesions of the thalamus, white matter and brainstem (7). Bilateral thalamic lesions have occurred in Influenza A types other than the pandemic 2009 strain (7,12).

CNS imaging characteristics associated with the pandemic 2009 H1N1 strain have been reported rarely, usually in children (4,11,13,14). Not all neurologic symptoms occurring in H1N1 patients produce MRI abnormalities (5). In one

series of 8 children with H1N1 encephalopathy, only 3 showed radiographic abnormalities, all as bilateral high intensity T2-weighted signals in the thalami and white matter (15). Lyon presented one of the first radiologic reports on H1N1 encephalopathy, a 12 year old girl with seizures and lethargy who had bilateral thalamus and brainstem T2 hyperintense lesions with restricted diffusion on DWI (16). Haktanir also reported a 3 year old girl with bilateral thalamic lesions which showed restricted diffusion (14). ANE has been reported in pandemic H1N1, as it has for other viruses (17). An autopsy specimen of a 7 year old boy who died of cerebral edema complicating H1N1 encephalopathy showed vasculopathy and acute necrotizing bilateral symmetrical lesions of the white matter, basal ganglia, thalami and brainstem, consistent with ANE (18).

Clinical-radiologic focal correlations of MRI-associated H1N1 abnormalities are rare. Godoth reported a patient with asymmetric right hemispheric T2 hyperintensities who developed a catatonic state (9). Occipital lobe involvement is specifically mentioned in one report involving a 2 year old girl who presented with seizures, though there was no description of her visual function (10). To our knowledge, the only cortical visual symptoms associated with H1N1 previously reported were in a 2 year old girl who presented with seizures, encephalopathy, drowsiness and rigidity and after 20 days was noted to have bilateral visual field defects and abnormal VEPs (19). Our patient appears to be the first reported adult with H1N1 who had cortical visual loss as a prominent and focal presenting symptom of H1N1 encephalopathy.

Although the radiologic area of involvement is similar to that seen with posterior reversible encephalopathy syndrome (PRES), restricted diffusion on MRI effectively rules out this entity. Hypoxia could result in restricted diffusion, but would also produce radiological evidence of cortical laminar necrosis, which was not found on the brain MRI of our patient. Also, the vascular territories involved are not representative of hypotension or arterial thromboembolism, and there was no evidence of venous thrombosis. Thus, the pattern of symmetrical cortical and nuclear T2 hyperintensities with restricted diffusion in our patient most likely represents a parainfectious encephalopathy.

There is no data to suggest that H1N1 strain of seasonal flu results disproportionately in neurologic sequelae compared to other strains of influenza A (3). However, the descriptions of H1N1 2009 seasonal flu have produced a valuable source of radiographic and clinical information. Our patient adds to this data, particularly to highlight the unique variety of presenting symptoms, including vision loss. Early recognition of this disease process may lead to a better understanding of its pathogenesis and treatment.

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Figure Legend

Figure 1. DWI and FLAIR MRI from a patient with H1N1 encephalopathy.

Axial diffusion-weighted images show restricted diffusion most prominent in the thalami, parietal and occipital cortex (a). Axial FLAIR sequences taken 10 days later show increased signal in the occipital lobes (b).