Brainstem folding in an influenza child with Dandy-Walker variant

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Abstract

BACKGROUND
Influenza in children is a major cause of morbidity and mortality worldwide. Nervous system diseases are a factor relating to increased mortality rate. However, reports of how these underlying diseases contribute to the death of children with influenza are rare.

CASE SUMMARY
A 4-year-old-girl developed type A influenza-related encephalopathy (IAE) with seizures, acute disorder of consciousness, and intracranial hypertension (cerebrospinal fluid pressure: 250 mmH2O), and the Dandy-Walker variant was found by her first magnetic resonance imaging (MRI) when admission. Three days later, she suddenly presented anisocoria, acute pulmonary edema, and coma, and the later MRI found that she had compressed brainstem, oblongata “Z-like folding”, and swelling bilateral basal ganglia. After admission, the patient were tested for routine and special biomarkers and underwent neuroimaging and neuroelectrophysiology examinations as well as Oseltamivir and intravenous immunoglobulin treatments. When predicting that unstable intracranial structures detected by MRI might have disastrous consequences in the progression of IAE, she was transferred into the pediatric intensive care unit and underwent continuous assessment of clinical condition while she did not have instability of basic vital signs; at the same time, her parents were fully informed about the risk and prognosis. Although she was ultimately dead from brain stem failure, the parents expressed understanding and did not trigger a doctor-patient conflict.

CONCLUSION
In case of finding an unstable intracranial structure, intensive care should be given to IAE patient and their clinical condition should be monitored.
INTRODUCTION

Influenza in children is a major cause of morbidity and mortality worldwide. Annual epidemics in adults and children are associated with an estimated 3-5 million cases of severe illness, and about 290000-650000 deaths. Neurological complications associated with influenza include febrile seizures, acute childhood encephalitis/encephalopathy (IAE), etc1,2. Factors related to increased mortality rate include3-8: Children under 5 years old (children under 2 years old are prone to higher incidence of serious complications); persons with the following diseases or symptoms: Chronic respiratory diseases, cardiovascular diseases (excluding hypertension), kidney disease, liver disease, blood system diseases, nervous system and neuromuscular diseases, metabolic and endocrine diseases, inhibition of immune responses (including low immune function induced by the use of immunosuppressants or HIV infection); obesity (body mass index greater than 30); concomitant infection by Staphylococcus aureus or Streptococcus pneumoniae, etc. Rarely, we have met a 4-year-old influenza patient who eventually died of brain stem function failure caused by brain stem folding.

CASE PRESENTATION

Chief complaints
Fever with frequent convulsions for half a day.

History of present illness
A 4-year-old girl (weighing 17 kg) got type A influenza with a high fever onset, who did not have influenza vaccination, and rapidly developed frequent convulsions, which resulted in her emergency admission. After admission, the patient underwent clinical and biochemical examinations (Table 1) as well as Oseltamivir and intravenous immunoglobulin treatments. On the second day of the illness, she developed an acute disorder of consciousness. Therefore, lumbar puncture was performed, and the cerebrospinal fluid (CSF) pressure was as high as 250 mmH2O (Table 1), then her first neuroimaging examination showed the Dandy-Walker variant (DWV) and pontocerebellar hypoplasia (PCH) (Figure 1). When predicting that unstable intracranial structures detected by magnetic resonance imaging (MRI) might have disastrous consequences in the progression of IAE, she was transferred into the pediatric intensive care unit immediately and underwent continuous assessment of clinical condition while she did not have instability of basic vital signs; at the same time, her parents were fully informed about the risk and prognosis.

On the fifth day of the disease, she suddenly developed anisocoria and disappearance of light reflection, irregular breathing rhythm, acute pulmonary edema, and deep coma. After this, her brain MRI (Figure 2) showed that the brainstem was significantly displaced by pressure, and the medulla oblongata exhibited “Z-like compressive folding”; cerebellar incision was observed; some ventricles disappeared; and there were multiple intracranial lesions. Before she was died of brain stem...
### Table 1 Clinical biochemistry

| Characteristic | Value |
|----------------|-------|
| Etiology of pharyngeal swab PCR | FA |
| Routine blood test | |
| White blood cells (×10⁹/L) | 9.6 |
| Neutrophils (×10⁹/L) | 7.1 |
| Lymphocytes (×10⁹/L) | 1.63 |
| Monocytes (×10⁹/L) | 0.86 |
| Hemoglobin (g/L) | 100 |
| Platelets (×10¹²/L) | 288 |
| CSF test after admission | |
| CSF pressure (mmH₂O) | 250 |
| White blood cells (×10⁹/L) | 1 |
| C-reactive protein (mg/mL) | 0.05 |
| Chloride (mEq/L) | 126 |
| Glucose (mmol/L) | 4.05 |
| MP (g/L) | 0.12 |
| Lactate dehydrogenase (U/L) | 8 |
| Electrolyte | |
| Na (mEq/L) | 133 |
| K (mEq/L) | 3.7 |
| Blood glucose | 6.3 |
| Lactate (mmol/L) | 1.4 |
| Biochemistry | |
| ALT (U/L) | 122 |
| AST (U/L) | 363 |
| ALT/AST | 0.34 |
| Lactate dehydrogenase (U/L) | 1129 |
| Creatinine kinase (U/L) | 4083 |
| Creatinine kinase MB (U/L) | 169 |
| Ammonia (μM/L) | 27.7 |
| Immune indexes | |
| IgG (U/mL) | 21.5 |
| IgA (U/mL) | 0.8 |
| IgM (U/mL) | 1.99 |
| C3 (U/mL) | 1.16 |
| C4 (U/mL) | 0.26 |
| IgE (U/mL) | 7 |
| Serum indexes | |
| AQP-4 Ab (ng/mL) | 388.154 |
| Human MOG Ab (ng/mL) | 5.21 |
| NMDAR Ab (ng/mL) | 471.03 |
| Caspase-3/7 (mg/mL) | 11.09 |
| MDA (ng/mL) | 665.99 |
| Blood coagulation | |
| Prothrombin time (s) | 12.3 |
| Activated prothrombin time (s) | 31 |
| INR | 0.92 |
| Fibrinogen (mg/L) | 5.79 |

PCR: Polymerase chain reaction; CSF: Cerebrospinal fluid; INR: International normalized ratio.

Functional failure, her neuroelectrophysiology examination showed electric silence (Figure 3). Although she was ultimately died within three weeks after onset, the parents expressed understanding and did not trigger a doctor-patient conflict.
History of past illness
She had backward neurodevelopment, and could not stand alone until being over 1 year old and walk alone until being over 2 years old. However, the cause had not been diagnosed until this admission.

Personal and family history
Unremarkable.

Auxiliary examination
The patient was diagnosed with influenza A by real-time reverse transcription polymerase chain reaction. Clinical biochemistry showed that blood ALT, AST, LDH, and CK were higher than those in the flu-survivor group, AQP-4 Ab in blood was positive (388.154 ng/mL), and CSF-pressure was as high as 250 mmH₂O with normal biochemical and routine indicators of CSF. On the second day after the onset, which was 3 d before brainstem lesions, she underwent the first brain MRI and was found to have DWV (Figure 1). Sagittal T1WI MRI showed posterior fossa cystic lesions, cyst-like dilatation of the fourth ventricle and communication with the cistern magnum (blue arrow), and hypoplasia of the inferior vermis of cerebellum. The developed superior vermis was elevated upwardly and rotated by posterior fossa cystic lesions (yellow arrow) and caused the death. The pons was smaller, and the medulla was not compressed (white arrow). Axial T2WI MRI magnetic resonance imaging showed that most of the posterior fossa was occupied by cystic lesions (blue arrow), the cyst had a large volume, the superior vermis was compressed upward, and the pons and medulla were not compressed (white arrow).

FINAL DIAGNOSIS
The patient’s final diagnosis was DWV (ICD-10: Q03.1001) with influenza-associated...
Figure 2 T2WI magnetic resonance examination after the condition suddenly deteriorated. The gyri were swelling, the sulcus became superficial (arrow), the supratentorial cranial pressure was increased, the pressure gradient pushed the supratentorial structure down (blue arrow), resulting in compression of posterior fossa cystic lesions and volume decrease, and the medulla moved down and folded into a "Z-like" shape (white arrow). Axial T2WI magnetic resonance imaging showed that the supratentorial structure pushed down the curtain, the pons and medulla were obviously compressed by the hemia tissue (blue arrow), and the surrounding cerebrospinal fluid gap disappeared. Posterior fossa cystic lesions shrank in volume under compression, with residual bilateral cystic areas (orange arrow).

encephalopathy (ICD-10: J10.8002+G94.8*) and secondary central brain herniation (ICD-10: G93.501) (brain stem shift) leading to brainstem functional failure.

TREATMENT

After admission, the patient was given Oseltamivir and intravenous immunoglobulin treatment in accordance with the "Protocol for diagnosis and treatment of influenza (2018 revised version)"[11] issued by the General Office of the National Health and Health Commission. And she was given advanced life support in time when her condition changed.

OUTCOME AND FOLLOW-UP

The patient died of acute brain stem function failure.

DISCUSSION

Nervous system diseases and no flu shots can increase the mortality rate and influenza-related complications[12-15]. The above two points were gathered on our patient. The imbalance between supratentorial and infratentorial pressure can lead to the occurrence of central brain herniation. The common causes of pressure increase include cerebral edema secondary to infection or trauma, stroke, etc. When suffering from type A influenza, the patient rapidly developed convulsive status and acute disorder of consciousness with normal biochemical and routine indicators of CSF, but CSF pressure was as high as 250 mmH\textsubscript{2}O, which could be clinically diagnosed as influenza-associated encephalopathy with intracranial hypertension, and severe intracranial hypertension related with IAE has been reported[16]. In our patient with DWV and PCH, IAE rapidly developed and manifested as diffuse edema of the cerebral cortex and basal ganglia, which created a positive pressure gradient over the tentorium and increased the risk of cerebral herniation. Therefore, it could be speculated that the sudden shrink of her cyst was associated with IAE with intracranial hypertension, especially the progressive swelling of the basal ganglia and above structure (Figure 3). The child’s DWV and PCH had not been diagnosed before. When she was diagnosed with IAE with intracranial hypertension and the unstable intracranial structure had been found, her competent doctor transferred her into the pediatric intensive care unit immediately and gave her continuous assessment while she did not have instability of basic vital signs; at the same time, her parents were fully informed about the risk and prognosis. These positive measures have prevented the doctor-patient conflict caused by the sudden deterioration and death of the child.
A: After brain stem folding, swelling of the bilateral putamen, caudate nucleus, frontal lobe, parietal lobe, and occipital cortex, increased T2WI signals, and slightly enlarged bilateral lateral ventricle can be seen; B: Three days before brain stem folding, no swelling was observed in the bilateral putamen, caudate nucleus, frontal lobe, parietal lobe, or occipital cortex, with normal signals, and no expansion was observed in the bilateral lateral ventricles.

Although the guidelines for Oseltamivir was followed, it did not help to avoid death[18].

As necrotic cells increased, necrosis-associated biomarker levels were reflected in blood, including LDH[19] and creatine kinase isoenzymes (CK-BB, etc.)[20]. The AQP-4 antibody could mediate neurological diseases by being associated with brain edema[21], which suggests that the immune mechanism might be involved in the pathogenesis of this case. The higher plasma levels of ALT, AST, LDH, CK, and AQP-4 antibody could contribute to an increased risk of death.

CONCLUSION

This case highlights a rare but severe complication of influenza in young children, and reminds that if influenza children with unstable intracranial structural abnormalities without flu vaccination developed neurological symptoms, the occurrence of influenza-related encephalopathy should be considered. Once confirmed, more active dynamical observation of changes in intracranial structures, more positive assessment and monitoring should be given, and the parents should be fully informed about the risk and prognosis.
Li SY et al. Abnormal intracranial anatomy promotes flu-patient death

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