Neurology Asia 2009; 14(2) : 153 – 155

Hemophagocytic lymphohistiocytosis in a child with rotavirus encephalopathy

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Abstract

We describe a 13-month-old girl who developed convulsive status during an episode of rotavirus gastroenteritis. Persistent disturbance of consciousness, recurrent seizures, slowing on EEG, high signal areas on diffusion-weighted MRI, and normal cerebrospinal fluid confirmed the diagnosis of encephalopathy. In addition, hepatosplenomegaly, cytopenias, and a histopathological finding of hemophagocytosis in bone marrow were all observed in this case, and these three conditions together meet the diagnosis of hemophagocytic lymphohistiocytosis. The patient improved after commencement of steroid pulse therapy. This case suggests that the pathogenesis of rotavirus-associated encephalopathy may share some basic pathophysiologic mechanisms with hemophagocytic lymphohistiocytosis.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is characterized by fever, hepatosplenomegaly, and pancytopenia. It develops as the result of a strong activation of the immune system, which may in turn be triggered by a severe infection.[1] In children affected with HLH, estimates of the rate of central nervous system (CNS) involvement range from 20%[2] up to 73%.[3]

Here, we report on a girl who developed simultaneous encephalopathy and HLH during an episode of rotavirus gastroenteritis. The coincidence of encephalopathy and HLH in association with rotavirus infection is rarely seen. To our knowledge, there is only one such previous case report.[1] The pathogenesis of encephalopathy associated with rotavirus infection remains controversial.[4-5] Our patient with HLH and encephalopathy help to support immune-mediated damage as underlying pathophysiology of rotavirus encephalopathy.

CASE REPORT

The patient was a girl with no family history of HLH. Her previous development had been normal. At 13 months of age, she was admitted to our hospital because of convulsive status that occurred during an illness which also has high fever, vomiting, and diarrhea. The seizure lasted for about one hour before it was stopped with an injection of diazepam. On admission, the patient was comatosed, but with normal spontaneous respiration. Her temperature was 40.3˚C. Her white blood cell count was 14,930/μl; red blood cell, 555 x 10^4/μl; platelet, 51.0 x 10^4/μl; and hemoglobin, 15.2 g/dl. Her blood sugar was high (188 mg/dl). Rotavirus antigen was detected in her stools by enzyme-linked immunosorbent assay (ELISA). EEG showed slowing. A cerebrospinal fluid (CSF) examination gave normal results. The patient's seizures were recurrent in spite of treatment with phenobarbital and lidocaine. Impairment of consciousness and fever also persisted.

Between the 4th and 8th days after admission, the patient exhibited pancytopenia: her white blood cell count was 1,970/μl; neutrophil, 1,284/μl; red blood cell, 395 x 10^4/μl; platelet, 8.8 x 10^4/μl; and hemoglobin, 10.8 g/dl. There were no findings of disseminated intravascular coagulation (DIC): Prothrombin Time-International Normalized Ratio (PT-INR) was 1.15; and D dimer, 1.1 μg/ml. Serum enzymes at the time of admission were just slightly over normal levels (AST 59, ALT 67, and LDH 467 IU/l). By the 4th day, however, they had elevated significantly (AST 528, ALT 686, and LDH 1890 IU/l). Measurements of cytokine levels in serum and CSF were not attempted. Hepatosplenomegaly was noted at this stage. On the 6th day, bone marrow aspirate showed hemophagocytosis, with no findings of malignancy. MRI on the same day showed high signal areas in the cerebral white matter, especially on diffusion-weighted

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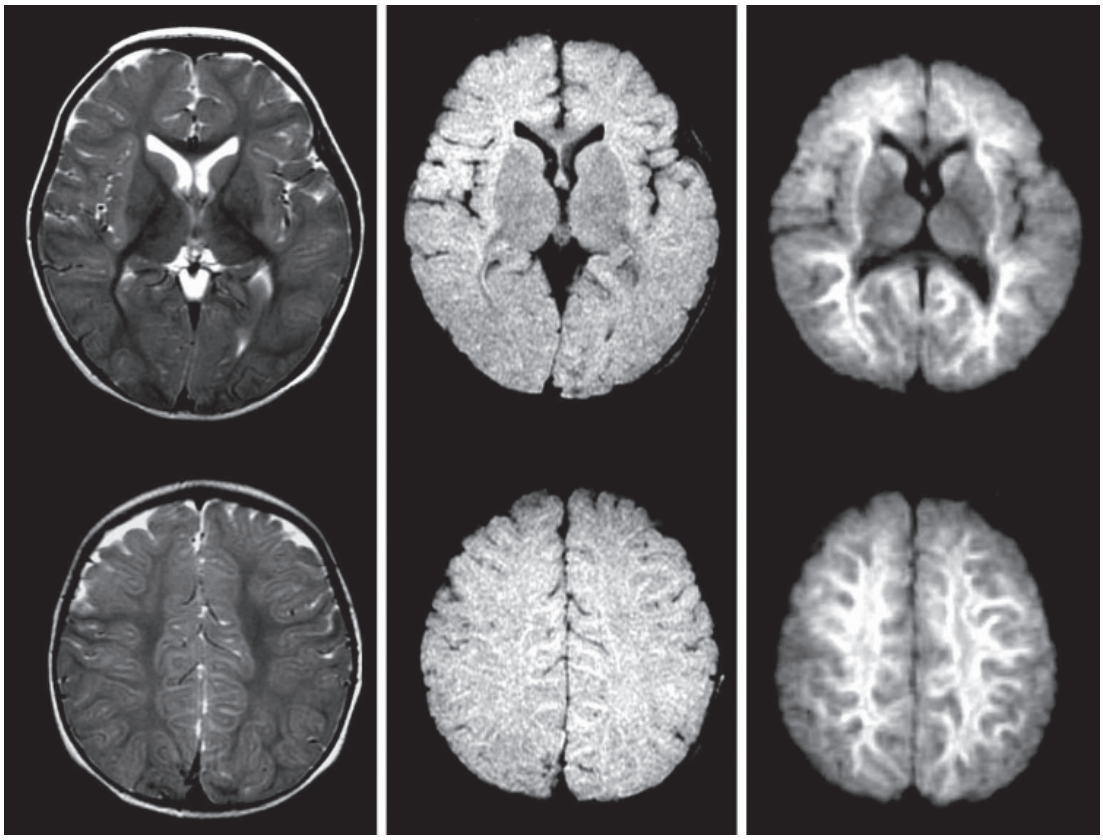

Figure 1. MRI on the 6th day. Left: T2 weighted image, middle: fluid attenuated inversion recovery (FLAIR), right: diffusion-weighted image. Note high signal areas in the cerebral white matter.

images (Figure 1). Dexamethasone was started on the 6th day. The patient partially responded to this therapy. Her seizures ceased, but the fever persisted and spasticity developed. At this point, methylprednisolone pulse therapy was started. The administration of 23 mg/kg of methylprednisolone for 3 days brought down the patient's fever and resolved the cytopenia. She regained consciousness on the 10th day after admission. Hematological examination on the 10th day showed her white blood cell count to be 9,680/μl, red blood cell 425 x 10^4/μl, and platelet 61.3 x 10^4/μl. She was severely handicapped at 4 years and 8 month of age; bedridden and could not speak.

DISCUSSION

In our patient, high fever, persistent disturbance of consciousness, recurrent seizures, slowing on EEG, high signal areas on diffusion-weighted MRI, and normal CSF confirmed the diagnosis of encephalopathy. The cytopenias were observed over the trilineage of blood cells, and DIC was not confirmed. Hyperthermia, hepatosplenomegaly, cytopenias and hemophagocytosis in bone marrow suggested the diagnosis of HLH.

A number of reports have described encephalitis and encephalopathy in association with rotavirus infections.[1,4-8] Two possible mechanisms by which rotavirus infection could cause neurological complications have been proposed: the first is by direct invasion of CNS; the second is by immune-mediated CNS damage.

Many authors have reported that rotavirus RNA can be present in the CSF.[4-7] All studies that have so far detected rotavirus RNA in the CSF have detected it by the reverse transcription polymerase chain reaction (RT-PCR) technique. In fact, as Nakagomi and Nakagomi[6] have shown, rotavirus antigen could not be detected by ELISA in the same CSF specimens from patients with encephalopathy in that rotavirus RNA had been positively detected by RT-PCR. This indicates that, if rotavirus was present at all in these specimens, it was present in extremely small quantities. The authors of the study did not consider their findings to constitute evidence of viral invasion to the brain. The problem with relying on the RT-PCR assay to detect rotavirus RNA is that the assay, while it

is very sensitive, is also prone to contamination.[6] To our knowledge, there has been only one case report describing the coexistence of rotavirus RNA and anti-rotavirus IgG in the CSF.[7] Based on these findings, we can only hypothesize that rotavirus directly invades the CNS, but the cause, mechanism and the effect of such an invasion remain unclear.[5]

Our case suggests an alternative mechanism. There were a few reports describing an elevation of cytokines in cases of rotavirus-associated encephalopathy. Shiihara *et al*.[8] were not able to detect any rotavirus gene segments in the CSF, but they detected high cytokine levels in a case of rotavirus-associated encephalopathy. Takahashi *et al*.[1] reported a case of encephalopathy with HLH during rotavirus infection in which they observed an increase in cytokines in the CSF. Although the pathogenesis of HLH is still controversial, it may develop when inflammatory cytokines activated by uncontrolled T-cells promote macrophage infiltration and formation of the cytokine network.[9] The overproduction of cytokines, which may be a local immune response within the CNS[1], may be responsible for the simultaneous occurrence of encephalopathy and HLH.

The association of encephalopathy and HLH in our patient suggests that cytokines were involved in the mechanism that resulted in the observed CNS complications; although cytokines were not examined in our case. The effectiveness of steroid pulse therapy also give some support to the hypothesis that rotavirus causes CNS damage through immune-mediated mechanism.

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