Dokkyo Journal of Medical Sciences
32(2) : 153～155, 2005

Case Report

Acute Necrotizing Encephalopathy of Childhood due to Influenza Type A Virus

George Imataka[1,2], Yuri Hagiwara[1], Tetsuya Mikami[1,2,4], Eiji Nakagawa[1,3], Hideo Yamanouchi[1] and Mitsuoki Eguchi[1]

[1] *Department of Pediatrics, Dokkyo University School of Medicine, Tochigi, Japan*
[2] *Department of Pediatrics, Shimotsuga General Hospital, Tochigi, Japan*
[3] *Department of Pediatric Neurology, National Center of Neurology and Psychiatry, Tokyo, Japan*
[4] *Department of Pediatrics, Yuuai Memorial Hospital, Ibaraki, Japan*

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.*[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[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.

Received May 30, 2005 ; accepted August 15, 2005

Reprint requests to : George Imataka MD, PhD
Department of Pediatrics, Dokkyo University School of Medicine, Mibu, Tochigi 321-0293, Japan.
E-mail : geo@dokkyomed.ac.jp

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 (cefaclor : CCL) and acetaminophen suppositories were administered. In the night on the same day, tonic febrile convulsion occurred for 3 minutes, and an anticonvulsive (Diapp® suppository 4mg for 1 time) was administered at the same clinic. On the following day, mefenamic acid was administered for fever

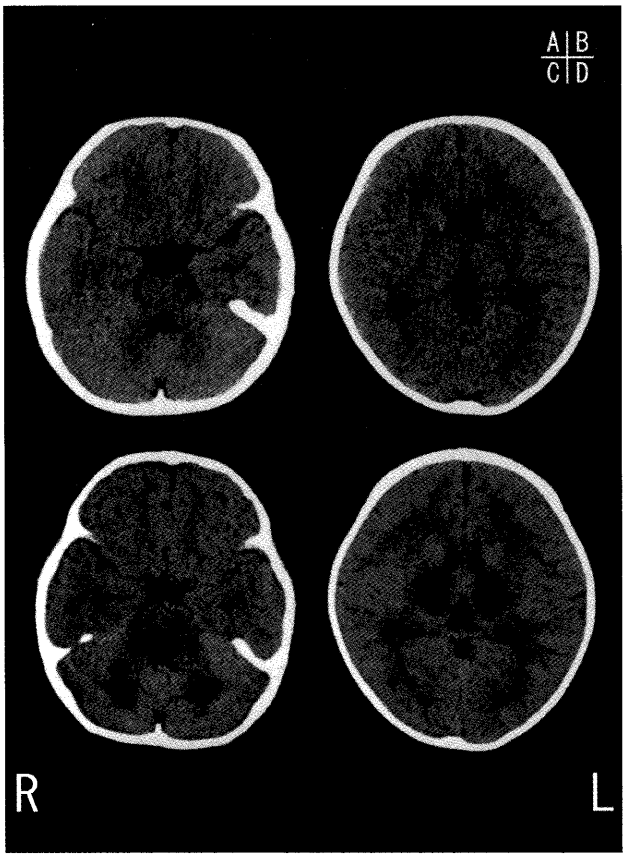

Fig. 1 Brain CT on admission (A, B), and brain CT after 12 hours from admission, revealed typical imaging of acute necrotizing encephalopathy (C, D).

at 40.1℃. Body temperature transiently decreased to 36.0℃, but re-increased to 40℃ 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℃. 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 × 10^4 ; AST 48 IU/l ; ALT 20 IU/l ; CK 86 IU/l ; Glu 291 mg/dl ; CRP 0.5 mg/dl ; and NH_3 63 μg/dl. No abnormal density was observed by brain CT (Fig. 1A, B). After admission, amantadine, Glyceol®, 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 A[1] and B[2] and HHV-6[3] have been reported to be the causative viruses. There have been only 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 discussed[4]. 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, mefenamic acid, has been suggested to be a factor of the development of this encephalopathy[5]. 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 reported[6]. On imaging examination of ANE, symmetric multiple brain lesions are characteristic on brain CT and MRI. Lesions in the bilateral thalami are essential, and lesions are also observed mainly in the cerebral cortex, internal capsule, putamen, tegmentum of the midbrain and pons, and cerebellar medulla[7].

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 die[8]. 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[9]. 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

1) Mizuguchi M, Abe J, Mikkaichi K et al. : Acute necrotising encephalopathy of childfood : a new syndrome presenting with multifocal, symmetric brain lesions. J Neurol Neurosurg Psychiatry, **59** : 555-561, 1995.
2) Huang SM, Chen CC, Chiu PC et al. : Acute necrotizing encephalopathy of childhood associated with influenza type B virus infection in a 3-year-old girl. J Child Neurol, **19** : 64-67, 2004.
3) Oki J, Yoshida H, Tokumitsu A et al. : Serial neuroimages of acute necrotizing encephalopathy associated with human herpesvirus 6 infection. Brain Dev, **17** : 356-359, 1995.
4) Porto L, Lanferman H, Moller-Hartmann W et al. : Acute necrotizing encephalopathy of childhood after exanthema subitum outside Japan or Taiwan. Neuroradiology, **41** : 732-734, 1999.
5) Nakashita Y, Aoki M. : Mild brain hypothermia for influenza encephalitis/encephalopathy and its significance. Nippon Rinsho, **58** : 2333-2337, 2000 (in Japanese).
6) Aiba H, Mochizuki M, Hojo H. : Predictive value of serum interleukin-6 level in influenza virus-associated encephalopathy. Neurology, **57** : 295-299, 2001.
7) Albayram S, Bilgi Z, Selcuk H et al. : Diffusion-weighted MR imaging findings of acute necrotizing encephalopathy. AJNR Am J Neuroradiol, **25** : 792-797, 2004.
8) Mizuguchi M, Imai M, Takashima S. Acute necrotizing encephalopathy of childhood : recent advances and future prospects. No To Hattatsu, **30** : 189-196, 1998 (in Japanese).
9) Studahl M. : Influenza virus and CNS manifestations. J Clin Virol, **28** : 225-232 : 2003.
10) Munakata M, Kato R, Yokoyama H et al. : Combined therapy with hypothermia and anticytokine agents in influenza A encephalopathy. Brain Dev, **22** : 373-377, 2000.