Case Report

Acute encephalopathy associated with influenza infection: Case report and review of the literature

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Abstract

Influenza has been associated with neurological complications. We describe the case of a toddler who presented with symptoms and signs of acute encephalopathy and hydrocephalus. Neuroimaging demonstrated cerebral edema and multifocal diffusion restriction in the thalamus and splenium of the corpus callosum. Influenza A was detected from the nasopharyngeal aspirate. The final diagnosis was acute influenza-associated encephalopathy. Despite treatment with a neuraminidase inhibitor and intravenous immune globulin, the toddler developed neurological sequelae. This case highlights a rare but severe complication of influenza in young children and the importance of influenza vaccination.

Keywords: *Encephalitis; Encephalopathy; Influenza.*

The condition of influenza-associated encephalopathy/encephalitis (IAE) is rare in Canada but has devastating neurological morbidity in almost half of the affected children. In this case, we describe the presentation of a toddler with IAE leading to severe brain edema and unresponsiveness. We then discuss the epidemiology, clinical, laboratory and radiological findings, treatment and prognosis of IAE.

CASE

An 18-month-old girl who was previously healthy presented to the emergency department at a peripheral hospital with a 1-day history of excessive sleepiness and vomiting. She had a preceding illness with 4 days of maculopapular rash, followed by 3 days of fever. She was fully immunized but had not received the influenza vaccine. Her 7-year-old brother and mother had cough, vomiting and fever 1 week prior to her presentation. They recovered completely. On examination, she was somnolent and had no fever, neck rigidity, seizure, lymphadenopathy, hepatosplenomegaly or rash.

The patient was admitted and over the next 24 hours she became unarousable and comatose with fixed pupil reactions bilaterally. Therefore, she was intubated and a computed tomography scan of the brain was performed urgently, showing severe acute hydrocephalus. Intravenous cefotaxime, vancomycin and acyclovir were initiated empirically for bacterial meningitis and herpes simplex virus encephalitis. Lumbar puncture was deferred until she was stabilized. The child was transferred to our centre for intensive care and management of acute hydrocephalus. An external ventricular device was inserted. Cerebrospinal fluid (CSF) demonstrated normal protein and glucose, negative gram stain and no white blood cells or red blood cells. CSF bacterial culture and polymerase chain reaction testing for herpes simplex virus and enterovirus were negative.

A nasopharyngeal aspirate sent from the peripheral hospital was positive for influenza A. A 5-day course of oseltamivir was initiated on day 2 after the onset of encephalopathy. Magnetic resonance imaging of the brain showed severe hydrocephalus, generalized cortical edema and a multifocal diffusion

restriction pattern in the thalami and splenium of the corpus callosum. The child's final diagnosis was acute influenza-associated encephalopathy.

On the 10th day of admission to the paediatric intensive care unit, the child was extubated and the external ventricular device removed. A repeat magnetic resonance imaging showed improvement of the hydrocephalus with interval evolution of the diffusion restriction pattern and ischemic changes. The neurology team elected to treat the child with intravenous immunoglobulin (IVIG). She was subsequently transferred to the paediatric medical unit for 6 weeks. Serial examinations showed intermittent vertical nystagmus, left-eye gaze, the inability to track objects, and hypertonia and hyperreflexia in the right lower leg. Visual evoked potentials revealed signs of cortical visual impairment. She was transferred to a rehabilitation centre for further care. On follow-up at 4 years of age (30 months after discharge), she continued to have visual impairment, as well as speech and gross motor delays. She had bilateral lower limb hypertonia and used a walker to assist with mobilization.

DISCUSSION

IAE is a rare, serious complication of influenza infection in children. Influenza causes approximately 5% of acute encephalitis cases in children (1,2). Population incidence of influenza-related encephalitis in Sweden is 0.21 per million person-years (3). In the US, the rate of influenza-related neurological complications (including seizure and IAE) is approximately four per 100,000 child-years (4). The mean annual incidence of IAE among Australian children is 2.8 per 1,000,000 population (5). In a study from the Canadian Immunization Monitoring Program Active (IMPACT) over eight nonpandemic seasons from 2004 to 2013, encephalitis was documented in 1.9% (78/4,155) of children hospitalized for influenza (6). Other neurological manifestations of influenza include febrile and nonfebrile seizures, transverse myelitis, Guillain-Barré syndrome, Reye's syndrome and stroke (1,4).

Children under 5 years of age are more frequently affected by IAE (1,7). IAE begins with a prodrome of fever, cough and coryza along with, or followed by, depressed level of consciousness, seizures, focal motor deficits and/or ataxia (1–3,7,8). The interval between the onset of respiratory symptoms and encephalopathy/encephalitis ranges from 1 to 14 days (1). Influenza is rarely isolated from the CSF which may be due to low viral load or the clearance of the virus from the CSF prior to sampling (9). Alternatively, the lack of detectable virus in CSF may suggest that IAE is due to postinfectious inflammation rather than a direct effect of the virus (7). CSF cytology, protein and glucose levels are normal in most cases, but mild pleocytosis or elevated protein levels are occasionally observed. Serum

and CSF proinflammatory cytokines, such as interleukin-6, may be elevated (10).

This patient's neuroimaging findings were classic for IAE. Neuroimaging studies may show diffuse or focal swelling of cerebral parenchyma (11). Among the clinicoradiographic encephalopathy syndromes associated with influenza, acute necrotizing encephalopathy is considered the most severe, associated with severe neurological sequelae and mortality (12).

Treatment is primarily supportive and may involve intensive care. Antiviral therapy with oseltamivir or zanamivir is recommended especially in patients who present within 48 hours of the onset of symptoms to reduce viral replication (13). However, no conclusive evidence exists that oseltamivir alters the course of IAE (13). Given her serious presentation, our patient received antiviral medication and IVIG. The efficacy of corticosteroids, IVIG, plasmapheresis and hypothermia requires further study (14).

Neurologic sequelae affect up to 57% of patients with IAE and children under 2 years of age are at highest risk (1,7). In one study, 2 of 13 patients died within 48 hours of admission (both had acute necrotizing encephalitis) and 5 of 11 survivors had neurological sequelae at discharge, including gait instability, facial nerve palsy, seizures and developmental delay (8).

The National Advisory Committee on Immunization strongly recommends influenza vaccination for children 6 to 59 months of age due to their high risk of complications from influenza, yet vaccine uptake remains low (15).

CONCLUSION

Influenza should be considered in the differential diagnosis of children presenting with encephalitis and/or acute onset of neurological symptoms during the influenza season. This case also highlights the importance of annual influenza vaccination to prevent its complications.

Conflict of Interest

All authors declare no relevant conflict of interest.

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