Complex Febrile Seizures Followed by Complete Recovery in an Infant with High-Titer 2009 Pandemic Influenza A (H1N1) Virus Infection[▽]

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We describe a 2009 H1N1 virus infection with a high viral load in a previously healthy infant who presented with complex febrile seizures and improved on oseltamivir without neurologic sequelae. Febrile seizures may be a complication in young children experiencing infection with high viral loads of 2009 H1N1 influenza virus.

CASE REPORT

In March of 2010, a previously healthy 8-month-old male presented to the emergency room (ER) with 2 days of upper respiratory symptoms, including cough, congestion, fever to 102.5°F, and seizure activity. Three seizures occurred prior to presentation to the ER, each episode lasting up to 2 h. These events were accompanied by perioral cyanosis and emesis. The family history was significant for complex febrile seizures in the patient’s mother and sister, who had no history of epilepsy. Upon arrival in the ER, the patient continued to have seizure-like activity described as “glassy-looking eyes” and limpness with concurrent myoclonal jerking of the head. His vital signs at presentation were as follows: rectal temperature, 103.3°F; heart rate, 132 beats per minute; respiratory rate, 40 breaths per minute. His level of consciousness was 9 on the Glasgow coma scale. His venous blood gas pH was 6.9, with a partial O₂ pressure (pO₂) of 77 mm Hg. Due to decreased breath sounds bilaterally, increased work of breathing, and diminished neurologic status, the patient was placed on mechanical ventilation and admitted to the intensive care unit (ICU). The results of noncontrasted computed tomography (CT) of the head, electroencephalogram (EEG), complete blood count (CBC), and a basic metabolic panel, including aspartate transaminase (AST) and alanine aminotransferase (ALT), were within normal limits, with the exception of a blood glucose level of 185 mg/dl. Urine, cerebrospinal fluid (CSF), blood, and respiratory specimens were collected for detection of potential pathogens. A nasopharyngeal swab (NPS) specimen revealed a positive PCR result for influenza A virus, which was further subtyped as 2009 H1N1. CSF studies were remarkable for pleocytosis, with 46 total cells in the chamber and a lymphocyte predominance and CSF glucose of 126 mg/dl; no red cells were observed. CSF protein was within normal limits at 30 mg/dl. A chest X-ray revealed a vague opacity suggestive of atelectasis, contusion, or infiltrate in the central left lung.

The patient was started simultaneously on 24 mg oseltamivir every 12 h for the positive NPS and 500 mg ceftriaxone every

12 h for the chest X-ray findings. Temperatures up to 104°F rectally were recorded overnight in the absence of overt seizure activity. The following morning, the venous blood gas values normalized, and the patient was extubated and weaned from O₂ supplementation. Ceftriaxone therapy was changed to an oral cephalosporin. Bacterial cultures of urine, blood, and CSF were all negative. The patient was treated with 24 mg oseltamivir every 12 h for 5 days, and family members received oseltamivir for influenza prophylaxis. On day 3 of admission, the patient continued to improve, with good oral intake and without further seizure activity, and was discharged home the following day with diazepam for future possible complex febrile seizures.

Viral culture using rhesus monkey kidney cells, direct fluorescent antibody (DFA) assay (Light Diagnostics Respiratory Virus Panel I DFA; Millipore, Billerica, MA), rapid immunodiagnostic assay (BinaxNow Influenza A&B; Inverness Medical Professional Diagnostics, Princeton, NJ), and a multiplex PCR respiratory virus panel (ResPlex II, Qiagen, Valencia, CA) was performed on an NPS specimen. Each was positive for influenza A virus, which was subtyped as 2009 H1N1 using the proFlu-ST multiplex real-time PCR assay (Prodesse, Madison, WI). No influenza virus was detected by reverse transcriptase PCR (RT-PCR) in a CSF specimen collected at the time of admission.

Influenza A virus titers in the NPS specimen were determined by both quantitative RT-PCR and culture. For viral load determination by RT-PCR, a quantification standard curve was achieved using four standards ranging from 1 to 1,000 50% tissue culture infective doses (TCID₅₀) (OptiQuant 2009 H1N1 quantification panel; AcroMetrix, Benicia, CA). Serial 10-fold dilutions of the original NPS specimen were tested in triplicate, and viral loads were extrapolated from the standard curve based on the average threshold cycle (C_T) values obtained. The calculated load was 1.3×10^6 TCID₅₀ per ml of sample. For quantitative viral culture, serial 10-fold dilutions of the NPS specimen in viral transport medium were prepared and inoculated into quintuplicate RMIX Too shell vials (Diagnostic Hybrids Inc., Athens, OH), followed by immunofluorescence staining at 48 h of incubation using a fluorescein isothiocyanate (FITC)-conjugated influenza A-specific monoclonal antibody (Millipore, Billerica, MA). Viral titers were determined by enumeration of fluorescent cells, and the infec-

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FIG. 1. (A) Direct immunofluorescence staining of 2009 H1N1 influenza A virus-infected cells in a nasopharyngeal swab specimen. (B, C, and D) An average of 43.7% of cells were positive for influenza A antigen. Pleomorphic staining patterns were recognized.

tious titer was 6.5×10^6 fluorescent focus units per ml. The viral burden was further characterized by assessing the proportion of influenza virus-positive cells in the DFA assay. An average of 43.7% of respiratory cells collected in the NP specimen were positive for influenza virus antigen among 214 cells examined across 10 fields viewed at $\times 20$ (Fig. 1).

Influenza A virus is known to be an important cause of complex febrile seizures in the pediatric population. There are, however, limited laboratory and clinical data characterizing neurologic complications such as seizures associated with pandemic 2009 H1N1 influenza virus infection of infants (6, 9–11, 13, 18, 23). Available literature addressing the neurologic complications of influenza A virus infection emphasizes serious neurological sequelae such as acute encephalopathy with biphasic seizures and late reduced diffusion, acute necrotizing encephalitis, Reye's syndrome, acute hemorrhagic encephalopathy, and transverse myelitis (3, 8, 14, 16, 19, 20). More recently, reports have appeared describing pandemic H1N1-associated neurologic complications followed by complete recovery. These include a first-time seizure in a 17-year-old male with encephalitis (7), 9 of 826 hospitalized patients ages 15 to 57 years old with first-onset seizure (21), and a case series of four patients ages 7 to 17 years old with influenza-like illness with seizures or altered mental status without neurologic sequelae (2). However, viral loads were not quantified for these patients. Peak viral titers occur early during the symptomatic period of 2009 pandemic H1N1 influenza virus infection and decrease gradually thereafter, with younger patients harboring higher viral loads (5, 17, 22). While virus was not isolated in the CSF of our patient, the high viral load in our patient probably generated a high indirect immunologic response through interleukins and cytokines rather than causing direct viral damage to the CNS, as has been shown in recent animal studies (12).

It has been postulated that younger age may predispose to a higher propensity for more serious neurological sequelae, and long-term neurological damage may result from hypercytokinemia and immune system dysregulation due to infection (1, 3, 4, 24). Perhaps increased influenza A virus loads borne by younger individuals provoke especially exuberant or aberrant immune responses that lead to CNS injury. The neurologic dysfunction may be transient, however, as observed for our patient and other pediatric subjects who experienced 2009 H1N1-associated neurologic disease (2). We suggest that the seizures suffered by our patient were associated with the high viral load, probably through indirect immunologic mechanisms, though direct viral damage to the CNS cannot be excluded. Further studies are necessary to fully elucidate the relationship of viral loads and various neurologic complications of H1N1 virus infection. Moreover, we agree with previous studies that rapid detection of influenza A virus should be considered in patients who present with complex febrile seizures (15). It is also important to recognize that high viral loads are likely to promote more efficient influenza virus transmission to susceptible individuals, and actions to prevent the spread of possible 2009 pandemic H1N1 influenza virus infection are appropriate while evaluating the etiology of febrile seizures.

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