Neurological Abnormality Could be the First and Only Symptom of Familial Hemophagocytic Lymphohistiocytosis: Report of Two Families

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To the Editor: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease which impacts many parts of the body including the digestive, circulatory, and respiratory systems. The central nervous system (CNS) can also be affected, particularly in patients with familial HLH-2 (FHL-2), responsible for approximately 20% of all FHL. FHL-2 is a result of mutations to the perforin 1 (PRF1) gene, which can occur at numerous sites on the gene.[1]

Studies demonstrate that CNS involvement, i.e., neurological symptoms, abnormal cranial magnetic resonance imaging (MRI), and/or cerebrospinal fluid (CSF), is indicators for a poor prognosis in HLH patients.[2] However, in some HLH patients, CNS impairment is the first and only symptom resulting in difficulties and delays for the diagnosis. Here, two HLH patients, who were initially misdiagnosed due to CNS impairment being the prominent clinical finding, are presented.

HLH was diagnosed after 5 months of investigations in a 3-year-old male patient. The patient suffered fevers, seizures, and vomiting and was diagnosed as encephalitis by the neurological department initially. Cranial MRI was performed and showed abnormal signals in his cerebral white-matter [Figure 1a]. The patient’s serum EBV-DNA was elevated to 2.51 × 10⁴ copies/ml and was given ganciclovir for antiviral treatment. Glucocorticoid was used to treat leukodystrophy. Three months later, the patient’s cranial MRI showed that the lesion progressed significantly [Figure 1b], and a whole-exome sequencing (WES) was performed. Five months after the first onset of the disease, he was referred to the hematology-oncology center. Since he suffered from fevers, seizures, hepatosplenomegaly, anemia, thrombocytopenia, hypertriglyceridemia, and hypofibrinogenemia, he was diagnosed with HLH. The WES showed PRF1 compound heterozygous mutations of c.1349G>A (p.T450M) and c.218C>T (p.C73Y), inherited from his father and mother, respectively. Unfortunately, the level of PRF1 was not determined before hematopoietic stem cell transplantation (HSCT). A retrospective review of the patient’s history revealed that he had a small decrease in blood cell number (particularly neutrophils) and splenomegaly during fevers when he was treated in neurological department at the beginning. The patients’ elder brother died of fevers, seizures, and vomiting at the age of 10 years, suggesting he might have had FHL-2. The HLH-2004 protocol was used for the treatment, and the patient had a partial remission after 4 weeks.[3] Intrathecal injection of dexamethasone and methotrexate was performed regularly. Two months after HLH-2004 treatment, HSCT was performed with a half-matched haploidal donor. The lesion seen on the MRI significantly improved but did not disappear [Figure 1c and 1d]. The patient appeared well at the last follow-up on June 30, 2018.

A 6-year-old female patient was admitted to the neurological department on July 28, 2015, with a complaint of “intermittent headaches, fevers, seizures, and unconsciousness for 2 days.” The patient had a Glasgow point of ten (eye-opening response: 4, verbal response: 2, and motion response: 4) with low muscular tension and negative pathologic reflex. An MRI showed extensive multifocal abnormal signaling in the gray matter, white matter, ependyma, and brainstem [Figure 1e], however, CSF was normal. The patient was diagnosed with acute disseminated encephalomyelitis and treated with immunotherapy including immunoglobulin and methylprednisolone. An MRI, at 4 months,
showed that the lesions had progressed. The patient had a low neutrophil count, and splenomegaly was detected, although a bone marrow smear was normal. The patient was diagnosed with CNS demyelinating disease and treated with continuous immunotherapy. The patient’s mouth dropped on the left after 1 month and was treated with immunotherapy periodically. The patient’s MRI then improved. Eight months later, the patient had seizures, vomiting, hypodynamia, blurred vision, and speech difficulties, and an MRI revealed that the lesions had progressed. Mannitol and a high dose of methylprednisolone were administered, which controlled the clinical symptoms. At the same time, her 45-day-old brother was diagnosed with FHL-2 (fever, hemocytopenia, hepatosplenomegaly, hypertriglyceridemia, and hyperferritinemia), with compound heterozygous mutations of c.1349C>T (p.Thr450Met) and c.853_855del (p. 285del) on PRF1. After an investigation, the same mutations were found in the female patient, and FHL-2 was confirmed. The level of PRF1 protein was low in both NK and CTL cells by 33% (normal range >81%) and below detection limits, respectively. Although the patient received intermittent immunotherapy, including methylprednisolone and immunoglobulin, HLH was diagnosed. The patient was treated using the HLH-2004 protocol, and partial remission after 4 weeks occurred. Meanwhile, the original nidus seen in the MRI lessened but did not disappear. Although c.853_855del (p.285del) is reported in the literature, its relationship with corresponding manifestations is unclear. Future studies need to investigate whether these mutations can result in CNS involvement.

Overall, patients who have CNS symptoms and extensive white-matter abnormality in cranial MRI, combined with mildly decreased blood cells and splenomegaly during fever should be observed closely. Early diagnosis and prompt treatment can result in a better prognosis for patients who are prone to misdiagnosis of other neurological diseases such as leukodystrophy.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s)/patient’s guardians has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the article. The patients/patient’s guardians understand that their names and initials will not be published and due efforts will be made to conceal the identity of the patient, although anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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