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Case Report

A case of acute encephalopathy with biphasic seizures and late reduced diffusion on respiratory syncytial virus infection

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Abstract

We report a case of respiratory syncytial virus (RSV) infection-associated encephalopathy. Abnormalities of cerebrospinal fluid (pleocytosis, increases IL-6 and positive for virus by highly sensitive assay) were documented. Her MRI findings and clinical course coincided with those of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD). Her partial seizures were controlled by treatments of lidocaine and methylprednisolone pulse therapy. However she finally had mild sequelae.

Introduction

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is clinically characterized by biphasic seizures on days 1, and 4 to 6 ; neuroimaging shows no acute abnormality during the first two days, while reduced diffusion in the subcortical white matter is seen during days 3 to 9, finally resulting in cerebral atrophy and several kinds of sequelae[1-3]. We report here a unique pediatric patient with clinically AESD associated with respiratory syncytial virus, in whom sequential magnetic resonance imaging (MRI) revealed cerebral swelling on day 10.

Case report

A 1-year-old girl with normal development was admitted to our hospital because of convulsion. Her family and past history were unremarkable. She had a fever and had generalized tonic seizure with esotropia on the second day. Her brain CT was normal. On 5 days after onset she had recurrent complex partial seizures with the left side dominant on the face and upper extremity, and was admitted to our hospital. Her temperature was 36.9°C, and the blood pressure was 98 mmHg. Her consciousness was unclear. The light reflex was prompt without anisocoria. Her deep reflex was normoactive. Her blood chemistry findings were normal, including white blood cell count, Hb, blood gas, CRP, AST, LDH and BUN, creatinine. Rapid assay for respiratory syncytial virus (RSV) of her nasopharyngeal aspirate was positive. The cerebrospinal fluid showed a high level of IL-6 (29.7 pg/ml, normal <4.0)[4] and positive results of RSV by loop-mediated isothermal amplification (LAMP)[5], compared with the level of serum IL-6 as 5.7 pg/ml. The cell count and concentration of protein and glucose were normal. Brain CT was normal on the day of admission. Because complex partial seizures were recurrent on the same day despite treatment with diazepam, intravenous lidocaine (2 mg/kg/h) were administered continuously, and her seizures ceased. Tapering

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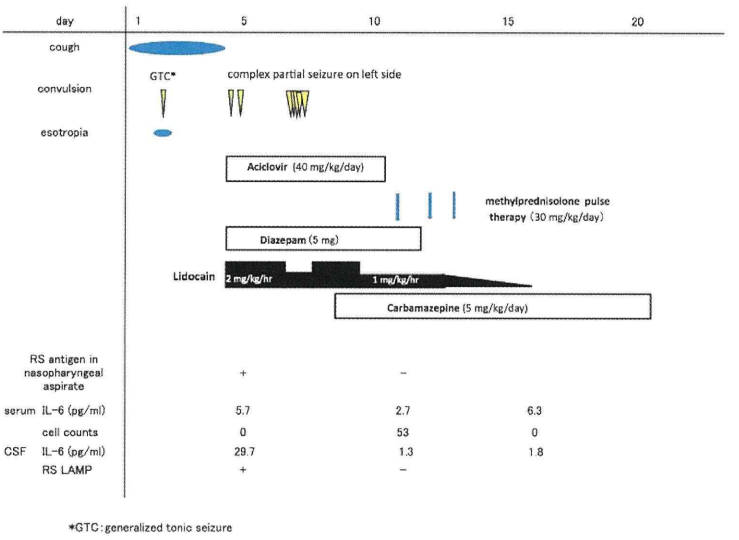

Fig. 1 The course of the patient.

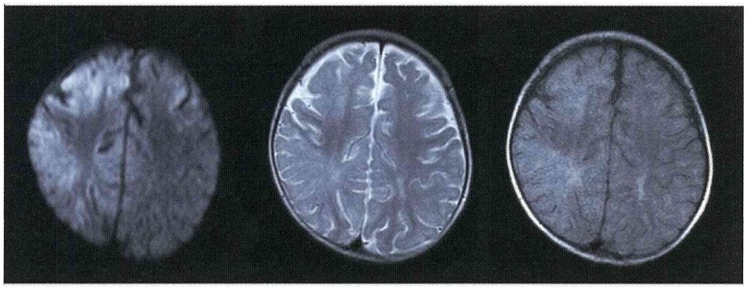

Fig. 2 Brain MRI (FLAIR and DWI). High signal intensity was noted in right frontal and temporal regions on 10 days after onset.

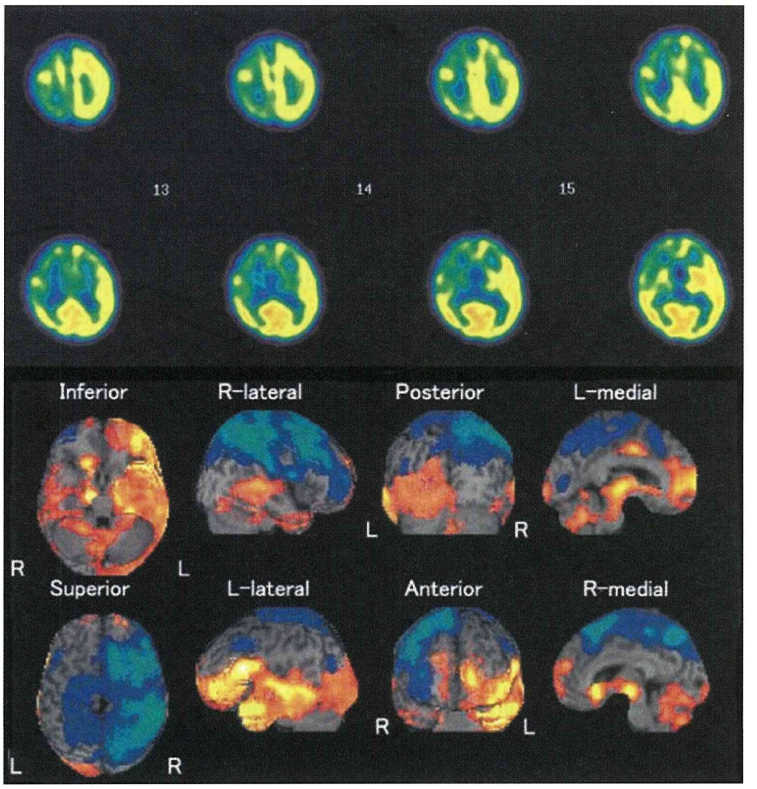

Fig. 3 Single Photon Emission Computed Tomography (SPECT) : hypoperfusion in frontal and temporal regions on day 10 after onset.

liodocaine on day 7 after onset the same partial seizures reappeared again (Fig. 1). Her diffusion-weighted MRI revealed hyperintensity in the temporal to frontal area at the 10th day after onset (Fig. 2). Interictal EEG revealed asymmetry. A slow wave was revealed in the right hemisphere. Single photon emission computed tomography (SPECT) revealed hypoperfusion in the temporal to frontal area (Fig. 3). A second lumbar puncture revealed pleocytosis (cell count 53/mm^3). We Started Methylprednisolone pulse therapy (30 mg/kg/day) under the diagnosis of RSV-associated encephalopathy to reduce hypercytokines and carbamazepine (5 mg/kg/day) per os, and liodocaine was tapered off without relapse. Hyperintensity in the temporal to frontal area on diffusion-weighted MRI disappeared on day 25 after onset. Mild mental retardation as a sequela appeared without relapse of seizure and hypoperfusion on SPECT continued 6 moths later under treatment of carbamazepine.

Discussion

RSV is a common cause of childhood respiratory infection resulting in significant debilitation and mortality. It is well known that young infants, premature birth without or with chronic lung disease, congenital heart disease, and T-cell immunodeficiency are conditions that predispose the subjects to more severe forms. On the other hand extrapulmonary manifestations have been reported including seizures and focal neurological abnormalities. Ng reported an incidence of encephalopathy of 1.8% in a total of 487 patients based on a study of a large number of children with RSV bronchiolitis[6]. Seizures were the presenting complication. Otake reported a case of RSV encephalopathy with elevated CSF IL-6[7]. In this study we presented a case (no history of heart diseases and apparent immunodeficiency) with seizures and unique neuroimaging findings which coincided with those of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD). The neuroimaging and high concentration of proinflammatory cytokine (IL-6) revealed RSV-associated encephalopathy. Her viral study for RSV was positive by LAMP which is highly sensitive[8)9)]. Viral and transcribed RNA in peripheral mononuclear cells from children were positive only in the acute phase by using RT-PCR. Those reports and our findings revealed that RSV has been shown to release several cytokines which could be neurotoxic and induce encephalopathy commonly through a direct invasion of virus. Pathological studies of the brain are needed to clarify the above.

Patients with a unique type of influenza-associated encephalopathy are reported in Japan. Mizuguchi classified virus-associated encephalopathy into three major categories. The first group, caused by metabolic derangement, consists of various inherited metabolic disorders and the classical Reye syndrome. The second group, characterized by a systemic cytokine storm and vasogenic brain edema, includes Reye-like syndrome, hemorrhagic shock and encephalopathy syndrome, and acute necrotizing encephalopathy. The third group, characterized by localized edema of the cerebral cortex, has recently been termed acute encephalopathy with febrile convulsive status epilepticus, and includes hemiconvulsion-hemiplegia syndrome and acute infantile encephalopathy predominantly affecting the frontal lobes. AESD is classified into the third group with specific imaging[10]. The pathophysiology is suspected to be caused by excitotoxicity and delayed neuronal death. In this report treatments with methylprednisolone pulse to reduce cytokines and lidocaine were likely to be effective. However there was a mild sequela and hypoperfusion continued during long period. In most patients with acute encephalopathy with febrile convulsive status epilepticus, pentobarbital infusion, steroid pulse therapy and mild hypothermia did not show apparent effects on the clinical course. Our data of the positivity for the viral gene in CSF reveal that neurological involvement might be caused by a direct invasion of virus. Therefore more specific therapy to prevent neurodamage should be developed such as anti-free radicals and anti-virus monoclonal antibodies. Hosoya reported that cytochrome c values in cerebrospinal fluid samples from patients with influenza-associated encephalopathy in the acute exacerbation and convalescent phase increased remarkably in patients with a poor prognosis and subsequent brain atrophy[11]. Therefore in order to prevent mitochondria impairment cyclosporine might be effective. More similar cases have to be collected in order to reach a clear conclusion.

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Respiratory Syncytial（RS）ウィルス感染に合併した2相性けいれんと遅発性拡散能低下を呈する急性脳症 (AESD) の一例

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我々は、Respiratory Syncytial Virus（RSV）に合併した特殊なタイプの急性脳症を経験したので報告する。髄液では細胞数増加、IL-6 増加、高感度法によるウィルス遺伝子陽性を示した。頭部 MRI と臨床経過は、二相性けいれんと発作と遅発性拡散能低下を呈する急性脳症（AESD）と一致した。部分発作は、リドカインとメチルプレドニゾロンパルス療法によりコントロールできたが、最終的に軽度な後遺症を残した。

〈キーワード〉 RS ウイルス、急性脳症、けいれん、MRI