Case Report

Acute Necrotizing Encephalopathy of Childhood due to Influenza Type A Virus

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SUMMARY
A 1 year and 11 month old boy developed convulsions and disturbance of consciousness after an antipyretic was administered. Influenza type A virus reaction was positive on rapid antigen test of nasal discharge. Although no significant abnormality was found by brain CT on admission, abnormal densities were observed in the bilateral thalami, brain stem and tegmentum on brain CT performed 12 hours later, so the patient was diagnosed with acute necrotizing encephalopathy (ANE) of childhood due to influenza type A virus. In spite of we diagnosed and performed methylprednisolone pulse and antithrombin III therapy in the early stage of this encephalopathy, which resulted in serious neurologic sequelae remaining. The clinical course of our case suggests that the early diagnosis and these treatments for ANE may not be effective. At present, we have no established therapy for this encephalopathy, so the vaccination is only a method for prevention of ANE due to influenza type A virus.

Key Words: acute necrotizing encephalopathy, influenza type A, vaccination

INTRODUCTION
Acute necrotizing encephalopathy of childhood (ANE) is a novel subtype of acute encephalopathy proposed by Mizuguchi et al.\textsuperscript{1} in 1995. ANE occurred predominantly affecting both infants and young children in mainly Japan and Taiwan in the winter season associated with influenza type A virus infection. The prognosis is usually poor and less than 10% of patients recover completely\textsuperscript{2}.

Here, we report on a 1 year old previously healthy boy presenting case of influenza A virus associated encephalopathy with ANE. The patient’s clinical course progressed in an acute phase and serious neurological sequelae remained, in spite of our diagnosis on brain CT imaging and initiation of treatments in the very early stage. The acute clinical course of this case reported and followed by a review of the literature.

CASE REPORT
The patient was a 1 year and 11 month old boy born by normal delivery in the 39 weeks with a body weight of 3,000 g. The boy had no previous disease, and development was normal. In January 2002, fever and vomiting developed. He was diagnosed with pharyngitis at a private clinic, and antibiotics (cefadroxil: CCL) and acetaminophen suppositories were administered. In the night on the same day, tonic febrile convulsion occurred for 3 minutes, and an anticonvulsive (Diapax\textsuperscript{8} suppository 4mg for 1 time) was administered at the same clinic. On the following day, mafenamic acid was administered for fever...
at 40.1°C. Body temperature transiently decreased to 36.0°C, but re-increased to 40°C after 12 hours. A second tonic convulsion occurred for 5 minutes, and the patient was brought to the emergency department of our hospital.

When brought to our hospital, body temperature was 41.1°C. As for the consciousness level, the patient moved extremities in response to pain stimulation and tended to be somnolent. Convulsions stopped, but tendon reflex of the extremities was enhanced. Swollen of the pharynx was observed. Influenza A rapid antigen detection was positive on the nasal diagnosis. Blood tests detected as follows: WBC 3,100 μ/l; Plt 13.9 × 10⁴; AST 48 IU/l; ALT 20 IU/l; CK 86 IU/l; Glu 291 mg/dl; CRP 0.5 mg/dl; and NH₃ 63 μg/dl. No abnormal density was observed by brain CT (Fig. 1A, B). After admission, amantadine, Glycel®, cefotaxime, and diazepam suppositories were administered. Tonic convulsion occurred again with concurrent respiratory failure 12 hours after admission. Low density areas were observed in the thalamus, pons/dorsal midbrain region, and cerebellar medulla on CT (Fig. 1C, D). and were diagnosed as acute necrotizing encephalopathy. On electroencephalography, high-amplitude slow waves were observed. For respiratory management, steroid pulse therapy using methylprednisolone and antithrombin III massive dose therapy were performed. There after his life was saved, but serious sequelae remained.

**DISCUSSION**

ANE occurs after viral diseases accompanied by fever, and causes convulsions and a rapid decrease in the consciousness level. Influenza A¹ and B² and HHV-6³ have been reported to be the causative viruses. There have been about 10 case reports of influenza virus associated with ANE. This is rare in Europe and America, while the overwhelming majority occurs in East Asia, including Japan and Taiwan frequently, and thus, racial factors have been discussed⁴. Kawasaki disease has been reported as another etiology with regional and racial differences, and the relationship with human leukocyte antigen (HLA) has been suggested, but the cause of ANE is still unknown. Another reason was discussed, relationship with administration of a non-steroid anti-inflammatory drug, diclofenac sodium, mafenamic acid, has been suggested to be a factor of the development of this encephalopathy⁶. In blood testing, elevation of the serum transaminase level varies, but the ammonia level is normal in many cases. Cerebrospinal fluid protein increases, while the cell count is normal in many cases. Elevation of the serum and cerebrospinal fluid levels of cytokines such as IL-6, TNF-α, and neopterin has been reported⁶. On imaging examination of ANE, symmetric multiple brain lesions are characteristic on brain CT and MRI. Lesions in the bilateral thalamus are essential, and lesions are also observed mainly in the cerebral cortex, internal capsule, putamen, tegmentum of the midbrain and pons, and cerebellar medulla⁷.

The clinical course is very rapid as in this patient, and disturbance of consciousness concurrently develops after convulsion. Most patients become comatose within 24 hours after the onset. Sequelae develops at a high frequency, and 1/3 of patients die⁸. Therefore, when the ANE is suspected, early diagnosis and treatment are essential, otherwise the prognosis is poor. In this patient, early diagnosis was made and therapy was initiated based
on the rapid culture and serial brain CT imaging, but serious sequelae remained. Recently, therapy for brain edema with ANE, antiviral therapy, γ-globulin therapy, steroid pulse therapy, antithrombin III massive dose therapy, plasma pheresis, cyclosporin therapy, and cerebral mild hypothermic therapy are being investigated \(^{10}\). As concerns successful treatment of ANE, Munakata et al.\(^{10}\) reported the combination of hypothermic therapy and methylprednisolone pulse therapy causes relatively fewer complications, and may be used as a protocol. However, no established therapy is most available for ANE. At present, vaccination of influenza virus is the only method for prevention of ANE.

REFERENCES


