

Serial Brain MRI Findings in CNS Involvement of Familial Erythrophagocytic Lymphohistiocytosis: A Case Report¹

Kyung Soo Cho, M.D., Jeong hyun Yoo, M.D., Jeong Soo Suh, M.D.,
Kyung Ha Ryu, M.D.², Ki Sook Hong, M.D.³, Hak Jin Kim, M.D.⁴

Familial erythrophagocytic lymphohistiocytosis is a fatal early childhood disorder characterized by multiorgan lymphohistiocytic infiltration and active hemophagocytosis. Involvement of the central nervous system (CNS) is not uncommon and is characterized by rapidly progressive tissue damage affecting both the gray and white matter. We encountered a case of familial erythrophagocytic lymphohistiocytosis with CNS involvement. Initial T2-weighted MRI of the brain demonstrated high signal intensity in the right thalamus, though after chemotherapy, which led to the relief of neurologic symptoms, this disappeared. After four months, however, the patient's neurologic symptoms recurred, and follow-up T2-weighted MR images showed high signal intensity in the thalami, basal ganglia, and cerebral and cerebellar white matter.

Brain MRI is a useful imaging modality for the evaluation of CNS involvement and monitoring the response to treatment.

Index words : Brain, diseases

Brain, MR

Infants, newborn, central nervous system

Histocytosis

Familial erythrophagocytic lymphohistiocytosis (FEL) is a rare and fatal hereditary disorder of unknown cause with multisystem involvement. Involvement of the central nervous system (CNS) is reported in approximately 30% of cases. Leptomeningitis, gliosis, demyelination, and lymphocyte and histiocyte infiltration of the cerebrum and cerebellum are the characteristic neuropathologic findings. We describe the serial brain MRI findings and neurologic symptoms in a case of FEL, and review

the literature.

Case Report

A 16-month-old male was transferred to our hospital due to dyspnea, tachypnea, fever, and aggravated abdominal distention, present for one week. He had previously been admitted to another hospital, with similar symptoms, five months earlier. His first and third older female siblings died at two months and two years of age, respectively of fever of unknown origin and hepatosplenomegaly. The second male sibling, eight years old, is currently alive.

Physical examination revealed hepatosplenomegaly, shifting dullness, anemic conjunctiva, and jaundice, and hematological study showed pancytopenia, hypofibrinogenemia, and hyperferritinemia : Hb, 6.1 g/dl; WBC,

¹Department of Radiology, Ewha Womans University Hospital

²Department of Pediatrics, Ewha Womans University Hospital

³Department of Clinical Pathology, Ewha Womans University Hospital

⁴Department of Radiology, Pusan National University Hospital

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Address reprint requests to : Jeonghyun Yoo, M.D., Department of Radiology, Ewha Womans University Hospital, 70 Chongro-6-Ka, Chongro-gu, Seoul 110-126, Korea.

Tel. 82-2-760-5231 Fax. 82-2-760-5046

E-mail: YooLee@mm.ewha.ac.kr

3300/μl; platelet, 37000/μl; fibrinogen <50 mg/dl, and ferritin 423.2 ng/ml. The results of a liver function test were abnormal, and were as follows : hypertriglyceridemia (246 mg/dl), AST 365 IU/L, ALT 316 IU/L, and total bilirubin 8.3 mg/dl. Examination of CSF showed an elevated total cell count and protein content: WBC, 20 cells/μl (lymphocyte 86%, monocyte 14%); RBC, 2730/μl; protein, 21 mg/d; and glucose, 53 mg/dl. Bone marrow biopsy revealed atypical lymphohistiocytic infiltration by hemophagocytic histiocytes, compatible with FEL (Fig. 1). Viral studies were all negative. Abdominal sonography showed massive hepatosplenomegaly, ascites, and pleural effusion.

Six days after admission, there were three episodes of eyeball fixation, each lasting for 1 - 2minutes, as well as convulsion associated with eyeball deviation, rigidity, and clonic movements. For brain MRI, a 1.5-T imaging

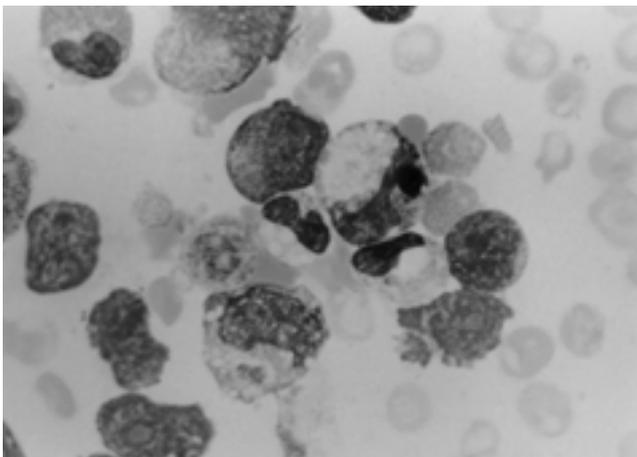


Fig. 1. The bone marrow biopsy demonstrates increased histiocytes with evidence of hemophagocytosis (Wright, × 1000).

system (Siemens, Erlangen, Germany) was used, and pre-and post-contrast T1-weighted and T2-weighted spin-echo images were obtained. The latter revealed a focal high- signal-intensity lesion in the right thalamus; T1-weighted images showed iso signal intensity, subtly increased peripherally, with no enhancement (Fig. 2).

The patient underwent chemotherapy with HLH-94, dexamethasone, VP16, and intrathecal methotrexate. Follow-up MRI performed five weeks after initial diagnosis showed complete resolution of the brain lesion (Fig. 3). The laboratory findings demonstrated improve-

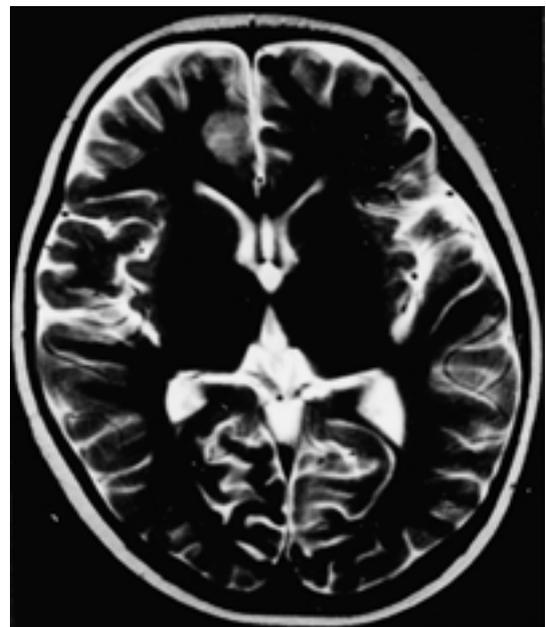
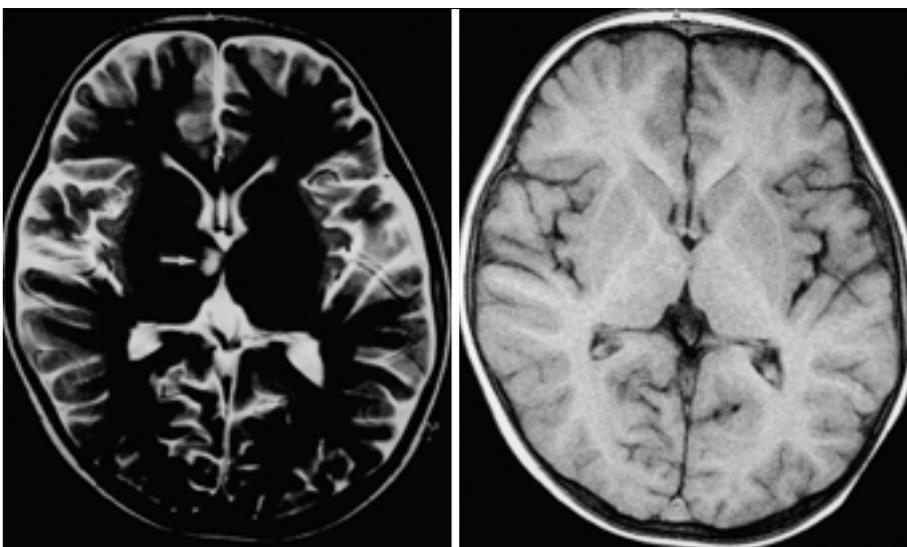


Fig. 3. Follow-up T2-weighted axial brain MRI obtained 5 weeks later shows complete regression of the right thalamic lesion.



A

B

Fig. 2. Brain MR axial scan shows a focal high-signal-intensity lesion at the right thalamus (arrow) on T2-weighted image (A), which showed iso-signal intensity with peripheral subtle increased signal intensity on T1-weighted image (B) and was not enhanced (not shown).

ment, but not complete normalization (Hb 9.1 g/dl, WBC 6500/ μ , plt 744,000/ μ), and the results of a liver function test were normal except for a slightly elevated ALT level (80 IU/L). CSF analysis showed a WBC count of 30 cells/ μ (lymphocyte 72%, monocyte 28%). During subsequent chemotherapy there were no signs of relapse or other neurologic symptoms.

About four months later, the patient was rehospitalized because of convulsions and a comatous mentality. T2-weighted brain MRI showed extensive bilateral, high-signal-intensity lesions affecting the thalami, basal ganglia, and white matter in the cerebrum and cerebellar hemisphere. T1-weighted images of the lesions showed mixed low and slightly increased signal intensity (Fig. 4). The patient's CNS symptoms had progressed rapidly, and he died 7 months after initial diagnosis. An autopsy was not performed.

Discussion

Familial erythrophagocytic lymphohistiocytosis (FEL) is a rare and fatal disease affecting infants in the first two years of life (1 - 6). It involves primarily the lymphoreticuloendothelial system and is classified as a histiocytic disorder (3). Although its etiology and pathogenesis remain uncertain, most reported cases indicate autosomal recessive inheritance. Clinically, it is characterized.

By failure to thrive, vomiting, high fever, nonspecific rash, hepatosplenomegaly, and pancytopenia. Hepatic manifestations include hyperlipidemia, increased

triglyceride levels, hypofibrinogenemia, and elevated transaminase levels (3).

CSF abnormalities are sensitive indicators of CNS involvement and usually precede neurologic symptoms (7). They include pleocytosis with an increased presence of lymphocytes and foamy histiocytes, and elevated protein levels (3).

The incidence of CNS involvement with neurologic symptoms and signs is known to be about 10 - 30% (1, 6 - 10). Neurologic manifestations of FEL are seizures, an altered level of consciousness, hemiparesis, nuchal rigidity, and ataxia (1, 6 - 12). The extent and incidence of CNS involvement in FEL is related to the duration of the illness. Mild involvement, consisting only of meningeal infiltration, is observed in patients with short survival, while more severe changes, with intraparenchymal involvement and necrotic lesions, are present in patients who survive for longer (7).

The characteristic histopathologic findings of CNS involvement are lymphohistiocytic leptomeningitis, perivascular and perineural lymphocytic infiltration of the cerebrum and cerebellum, gliosis and demyelination (2, 3, 5, 11 - 12). Takano et al. (4) reported that perivascular and vascular calcification and vessel occlusion due to subendothelial fibrosis were prominent in the basal ganglia, thalamus and dentate nucleus. Calcifications in the brain parenchyma manifest late in the evolution of the disease, and correspond, histologically, to mineralization of residual neurons and their processes adjacent to white matter necrosis (3).

Several neuroradiologic findings have been reported.

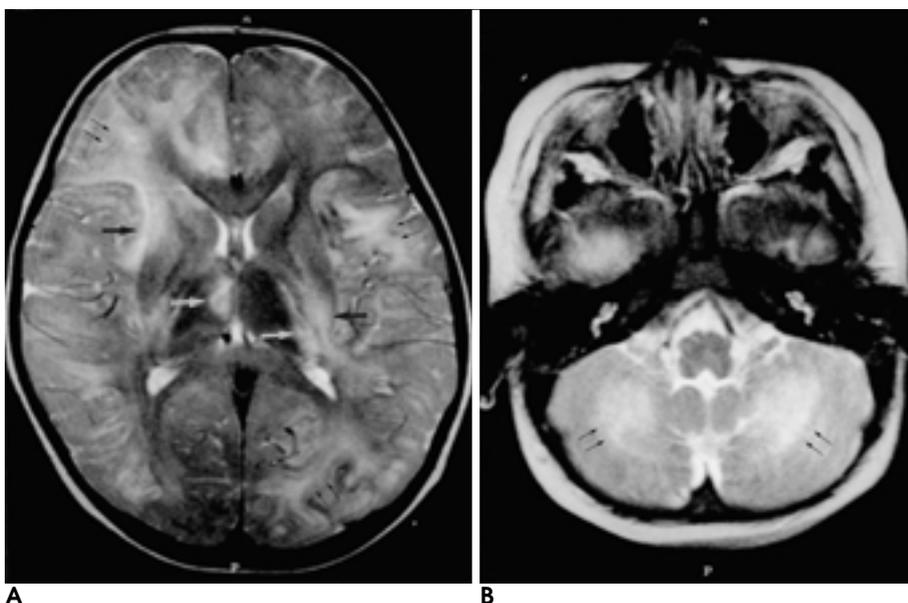


Fig. 4. Second follow-up brain MR T2-weighted images obtained about four months later show bilateral extensive high signal intensities in deep gray matter of thalami (white arrows) and basal ganglia (black arrows), subcortical and deep white matter, especially on the right frontal, left temporal and occipital (double small arrows) (A) and bilateral cerebellar white matters (double small arrows) (B).

Diffuse, nonspecific brain atrophy and low attenuated parenchymal lesions have been revealed by brain CT (2, 5), while MRI has revealed low signal intensity on T1-weighted images and high signal intensity on T2-weighted images of the gray and white matter of the cerebrum and cerebellum, including both basal ganglia and thalami (3, 5, 6).

Pathologically, white matter lesions correspond to demyelination and gliosis, and begin in the peritrigonal area, progressing, in severe cases, to the entire cerebral and cerebellar white matter (2 - 5). The focal lesion of the basal ganglia is known as perivascular infiltration of lymphohistiocytes. Gadolinium enhancement of the CNS lesion may be present, and most probably corresponds either to areas of active demyelination, with surrounding inflammation, or to ischemia.

Current therapy for FEL includes combined systemic VP-16 with steroids, and early aggressive CNS therapy with intrathecal methotrexate and cranial irradiation (13). The outcome of FEL is uniformly fatal; mortality is nearly 50% within one month of diagnosis, and 90% at four months (14). Relapses and progression of CNS disease lead to more severe neurological lesions and, ultimately, death within months. Our case also showed recurrent neurologic symptoms after four months, with extensive brain MR abnormalities.

Bone marrow transplantation, if performed soon after remission is induced, is thought to be the only available treatment option providing hope for a cure (6).

In conclusion, CNS involvement is common in FEL, and is characterized by rapidly progressing tissue damage affecting both gray and white matter. Abnormal signal intensity in the white matter, seen on T2-weighted images, and a focally hyperintense lesion involving both the gray and white matter, reflect the histologic changes which cause neuronal deterioration and death, gliosis, ischemia, and demyelination. Brain MR imaging findings correlate with CSF abnormalities and neurologic signs, and provide a means of assessing the severity of

the disease and recurrent lesions, and of monitoring the response to treatment.

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