*Case Reports*

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# Death in children with influenza A (H3N2) virus infection-associated encephalopathy: two case reports

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## Abstract

We herein report two cases involving children who died of influenza A (H3N2) virus infection-associated encephalopathy/encephalitis (IAE). Both children developed convulsions and impaired consciousness within a relatively short period and eventually died of brainstem failure. Patient 1 presented with high fever, vomiting, and diarrhea. Laboratory tests indicated persistently high lactate, alanine aminotransferase, and urea nitrogen concentrations in the blood as well as a high protein concentration in the cerebrospinal fluid. Patient 2 presented with persistent hyperthermia and progressive disturbance of consciousness, but the cerebrospinal fluid remained normal during the disease course. Both patients were actively given oseltamivir antiviral treatment after diagnosis of influenza virus infection. However, the disease progressed and invasive mechanical ventilation was performed. Both children's condition quickly progressed to IAE, and they eventually died. IAE is a rare complication of influenza virus infection with high mortality, and its pathogenesis remains unclear. The purpose of this report is to draw attention to the serious central nervous system complications of influenza infection and raise awareness of the fatal consequences of this disease among pediatricians.

## Keywords

Influenza, encephalopathy, encephalitis, children, mortality, case report

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## Introduction

Influenza virus is one of the major pathogens responsible for acute respiratory infections that are prone to seasonal epidemics.[1] Despite the self-limited nature of the illness, severely ill children presenting with high fever often progress rapidly to respiratory failure, heart failure, septic shock, acute renal failure, influenza virus infection-associated encephalopathy/encephalitis (IAE), and even death.[2] IAE is a rare complication of influenza with a high mortality rate, and survivors often develop neurological complications.[3] However, the pathogenesis of IAE remains unclear, and no specific treatment has been established. In the following case reports of two children with IAE, we describe the disease course from onset to death and review the relevant literature to improve our understanding of IAE and avoid misdiagnosis. We hope that our report will provide a basis for the clinical management and prognosis of this disease.

## Case reports

### *Patient 1*

A previously healthy 3-year 3-month-old girl weighing 12 kg who had not been vaccinated against influenza visited the emergency department of Hainan General Hospital with a history of hoarseness for 3 days, fever, diarrhea for half a day, and three episodes of convulsions. The child had developed cough and hoarseness on Day 1 and was treated with oral antibiotics and cough suppressants. She was first admitted to the outpatient clinic with fever, vomiting, and diarrhea on Day 4. However, she was then transferred to the pediatric intensive care unit (PICU) on the same day after receiving emergency treatment with diazepam, phenobarbital, cefmetazole, and methylprednisolone because of the development of a high fever and three generalized convulsions. The manifestations of the generalized convulsions included loss of consciousness, upward gaze, and rigidity of the extremities, and each convulsion lasted about 3 minutes. The child was drowsy between convulsion episodes. Each convulsive episode could be controlled by medication. On examination, her body temperature was 36.2°C, respiratory rate was 24 breaths/minute, heart rate was 132 beats/minute, and blood pressure (BP) was 92/62 mmHg. The child was put under continuous sedation with midazolam. While sedated, her bilateral pupils were equal in size and round with a blunted light reflex, meningeal irritation was negative, breathing was regular, respiratory sounds were coarse in both lungs, and sputum sounds could be heard. The remaining investigations showed no abnormalities. After admission to the PICU, a nasopharyngeal exudate was positive for H3N2. Routine blood tests showed a low serum potassium concentration; high blood lactate, alanine aminotransferase, and aspartate aminotransferase concentrations; normal copper cyanide and blood ammonia concentrations; and evidence of coagulation dysfunction. Blood gas analysis showed that the pH was 7.34, $PaCO_2$ was 29.7 mmHg, $PaO_2$ was 98.5 mmHg, $HCO_3^-$ was 16 mmol/L, and base excess was −7.8 mmol/L. Furthermore, the cerebrospinal fluid (CSF) was colorless and transparent, with a markedly high protein concentration (1.69 g/L; reference range, 0.15–0.45 g/L) and a normal glucose concentration, chloride concentration, and cell counts. Cellular and humoral immune function test results as well as cranial computed tomography examination findings were normal (Figure 1). The specific laboratory test results are listed in Table 1.

The child was diagnosed with severe influenza A and influenza virus-associated encephalopathy. She was given midazolam for continuous sedation, an ice blanket for continuous physical cooling, mannitol for

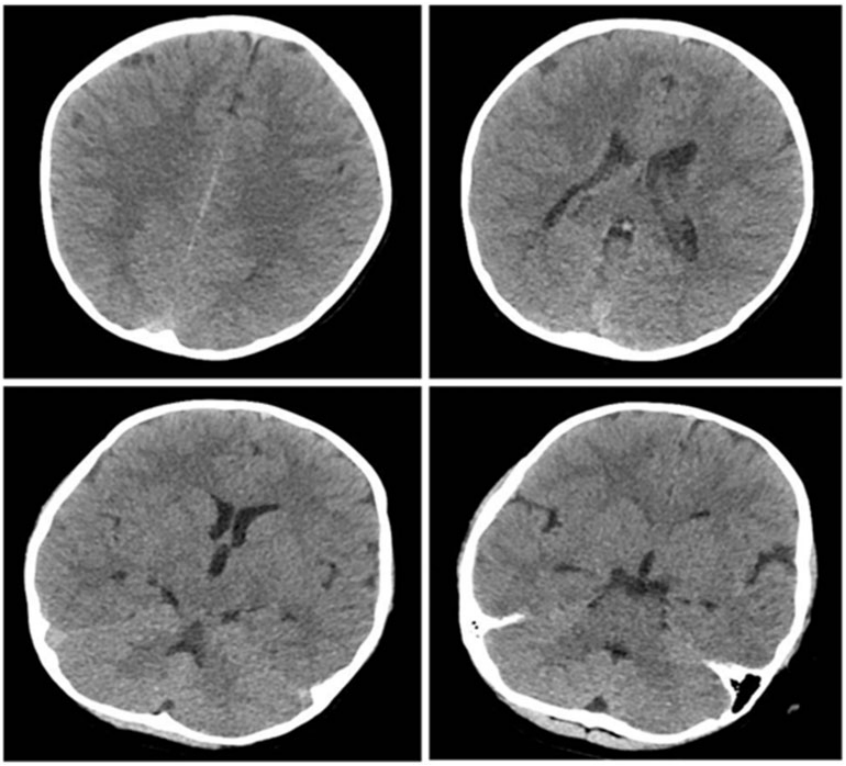

**Figure 1.** Cranial computed tomography findings in Patient 1.

dehydration to lower her intracranial pressure, oseltamivir for antiviral treatment (30 mg nasogastrically twice a day), ceftriaxone for anti-infection therapy (100 mg/kg per day), dexamethasone for anti-inflammation therapy, correction of hypoglycemia, prothrombin complex infusion for improvement of coagulation, and liver protection therapy. About 5 hours later, an echocardiographic examination of the child was normal but an elevated cardiac troponin T concentration was observed (0.257 μg/L), suggesting myocardial damage. The child subsequently received vitamin C and calcium dibutyryladenosine cyclophosphate through an intravenous drip. About 9 hours later, she exhibited a poor response to painful stimuli and shallow and irregular breathing. The child's Glasgow coma scale score was 4 (best eye response +1, best verbal response +1, and best motor response +2). With a fever of 39.0°C, central respiratory failure was considered. The child then underwent endotracheal intubation and invasive ventilation, and symptomatic treatment was given to maintain the stability of the internal environment. The child's internal environment was dynamically monitored during the treatment period, and the biochemical blood test results suggested severe hepatic impairment, coagulation dysfunction, myocardial impairment, acidosis, and hypokalemia (Table 1). About 14 hours later, she exhibited deterioration of her BP (80/60 mmHg), oliguria, and hyperlactatemia and was treated with low-dose dopamine (4 μg/kg/minute). About 33 hours later, the child developed unstable BP, bilaterally dilated and fixed pupils, loss of light reflex, and

**Table 1.** Changes of major routine blood indexes and other indexes in Patient 1.

| Indexes \ Time, Day | 09:16, Day 4 | 19:40, Day 4 | 18:25, Day 5 | Reference range |
|---|---|---|---|---|
| Hb (g/L) | 145 | 151 | 120 | 112–149 |
| WBC ($\times 10^9$/L) | 8.25 | 10.03 | 6.3 | 4.4–11.9 |
| NE (%) | 81 | 90.1 | 82.3 | 22–65 |
| LY (%) | 17.1 | 9 | 15.4 | 23–69 |
| MO (%) | 0.08 | 0.8 | 2.1 | 2–11 |
| PLT ($\times 10^9$/L) | 224 | 177 | 62 | 188–472 |
| PCT (ng/mL) | 44.16 | / | / | <0.046 |
| CRP (mg/L) | 11.26 | 39.09 | 31.83 | 0–8 |
| K+ (mmol/L) | 2.34 | 5.66 | 2.90 | 3.7–5.2 |
| Na+ (mmol/L) | 138.3 | 136.9 | 137.1 | 135–145 |
| Lac (mmol/L) | 3.86 | 7.35 | 3.62 | 0.6–2.2 |
| Glu (mmol/L) | 2.46 | / | 16.51 | 3.9–6.1 |
| AST (U/L) | 974.1 | 11,535.3 | 10,705.8 | 14–44 |
| ALT (U/L) | 482.8 | 6135.8 | 5879.8 | 7–30 |
| PT (s) | 20.4 | 25.4 | 20.0 | 11–15 |
| APTT (s) | 56.0 | 45.3 | 59.8 | 28–43 |
| INR | 1.75 | 2.19 | 1.72 | 0.85–1.27 |
| FIB (g/L) | 3.01 | 2.10 | 1.6 | 2–4 |

Hb, hemoglobin; WBC, white blood cell count; NE, neutrophils; LY, lymphocytes; MO, monocytes; PLT, platelet count; PCT, procalcitonin; CRP, C-reactive protein; K+, potassium; Na+, sodium; Lac, lactic acid; Glu, glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; FIB, fibrinogen.

progressive increase in her blood glucose concentration, suggesting brain failure. The child died within 48 hours after admission.

## *Patient 2*

An 8-year-old girl weighing 24 kg who had not been vaccinated against influenza developed fever on Day 1. Her highest body temperature was 41.3°C. The fever was accompanied by dizziness, headache, sore throat, runny nose, and other symptoms. She was treated with cefixime, aminoglutethimide oral solution, and acetaminophen. However, no improvement was noted; she still had a recurrent high fever and even developed a convulsion on one instance. She visited Hainan General Hospital on Day 3 after treatment and received intramuscular injection of phenobarbital, methylprednisolone, and an antipyretic drug. On examination, her temperature was 41.3°C, respiratory rate was 38/minute, heart rate was 181 beats/minute, and BP was 83/63 mmHg. The patient exhibited drowsiness, and skin mottling was observed all over her body. Her bilateral pupils were equal in size and round, with a blunted light reflex; meningeal irritation was negative; breathing was regular; respiratory sounds were coarse in both lungs; and audible phlegm and dry rales could be heard. The remaining investigations including nerve reflexes showed no abnormalities. After admission to the PICU, testing of a nasopharyngeal exudate specimen was positive for H3N2. Routine blood tests showed that the white blood cell count was $6.31 \times 10^9$/L with 70.6% neutrophils, 27.9% lymphocytes, and 1.3% monocytes. The lactic acid concentration

was high at 4.07 mmol/L, but the CSF showed no abnormality. The child was diagnosed with severe influenza A and influenza virus-associated encephalopathy. She was given midazolam for continuous sedation, an ice blanket for continuous physical cooling, mannitol for dehydration to lower her intracranial pressure, oseltamivir for antiviral treatment (60 mg nasogastrically twice a day), ceftriaxone for anti-infection therapy (100 mg/kg per day), dexamethasone for anti-inflammation therapy, and fluid to maintain the internal environment. Two hours later, the child was still hyperthermic and exhibited gradually increasing consciousness and irregular breathing. Blood gas analysis showed that the pH was 7.32, $PaCO_2$ was 40 mmHg, $PaO_2$ was 68 mmHg, and base excess was −11.5 mmol/L. About 11 hours later, the child's temperature decreased and she was poorly responsive to the outside world. Her Glasgow coma scale score was 6 (best eye response +1, best verbal response +1, and best motor response +4), and she began invasive mechanical ventilation. Cool extremities and skin mottling of the limbs were observed. Seventeen hours later, the child was in a deep coma and developing multiorgan failure (coagulation failure and liver failure). Coagulation testing showed a prothrombin time of 25.5 s, activated partial thromboplastin time of 63.9 s, fibrinogen concentration of 1.74 g/L, and international normalized ratio of 2.67. Liver function testing showed that the alanine aminotransferase concentration was 2440.6 U/L. Twenty hours later, echocardiographic examination of the child was normal. However, 37 hours later, the another echocardiographic examination showed that the left ventricular wall motion was reduced. The child's capillary refill time was 5 s, heart rate was 151 beats/minute, and BP was 64/48 mmHg. She was treated with continuous intravenous dopamine (8 μg/kg/minute) and adrenaline (0.2 μg/kg/minute). Cerebrovascular Doppler ultrasound showed termination of the right cerebral hemisphere circulation, residual left cerebral hemisphere circulation, and termination of the posterior circulation. Forty-eight hours later, cerebrovascular Doppler ultrasound showed termination of all cerebral circulation, and electroencephalography showed signs of brain death.

The reporting of these two cases conforms to the CARE guidelines.[4]

## Discussion

Influenza-associated neurological complications were first reported by scholars in the 1970s, and IAE is an important cause of death from influenza virus infection in children. IAE is characterized by a series of central nervous system (CNS) dysfunctions during the acute phase of influenza virus infection.[5–7] In Japan, the incidence of IAE among children is 28.3 per 100,000, which is 15 times that among adults.[8] The incidence of IAE in China is unknown, and most of the reports in the domestic literature are case reports; the present case report is the first in Hainan. Patients with IAE may have typical symptoms of influenza in the initial stages of the illness, and neurological symptoms such as loss of consciousness, recurrent convulsions, motor or sensory dysfunction, and subsequent brainstem failure may occur within a short period of time. Neurological disorders are the main cause of death in critically ill patients with influenza virus infection.

Influenza viruses are classified as A, B, C, and D according to the antigenicity of their nucleoproteins and major matrix proteins. Among these, A and B viruses are most often associated with human disease. Data show that most cases of IAE are due to influenza A (H1N1, H3N2) infection, whereas influenza B is responsible for about 10% of cases.[9] Of these, infection by H1N1 (the pandemic strain of 2009) occurred in 80% of patients with IAE.

A few studies have revealed that patients with influenza A(H1N1)pdm09 infection have a higher incidence of IAE than those with seasonal influenza because of the different pathophysiology between IAE due to the A(H1N1)pdm09 virus and that due to seasonal influenza viruses.[8] In Hainan, the influenza A (H3N2) virus predominated during the June 2022 influenza season. The two herein-reported cases of IAE were caused by H3N2 infection. However, we have observed no deaths due to IAE among children with infection by the predominant subtypes (H1N1, H3N2, B/Victoria, and B/Yamagata) during the past several seasons in our hospital.

Although the pathogenesis of IAE is incompletely understood, the cytokine storm hypothesis is now widely accepted to be involved. This hypothesis suggests that influenza virus infection induces an inflammatory response in the host organism that triggers an increase in cytokines. This increase in cytokines leads to a cytokine storm that enters the CNS through the damaged blood–brain barrier and causes lesions.[10] The time from the appearance of neurological symptoms to death was short (about 48 hours) in the two patients described herein, also suggesting that the disease lesion may be related to an inflammatory storm. Moreover, relevant data also show that the pathogenesis involves direct infection of the CNS by the influenza virus, glial activation, metabolic disorders, genetic factors, and viral mutations.[11]

The CSF of most patients with IAE lacks significant abnormalities, and only a small percentage of patients show an elevated protein concentration and lymphocyte count.[12] Patients with increased CSF proteins generally have a poor prognosis.[5] Both of our patients showed normal CSF cell counts. Although the association between significantly increased CSF proteins and death in Patient 1 was consistent with the previous reports in the literature,[5] Patient 2 died of IAE with no abnormal changes in the CSF protein concentration. Thus, the lack of CSF changes does not exclude influenza-associated neurological complications, including IAE. At present, there are no validated biomarkers with which to predict the outcome of IAE. Some studies have shown that increases in the hemoglobin, alanine aminotransferase, urea nitrogen, and lactate concentrations as well as lack of vaccination are risk factors for death in children with influenza.[13] Additionally, one study showed that IAE is often combined with elevated serum transaminase concentrations without hyperammonemia.[14] Patient 1 in the present report had early onset of high alanine aminotransferase, urea nitrogen, and lactate concentrations without hyperammonemia, which is consistent with the above-mentioned literature. Clinical signs such as fever, cough, gastrointestinal symptoms, coma, seizures, and extensive changes in magnetic resonance imaging as well as the number of days after onset of oseltamivir are reportedly associated with disease severity.[13,15] The neuroimaging findings of IAE include cortical and subcortical white matter signal alterations with focal or multifocal edema as well as bilateral symmetrical multifocal lesions on the thalamus and cerebellar medulla.[15] Because of the rapid disease progression in our patients, more cranial imaging data were not obtained to further understand the neuropathy in these children.

No specific treatment for IAE has been established. Treatment options often involve symptomatic supportive therapy such as antiviral therapy, plasma exchange, and administration of high-dose corticosteroids and intravenous immunoglobulin. Although there is insufficient evidence for an oseltamivir-induced favorable outcome that improves the prognosis of IAE, empirical use of oseltamivir during the influenza season may be beneficial considering the severity of the disease, the duration of

neurological symptoms, and the possible role of infection in the incipient CNS inflammation.[12] One study showed that initiation of anti-influenza viral therapy within 48 hours of onset of influenza in children with severe illness or risk factors resulted in better clinical outcomes, and some clinical benefit was also attained for more than 48 hours after onset of influenza.[16] However, some experts have pointed out that the effectiveness of high-dose corticosteroids is uncertain. Although corticosteroids inhibit cytokine production in the acute phase and reduce damage to brain tissue by inflammatory factors, they prolong the duration of influenza virus infection and increase rate of secondary bacterial and fungal infections, leading to adverse clinical outcomes and an increased risk of death.[17] Both of our patients with IAE eventually died despite the initial use of various interventions such as anticonvulsants, intracranial pressure reduction, temperature control, and administration of antivirals and glucocorticoids. The failure to administer oseltamivir within 48 hours of onset may have been an important factor in these patients' death. Some experts suggest that immunosuppression is associated with the pathogenesis of IAE. Thus, application of intravenous immunoglobulin remains controversial.[18]

The findings of these two cases emphasize that in patients presenting with persistent fever, seizures, consciousness disorder, and multi-system impairment, rapid diagnostic tests for influenza should be conducted to facilitate early diagnosis and management of IAE in flu seasons. Additionally, given the rapid progression of IAE and its complications of disturbed gastrointestinal function and impaired absorption, the intravenous route of administration may be preferred over the oral route to achieve rapid onset of the antiviral drug effect. Additionally, because cytokine storm may be a cause of IAE, blood purification treatment may improve the prognosis of patients. Further investigation is warranted to validate these ideas.

Neither of our two patients had been vaccinated against influenza. Vaccination against influenza is the most effective means of preventing influenza and significantly reduces the risk of influenza and its serious complications. Data show that most influenza-related deaths occur in unvaccinated children.[18] Therefore, we advocate vaccination of children during the flu season.

In summary, IAE is a rare morbidity of influenza virus infection, and its pathogenesis is not clearly understood. More case data are needed to further elucidate the development and prognostic course of the disease. Physicians should carefully monitor patients who rapidly develop impaired consciousness or convulsions during the influenza season. All children with acute neurologic symptoms during the influenza season should be evaluated for influenza-associated neurological complications, including IAE.

## Authors' contributions

Shi-Guang Li and Hong Liang wrote the first draft and were responsible for the data collection. Yu-Wen Chen reviewed the literature and critically revised the manuscript. Yu-Sheng Pang wrote the protocol of this manuscript.

## Declaration of conflicting interests

The authors declare that there is no conflict of interest.

## Ethics and consent statements

The procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The study protocol was approved by the Medical Ethics Committee of Hainan General Hospital (ethics approval no. Med-Eth-Re[2022] 559; 21 September 2022). Verbal and written informed consent was

obtained from the children's parents for publication of this case report.

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