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Case Report

A Patient with Influenza A-associated Encephalopathy Treated with Mild Hypothermic Therapy and Methylprednisolone Pulse Therapy

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SUMMARY

A case of influenza A-associated acute encephalopathy treated with mild hypothermic therapy and methylprednisolone pulse therapy is reported. The patient was a 1 year and 1 month-old girl. Disturbance of consciousness was protracted after fever accompanied by status convulsives, thus she was diagnosed with acute encephalopathy. Influenza A reaction was positive on rapid diagnosis from her nasal mucosa. Hypothermic therapy was initiated in the early stage, and body temperature was kept at 35℃ as rectal and ear drum membrane temperatures for 72 hours. As steroid therapy, 30 mg/kg/day methylprednisolone was administered for 3 days. During the course, 7 mg/kg amantadine was administered for 5 days. After the combination of therapy, the patient recovered without sequela. No major adverse event occurred during the combined therapy. Still now, there are no established clinical guidelines for this encephalopathy. The combined therapy was effective for influenza A-associated encephalopathy in this patient.

Key Words : influenza A, encephalopathy, hypothermic therapy, steroid pulse, methylprednisolone

INTRODUCTION

Hypothermic therapy was confirmed to be effective as intensive therapy for cerebral trauma and cerebrovascular disorders in adults[1]. Recently, its effectiveness as a therapy for acute encephalopathy of childhood has been reported[2]. In addition, protection of the brain by steroid pulse therapy using methylprednisolone has also been reported[3]. Based on these report, we reported here a concurrently administered these two therapies to a child with influenza A-associated acute encephalopathy, and obtained a good prognosis.

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CASE REPORT

The patient was a 1 year and 1 month-old female without abnormal delivery, previous medical history, or development. Tonic status convulsives were continued for 40 minutes with fever, and convulsions were stopped by intramuscular injection of 50mg of phenobarbital and 1mg of haloperidol by the previous physician. On arrival at our hospital, her glasgow coma scale was 6 (eye opening to pain 2, abnormal flexion best motor response 3, nil vebal response 1). She slightly brushed away pain stimulation from the extremities. Disturbance of consciousness was protracted. Deep tendon reflex of the extremities was enhanced. A rapid influenza A antigen reaction test using

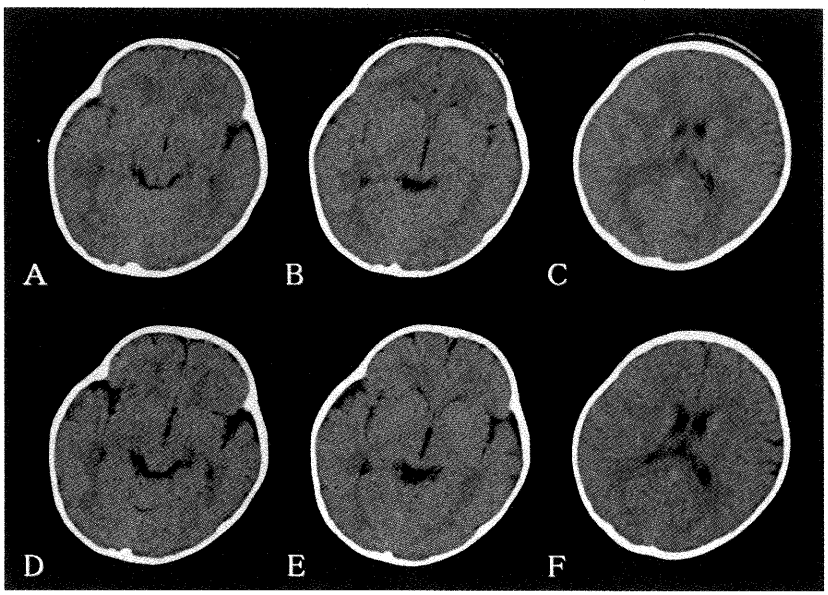

Fig. 1 Brain CT
Mild brain edema was showed at arrival our hospital (A, B, C). After combined therapy with mild hypothermia and steroid pulse employing methylprednisolone, the edema was improved (D, E, F).

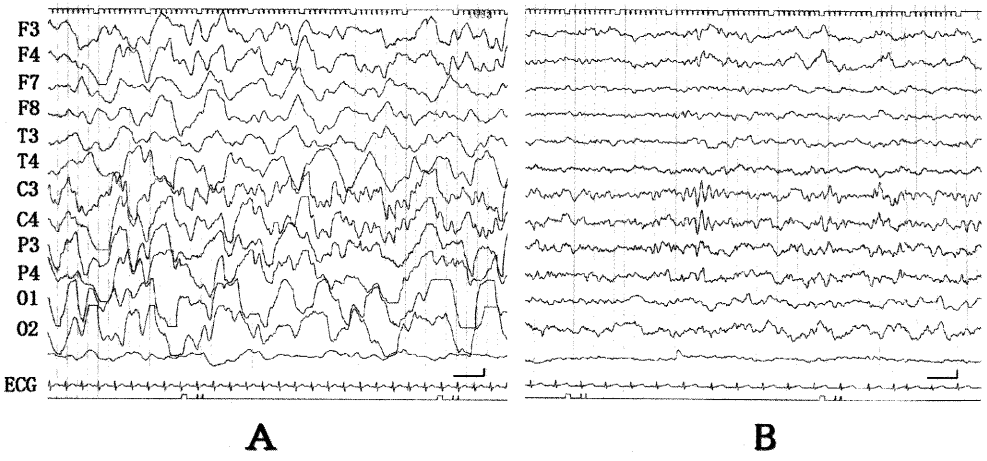

Fig. 2 Electroencephalography
Generalized high-amplitude and slow waves revealed on admission day (A), and there were disappeared on the 5th day, after combined treatment with hypothermic therapy and methylprednisolone pulse therapy (B).

a nasal mucosa was positive. On blood testing, WBC 13,300 μ/l ; Plt 29.6 × 10^4 ; AST 33IU/l ; ALT 13IU/l ; NH_3 37 μg/dl ; Na 135 mEq/l ; Cl 99 mEq/l ; CK 85 IU/l ; Glu 324 mg/dl ; lactate 14.5 mg/dl, pyruvate 0.95 mg/dl and CRP less than 0.3. On brain CT at arrival (Fig. 1A, B, C), mild brain edema was observed. Electroencephalography (Fig. 2A) showed generalized high-amplitude and slow waves. Lumbar puncture was not performed for her general condition. The patient was diagnosed with influenza A-associated acute encephalopathy.

Immediately, mild hypothermic therapy at 35℃ as rectal and ear drum membrane temperatures was initiated under artificial ventilation 3 hours after the diagnosis. The head and lateral neck were cooled using ice bags. Steroid pulse therapy using methylprednisolone (30 mg/kg/day) was concurrently performed for 3 days. Amantadine hydrochloride (7 mg/kg/day) was administered for 5 days. During the course, anticoagulation drugs were concurrently administered. Midazolam (0.6 mg/kg/hr) was administered by continuous drip infusion. For muscular

relaxation, vecuromium was administered appropriately. Hypothermic therapy was continued for 72 hours, thereafter body temperature was gradually rewarmed for over 48 hours. On the 5th day after onset of convulsions, cerebral edema disappeared on brain CT (Fig. 1D, E, F), and her electroencephalograph was improved on EEG (Fig. 2B). The patient was discharged on the 20 th day from onset. No sequela developed as of 3 years after discharge.

DISCUSSION

Hypothermic therapy performed not only for adult brain disorders but also drowning[4] and acute encephalopathy in children[2] has recently been reported. Hypothermic therapy is classified into normothermia maintaining the body temperature at 37℃ to 36℃, mild hypothermia at 36℃ to 34℃, moderate hypothermia at 32℃ to 28℃, deep hypothermia at 25℃ to 15℃, and profound hypothermia at 15℃ to 5℃. The reported duration of hypothermia is 3 to 7 days. Hayashi *et al.*[5] reported that the indication for children is mild hypothermia in consideration because it protects the brain and maintains cerebral perfusion pressure. Nevertheless, even mild hypothermia is effect for the immune, circulatory, and coagulation systems in childhood, and complications such as hypotension, arrhythmia, and abnormal coagulation may occur. Moreover, since central venous management and artificial respiratory management are necessary for hypothermic therapy. In addition, complications such as pneumonia and laryngeal edema may occur[5~7]. Therefore, therapy can be performed at limited facilities that are able to perform intensive therapy.

In our patient, body temperature was controlled at 35℃ for 72 hours with concurrent steroid pulse therapy using methylprednisolone. No complication occurred during the hypothermic period, and the prognosis was good. Bracken *et al.*[3] reported that steroid pulse therapy using methylprednisolone protects the brain in patients with cerebrospinal trauma. Regarding the combination of hypothermic therapy and methylprednisolone pulse therapy, Kimura *et al.*[2] reported the successful treatment of acute encephalopathy of childhood, and Munakata *et al.*[6] reported the therapy to patients with acute necrotizing influenza encephalopathy. And they concluded the combination of these two methods for influenza encephalopathy in children causes relatively fewer complications, and may be used as a protocol. Another therapy for influenza encephalopathy, γ-globulin therapy, antithrombin Ⅲ therapy, plasma pheresis and cyclosporine therapy have been occasionally reported, but no therapy has been established[7]. To date, recommendation of vaccination is the only method for prevention of patient with influenza A-associated encephalopathy, but not completely blocked yet.

The precise mechanisms of influenza encephalopathy have not been elucidated, involvement of inflammatory cytokines such as IL-6, neopterin and TNF-α has been reported[6, 8~10]. Steroid pulse therapy using methylprednisolone also reported to inhibit production and transition effect for the brain of cytokines. Anti-cytokine action of steroids may be effective for the reason of influenza encephalopathy. Mild hypothermic therapy is also reported same effect to the brain of cytokines. Since the therapeutic strategy for this patient included the initiation of hypothermic therapy as soon as possible after the diagnosis, her cerebrospinal fluid was not examined. Accumulation of these cases and this combined therapy were administered is expected.

Currently, there are no established guidelines facilitating the definitive diagnosis of influenza encephalopathy immediately after its onset. In addition, there is at present no modification corresponding to the serious encephalopathy degree for these combine treatment. Therefore, it remains controversial whether intensive care, including hypothermic therapy, should be administered in all patients in whom the development of influenza encephalopathy is suspected. However, the mortality of influenza encephalopathy is high, and its prognosis is poor in most patients[11]. Therefore, in medical facilities where intensive care such as hypothermic therapy can be performed, the administration of this combined therapy should be considered before determining the therapeutic strategy for this encephalopathy. The further case's accumulation is necessary for clinical management of influenza A-associated encephalopathy.

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