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LETTER TO THE EDITORS

Pandemic influenza A (H1N1) 2009-associated hemolytic uremic syndrome

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Sirs,

Influenza A virus-associated hemolytic uremic syndrome (HUS) has been very rarely recognized in children and only five patients have been reported [1]. Pandemic influenza A (H1N1) 2009 has been associated with nonpulmonary acute organ dysfunction of multiple organs; however, H1N1-associated HUS has not been reported [2]. Since both H1N1 and *Streptococcus pneumoniae* share neuraminidase activity and *S. pneumoniae* has been related to HUS, H1N1 could induce HUS via the same pathway [3]. It has also been recognized that neuraminidase of influenza virus may cause erythrocyte fusion and hemolysis [4].

We describe a case of a child with pandemic influenza A (H1N1) 2009-associated HUS. In November 2009, a previously healthy 7½-year-old Caucasian boy, presented to us with a 3-day history of fever, sore throat, malaise, cough, and three episodes of blood-tinged vomiting. Two days later he developed oliguria. On admission, physical examination demonstrated body temperature 38.5°C, pulse rate 120/min, respiratory rate 30/min, blood pressure 110/70 mmHg, and mild periorbital edema. A respiratory specimen for H1N1 was taken due to the severe malaise of the child associated with respiratory tract symptoms. The initial laboratory data revealed anemia [hemoglobin (Hb) 7.5 g/dl], with marked anisocytosis and schitocytosis, thrombocytopenia (platelets 30,000/μl), severe renal failure with blood urea nitrogen (BUN) of 223 mg/dl, creatinine of 3.4 mg/dl, and metabolic acidosis, findings consistent with hemolytic uremic syndrome (HUS). Fibrinogen levels, and prothrombin and partial thromboplastin times were normal. Direct and indirect Coombs' tests were negative and chest X-ray revealed normal findings. During the first few hours after admission Hb declined to 6.2 g/dl and platelets to 12,000/μl. Packed red cells and platelets were transfused and a peritoneal (Tenkoff) catheter was inserted for initiation of peritoneal dialysis. Plasma therapy was initiated because of the atypical presentation of HUS. On day 3, polymerase chain reaction demonstrated H1N1 in respiratory specimens and oseltamivir was started in doses adjusted for renal failure. Immune investigation, including complement factors C3 and MCP (CD46), as well as von Willebrand factor-cleaving protease (ADAMTS-13), revealed normal findings. On day 5 the child continued to be febrile and suffered respiratory distress with pCO_2 of 45, pO_2 of 59, respiratory rate 40 breaths per minute, and oxygen saturation of 88% while he was breathing 4 l by nasal cannula. His chest X-ray showed diffuse bilateral infusions, findings consistent with viral pneumonitis. The respiratory distress worsened and the child was transferred to the Intensive Care Unit (ICU) where he received mechanical ventilation and treatment with vancomycin and ceftriaxone. Because of hypertension he also received nifedipine and captopril treatment. His course was further complicated by generalized convulsions, barely controlled by valproic sodium and phenytoin. Magnetic resonance imaging (MRI) revealed multiple lesions in the white matter that were hyperintense on T2-weighted images, situated in the temporo-parieto-occipital regions and fewer in

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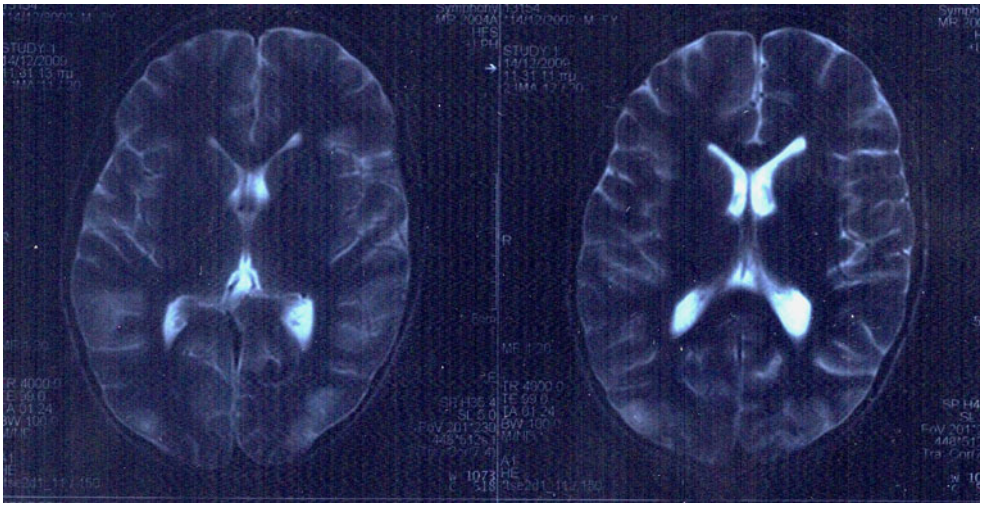

Fig. 1 Magnetic resonance imaging (T2-weighted) revealed multiple lesions in the white matter, situated in the temporo-parieto-occipital regions and fewer in the frontal region, findings fulfilling the criteria for posterior reversible encephalopathy syndrome

the frontal region, findings fulfilling the criteria for posterior reversible encephalopathy syndrome due to HUS central nervous system involvement (Fig. 1). On day 14 his renal function started to improve. The child was discharged on day 27, with normal renal function, clear chest X-ray and improvement of MRI findings on valproic sodium and phenytoin. Five months later a further improvement of the MRI findings was noticed and he received tapering doses of valproic sodium and phenytoin. Taking into account our patient's complicated H1N1 infection course, as well as the atypical presentation of HUS, we decided during his follow-up period to re-evaluate his complement profile, using the Wielisa kit COMPL 300 (Euro-Diagnostica, Malmo, Sweden), which is an enzyme immunoassay for simultaneous qualitative determination of functional classical, lectin, and alternative complement pathways. The procedure was performed according to the manufacturer's instructions and revealed normal findings excluding factor H, I or B dysfunction.

To our knowledge, this is the first reported case of H1N1-associated HUS. Whether H1N1 infection acts simply as a trigger for HUS or there is a specific interaction, rather like in cases of *Streptococcus pneumonia*, via neuraminidase, is not clear. Unfortunately, we did not perform in our patient the T-antigen test on red blood cells on admission, as he had no clinical or radiographic findings of pneumonia.

The normal immune, including the complement, profile of the child leads us to believe that this was an H1N1-induced HUS and not an HUS due to a defect in the alternative complement pathway triggered by the viral infection [5].

The child required mechanical ventilation and intensive care, although he had no underlying medical conditions known to be risk factors for severe influenza [6]. Recent data have shown that oseltamivir is well absorbed enterically in critically ill patients and the adjustment of the dosage in patients with renal dysfunction requiring continuous renal replacement therapy is appropriate [7]. However, early initiation of a neuraminidase inhibitor did not prevent development of HUS or the respiratory distress in our case. Despite the critical condition of our patient, the course of the disease, even complicated by HUS with central nervous system involvement, was favorable.

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