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Case Report

# Neurological symptoms of familial hemophagocytic lymphohistiocytosis type 2

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Hemophagocytic lymphohistiocytosis with central nervous system involvement is caused by inflammatory factor storms. The inflammatory factors invade the blood-brain barrier and further infiltrate brain tissue resulting in associated neurological and/or psychiatric symptoms in hemophagocytic lymphohistiocytosis with central nervous system involvement patients. This case report is based on a 14-year-old male patient who experienced intermittent dizziness and blurred vision about five years before admission as well as lower limb weakness and unstable walking approximately three years before admission. His brain MRI showed abnormal signals in the bilateral cerebellar hemisphere and vermis, right occipital lobe, and bilateral basal ganglia. The cerebrospinal fluid examination revealed an increase in nucleated cells, mainly monocytes, and elevated protein. He had no typical manifestation of hemophagocytic lymphohistiocytosis in the early stage, such as fever, cytopenia, or hepatosplenomegaly. He was misdiagnosed with meningoencephalitis or tuberculous meningitis. Perforin gene detection revealed a mutation in the PRF1 gene. The final diagnosis of type 2 familial hemophagocytic lymphohistiocytosis was made based on the neurological symptoms and genetic test. The possibility of hemophagocytic lymphohistiocytosis needs to be considered in patients with unexplained central nervous system symptoms, even if the patient does not have typical hemophagocytic lymphohistiocytosis symptoms, such as fever, cytopenia, or hepatosplenomegaly. We present the neurological symptoms of familial hemophagocytic lymphohistiocytosis type 2.

*Keywords*

Familial hemophagocytic lymphohistiocytosis type 2; central nervous system; neuroimmunology

## 1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease. Defects in cytotoxic function are the essence of primary HLH. HLH with central nervous system involvement (CNS-HLH) patients then exhibit relevant neurological and/or psychiatric symptoms. These symptoms can present at the first onset or occur at a later stage of HLH. This article reports a case of primary HLH with central nervous system symptoms as the first and foremost clinical manifestations.

HLH is a rare disease. Depending on different causes, it is usually classified into two categories: primary/hereditary and secondary/acquired. Primary HLH has a well-defined family inheritance and/or genetic defect. Approximately 70-80% of patients develop the disorder within the first year of life, and 90% develop it within the first two years of life. However, with the advancement of molecular diagnostic techniques, it has been confirmed that primary HLH can also occur in adolescence or adulthood (Zhang et al., 2011). This patient had symptom onset at the age of 8 years and 9 months, and the main signs were mental and neurological symptoms. He had no typical manifestation of HLH, such as fever, cytopenia, hepatosplenomegaly, or abnormal liver function. The onset of this case was not with the primary HLH high-incidence age, and the patient had no related family or and typical HLH systemic performance. The disorder was easy to misdiagnose.

The nature of primary HLH is a defect in cytotoxic function. Familial hemophagocytic lymphohistiocytosis type 2 (FHL-2) is located on chromosome 10q21-22. The related defect genes are PRF1 and encoding perforin protein, accounting for 13-50% of FHL (Gholam et al., 2011). When the PRF1 gene is mutated, the expression, activity, and stability of perforin decrease. At this time, the damaged perforin cannot form a pipeline on the target cell membrane, resulting in the impaired killing of target cells by the attacking cells and accumulating a large number of inflammatory factors, which leads to HLH. In this patient, the expression rate of perforin in Natural Killer Cells (NK cells) and Cytotoxic T lymphocyte (CTL) was below the lower limit, and a further gene test found the mutation site of the perforin gene, as shown in Table 1. Based on these findings combined with fever, decreased NK cell activity, and hemophagocytosis found by bone marrow puncture, the patient was finally diagnosed with type 2 familial hemophagocytic lymphohistiocytosis, according to the HLH-2004 diagnostic criteria, and the central nervous system was involved.

CNS-HLH can occur at the onset of the disease, during treatment, after treatment, and when the disease relapses. It has been reported that 30-73% of HLH patients have central nervous system involvement (Trottestam et al., 2011; Yang et al., 2010). However, reports of neurological symptoms as the first symptom of

Table 1. Perforin gene mutation site in the patient

| Gene | Chromosome position | Nucleic acid change (exon number) | Amino acid change (variant number) | RS No. | MAF | ACMG Pathogenicity level | Proband (male) | Father | Mother (normal) | Related diseases and genetics |
|---|---|---|---|---|---|---|---|---|---|---|
| PRF1 | Chr10:72360594 | c.65 (exon2) de1C | p.P22Rfs*29 (NM_001083116) | rs761651233 | 0.0001 | Pathogenic | heterozygote | Unknown | Wild type | Hemophagocytic lymphohistiocytosis |
| | Chr10:72360156 | c.503 (exon2) G > A | p.S168N (NM_001083116) | rs779399414 | 0.0003 | Likely pathogenic | heterozygote | Unknown | heterozygote | type 2 (603553), AR |

HLH are rare. These cases require close clinical attention. Akyol et al. (2019) reported a patient bearing a homozygous truncation mutation in UNC13D (c.2650C > T.p.Gln884Ter) presented with central nervous system involvement and skin rash. Giardino et al. (2017) reported two brothers with atypical, late-onset HLH in which whole-exome sequencing revealed a homozygous pathogenic UNC13D variant. In the second brother, a progressive neurological deterioration was observed. The clinical manifestations of CNS-HLH are not specific and are often related to the affected system and the range and extent of its involvement. They may also show mental changes, including mood disorders and delirium. This patient started with psychiatric symptoms of dizziness, blurred vision, and mood changes. The neurological symptoms gradually appeared in the later stage, manifesting as dyskinesia of the extremities, difficulty in raising the head and turning over, coughing during drinking, unclear speech, dysuria, and seizures. He was seen by the neurology departments of many hospitals and was misdiagnosed with meningoencephalitis and tuberculous meningitis. He received anti-infective and anti-tuberculosis treatment. The symptoms did not improve but got worse. Then, gamma globulin, methylprednisolone, and cyclosporine were administered and significantly relieved the symptoms.

HLH may be associated with abnormal findings in the cerebrospinal fluid (CSF), such as increased cells, increased protein, and/or hemophagocytosis. Increased CSF cells are seen in 10-47% of patients with HLH (Trottestam et al., 2011; Yang et al., 2010). Elevated levels of CSF protein are seen in 11-41% of patients with HLH (Trottestam et al., 2011). The protein level often mildly increases (500 to 1,000 mg/L; normal range, 150-400 mg/L) (Yang et al., 2010). HLH neuritis should be suspected in children with encephalopathy with increased CSF protein. It has been reported that hemophagocytosis exists in 91% of HLH patients' meninges. It is less common in CSF (39%) (Horne et al., 2017). Multiple CSF exams were conducted on this patient. The results revealed an increase in nucleated cells, which were mainly monocytes and mildly elevated protein. These results were consistent with CNS-HLH CSF abnormalities.

Brain magnetic resonance imaging (MRI) is the preferred imaging exam for suspected CNS-HLH patients. MRI findings for CNS-HLH include diffuse leptomeningeal enhancement and perivascular enhancement due to infiltration of tissue cells and lymphocytes; T2-weighted high-signal white matter degeneration of the cerebrum, cerebellum, and spinal cord; annular enhancement of cerebrum parenchymal necrosis; and a diffuse cerebrum and cerebellar atrophy (Deiva et al., 2012). This patient's brain MRI showed abnormalities in the bilateral cerebellar hemisphere and vermis, right occipital lobe, and bilateral basal ganglia. These results indicated that the patient had brain parenchymal injury. Özdemir et al. (2006) reported a 19-month-old boy with CNS involvement. Brain MR imaging revealed non-specific confluent white-matter involvement. On MRS major metabolite ratios were found as: NAA (N-acetylaspartate)/Cho (choline) 1.85, NAA/Cre (creatine) 2.40, and Cho/Cre 1.29, which did not statistically differ from the control group ($P > 0.05$).This presence of lactate indicates that the normal cellular oxidative respiration is no longer in effect and that carbohydrate catabolism is taking place. Unfortunately, the patient did not receive proton MR spectroscopy.

CNS-HLH is defined as the presence of neurological symptoms, CSF cell and/or protein abnormalities, or brain parenchyma or meningeal abnormalities in cranial imaging (Akima and Sumi, 1984). Although the definition of CNS disease remains controversial, there is a consensus that activated lymphocytes and macrophages infiltrate the meninges and brain. CNS-HLH is divided into three pathological stages: stage I, meningitis; stage II, perivascular infiltration; stage III, massive tissue infiltration, vascular destruction, and tissue necrosis (Akima and Sumi, 1984). The symptoms and MRI abnormalities may improve after treatment. The neurological symptoms are not included in the HLH-2004 diagnostic criteria. However, the possibility of HLH needs to be considered in patients with unexplained central nervous system symptoms, even if the patient does not have typical HLH symptoms, such as fever, cytopenia, or hepatosplenomegaly. Early diagnosis and treatment are important to prevent irreversible CNS injury and improve prognosis.

## 2. Background

The patient is a 14-year-old male. Five years ago (at 8 years and 9 months of age), he experienced intermittent dizziness and blurred vision without obvious causes. The symptoms were accompanied by emotional symptoms, which manifested as mental irritability and decreased academic performance. He had no fever, nausea, or vomiting. No treatment was given. About half a year before admission, the above symptoms resolved spontaneously except occasional dizziness. Three years ago (at 10 years and 8 months of age), the patient began to experience lower limb weakness and unstable walking without obvious causes. The symptoms gradually became worse within two weeks before admission, and he could not stand up from a squatting position. He could not ascend or descend stairs by himself. He also had increased dizziness, nausea, vomiting, and anorexia. The brain MRI showed abnormal signals in the bilateral cerebellar hemisphere and vermis, right occipital lobe, and bilateral basal ganglia. The lumbar puncture results were as follows: pressure, 165 mmH2O; nucleated cells, 767 × 106/L; mononuclear cells, 89%; protein, 1,262

mg/L (normal value, $<$ 450 mg/L); glucose, 3.83 mmol/L (normal range, 2.8-4.5 mmol/L); chlorine, 121 mmol/L (normal range, 120-132 mmol/L). Possible diagnoses of meningoencephalitis and acute disseminated encephalomyelitis were considered. After anti-infective, antiviral, and methylprednisolone treatments, the symptoms improved significantly, and he recovered to an almost normal state. However, the symptoms reappeared after the reduction and discontinuance of the methylprednisolone (the entire course of treatment was about 20 days).

Lumbar puncture was performed again, and the result was as follows: pressure, 130 mmH2O; nucleated cells, 116 $\times$ 106/L; mononuclear cells, 80%; protein, 1,372 mg/L; glucose, 2.8 mmol/L; chlorine, 116 mmol/L. The adenosine deaminase (ADA) content of cerebrospinal fluid (CSF) was 1 U/L (normal range, 4-18 U/L). The CSF virus test: EBV-DNA (-), CMV-DNA (-), Herpes simplex type I-IgG (-), Herpes simplex type I-IgM (-), Herpes simplex type II-IgM (-). Hence, a tentative diagnosis of tuberculous meningitis was given. Anti-tuberculosis treatment with isoniazid, rifampicin, and pyrazinamide was administered. However, the patient's condition became worse. His lower limbs gradually became weaker, and he could not walk. He also had progressing upper limb dyskinesia, which was manifested through difficulty in using chopsticks. He even had difficulty in raising his head and turning over. He also had symptoms such as intermittent dizziness, nausea, vomiting, blurred vision, coughing during the drinking of fluids, speech ambiguity, and dysuria.

Two years ago, the patient began to have seizures intermittently. The seizures were characterized by eye flipping, mouth smacking, and right-hand rhythmic twitching, lasting for about 3-4 minutes. The patient also had an intermittent fever of up to 38.5 $^{\circ}$C. He received anti-infection and glucocorticoid therapy in a local hospital. The patient had worsened weakness and could not walk. The patient's intelligence scale results were as follows: total intelligence, 69 points; verbal reasoning, 82 points; perceptual reasoning, 67 points. The thyroid function was normal, and thyroid antibodies were negative. The adrenocorticotropic hormone (ACTH) level was 2.61 pg/mL, cortisol was 2.39 $\mu$g/dL, and serum testosterone was 0.1 ng/mL. The children's endocrinology consultation determined that he had not yet shown puberty development. The complete blood counts (CBCs) results were as follows: White blood cell (WBC), 2.91 $\times$ 109/L; Neutrophils, 0.76 $\times$ 109/L; Hemoglobin (Hgb), 126 g/L; Platelet (PLT), 143 $\times$ 109/L. Oligoclonal regions of blood, cerebrospinal fluid, and neuron surface antibodies and AQP4 antibodies of blood and cerebrospinal fluid were negative.

The brain MRI (see Fig. 1) showed multiple abnormalities in the bilateral semi-oval center, radial crown, lateral ventricle, corpus callosum, bilateral posterior limbs of the internal capsule, and bilateral white matter areas of the frontal, apical, and occipital regions, bilateral cerebellar hemispheres, and the brainstem. The cerebellum had multiple old bleeding sites. The following possible diagnoses were considered: central nervous system inflammatory demyelination and leukopenia. High doses of gamma globulin and methylprednisolone and 100 mg/day (3.3 mg/kg/d) cyclosporine were given. The patient's dizziness, nausea, and walking ability improved. The fine movements of the upper limbs were still weak. The dysarthria and dysphagia were improved. The patient had occasionally delayed urination, yet he had no fever. However, the patient's symptoms recurred after the glucocorticoid withdrawal. The history and family history showed no unusual findings.

Physical examination showed the following results: Body temperature, 36.5 $^{\circ}$C; Pulse rate, 76/min; Respiration rate, 18/min; Blood pressure, 115/70 mmHg. The facial, limb and back hair increased; the lymph nodes were not swollen; there was no hepatosplenomegaly; the patient was alert and oriented; the vision was 0.8 for both eyes, and the speech was slow; the patient could walk with help, but the gait was unstable; muscle strength was 5/5 in the upper limb, 3/5 in the proximal lower limbs, and 4/5 in the distal muscle; the lower limbs' tension was high, and muscle volume was low; the bilateral knee reflex was active; the ankle clonus was positive; bilateral Babinski and Hoffmann signs were positive, and meningeal irritation was negative. The result of NK cell activity was 14.11% (normal range: $\geq$ 15.11%). Occasional hemophagocytosis was seen in the bone marrow smear. The sCD25 was 976 pg/mL ( $<$ 6,400 pg/mL), ferritin was 33.4 ng/mL, and triglyceride was 2.05-2.08 mmol/L. EBV-DNA in the blood cells and plasma were both below the lower limit. An abdominal ultrasound showed that the spleen was 4.0 cm thick and about 11.9 cm long. Perforin gene detection revealed compound heterozygous mutations in exon 2 of the perforin gene (PRF1) on chromosome 10 (c.65 de1C and c.503 G $>$ A) (Table 1). This mutation was pathogenic for autosomal recessive familial hemophagocytic lymphohistiocytosis-2 (FHL-2). A perforin protein test showed that both NK cell and CTL levels were below the lower limit. The final diagnosis of FHL-2 with central nervous system involvement was made. The patient was subsequently given a weekly intrathecal injection of methotrexate (10 mg) and dexamethasone (5 mg). Allogeneic hematopoietic stem cell transplantation is currently planned.

## 3. Discussion

The final diagnosis of type 2 familial hemophagocytic lymphohistiocytosis was made based on the central nervous system symptoms such as multiple abnormalities in the bilateral semi-oval center, radial crown, lateral ventricle, corpus callosum, bilateral posterior limbs of the internal capsule and bilateral white matter areas of the frontal, apical, and occipital regions, bilateral cerebellar hemispheres, and the brainstem. The cerebellum presented with multiple old bleeding sites. What are the neuroimmunological causes of these systems? The genetic mutations of FHL impair the function of Natural Killer Cells (NK cells) and Cytotoxic T cells by interfering with the perforin gene or genes important in the exocytosis of cytotoxic granules. These genes are essential to apoptosis and play an important role in down-regulating the immune response (Horne et al., 2017). Dysfunction in this pathway leads to histiocyte proliferation and hypercytokinemia (Meeths et al., 2015), which cause end-organ damage. The inflammatory cells can also cause CNS involvement by crossing the blood-brain barrier (Gratton et al., 2015). Studies have shown that macrophages and activated T lymphocytes can infiltrate the meninges and brain parenchyma along the perforating vessels, while inflammatory cells infiltrating CNS can secrete cytokines and other neurotoxic factors, leading to demyelination changes. Also, inflammatory cell infiltration may activate normal

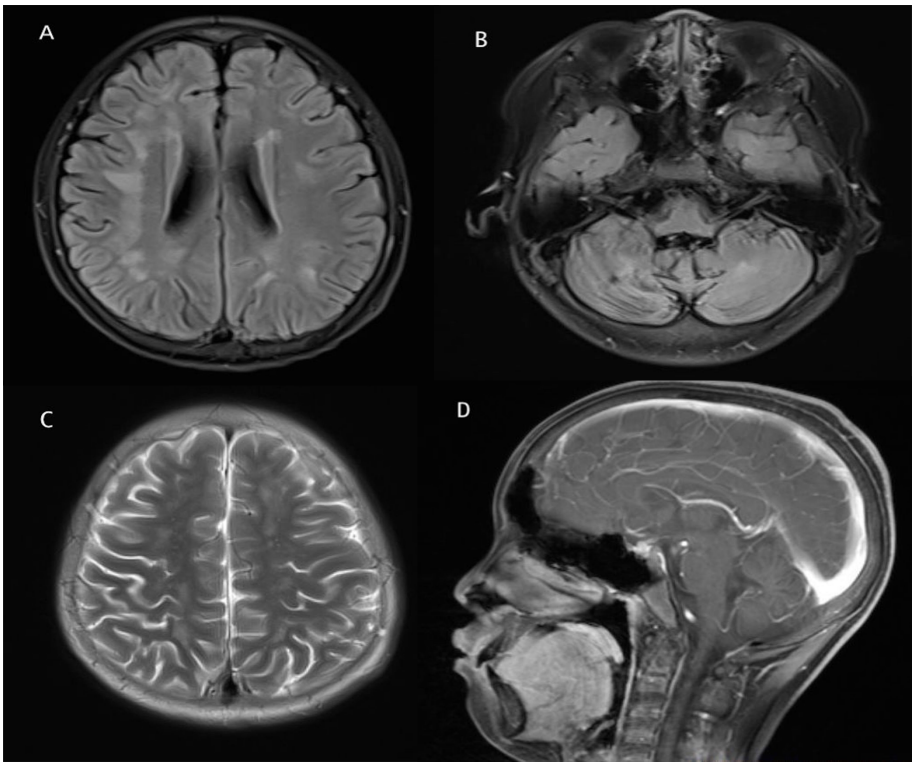


Figure 1. The brain MRI showed abnormal signals in the case of FHL-2. White matter lesions; bilateral cerebellar hemisphere abnormal signals indicated old hemorrhagic sites; bilateral leptomeninges seemed to be slightly thickened with an enhanced signal. (A: Multiple patch-like abnormal signals in the white matter of the bilateral frontal-parietal and lateral ventricles. T2W1 showed high signal and blurred borders. B: Point-like and small-patch abnormal signals could be seen in the bilateral cerebellar hemisphere. T2W1 FLAIR showed low signal, and DW1 also showed a weak signal. C: T2 enhanced scan showed a slight thickening with an enhanced signal of the partial bilateral leptomeninges. D: T1 showed slightly thickened and enhanced leptomeninges.)

brain macrophages (microglia) and astrocytes, which in turn secrete neurotoxic amino acids and free radicals, resulting in CNS damage. With the progression of the disease, inflammatory cells infiltrate into the perivascular space, causing reactive proliferation of astrocytes and microglia, followed by infiltration of brain tissue, especially white matter involvement and localized necrosis (Henter and Nennesmo, 1997). This is consistent with the pathological features of CNS-HLH.

## Abbreviations

ACTH: adrenocorticotropic hormone; ADA: adenosine deaminase; CBCs: complete blood counts; CNS: central nervous system; CSF: cerebrospinal fluid; CTL: Cytotoxic T lymphocyte; FHL-2: Familial Hemophagocytic Lymphohistocytosis Type 2; Hgb: Hemoglobin; HLH: Hemophagocytic lymphohistiocytosis; MRI: Magnetic resonance imaging; NK: Natural killer; PLT: Platelet; WBC: White blood cell.

## Authors' contributions

JSW collected data and wrote the manuscript. HZT revised the manuscript. LW and XKW prepared the clinical data. ZW designed the study.

## Ethics approval and consent to participate

The University approved this study. Written informed consent was obtained from this patient for publication of the case report and any accompanying images.

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## Conflict of Interest

The authors declare no competing interests.

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