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CASE REPORT

Isolated Central Nervous System FHL3 in an Asian Pediatric Patient: A Case Report and Literature Review

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Abstract: Familial hemophagocytic lymphohistiocytosis (FHL) is a genetic inflammatory response syndrome involving many organs. Central nervous system (CNS)-isolated FHL is a rare, neuroinflammatory condition. Here, we report a case of CNS-isolated FHL3. Brain magnetic resonance imaging (MRI) showed CNS lesions mimicking chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids and multiple sclerosis. Whole-exome sequencing (WES) demonstrated likely pathogenic, parentally inherited homozygous variants of *UNC13D* (c.2588G>A, p.G863D). Neuropathological examination of a brain biopsy specimen revealed lymphocyte infiltration. Reduced levels of CD107a were also observed. CNS-isolated FHL was final diagnosis. The patient's clinical and radiological condition improved after allogeneic hematopoietic stem cell transplantation (HSCT). A study of five isolated CNS FHL3 cases (onset: 7–31 years; three females, one male, and one unknown) identified the hotspot variants c.2588G>A and c.2346_2349del. Possible triggers include the Epstein-Barr virus and herpes simplex virus. Common CNS symptoms included headache, seizures, diplopia, and ataxia (3/5 each). MRI revealed multifocal cerebral/brainstem/spinal cord lesions. Cerebrospinal fluid revealed nonspecific inflammation. Biopsies revealed T-cell predominant lymphocytic infiltration (3/3). Reduced CD107a expression was observed in four patients. Two developed systemic hemophagocytic lymphohistiocytosis (HLH). Steroids (5/5) and intravenous immunoglobulin (4/5) were the primary treatments and HSCT (4/4) achieved good outcomes. One died of HLH. To date, homozygous variants of *UNC13D* (c.2588G>A, p.G863D) have not been reported in CNS-isolated FHL. Symptoms and brain MRI of CNS-isolated FHL simulate some neuroinflammatory diseases; however, WES and functional analysis may be useful for distinguishing between them. HSCT might be an effective therapeutic strategy.

Keywords: familial hemophagocytic lymphohistiocytosis, central nervous system, *UNC13D*, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids, allogeneic hematopoietic stem cell transplantation

Background

Familial hemophagocytic lymphohistiocytosis (FHL) is a primary systemic inflammatory response syndrome triggered by an excessive genetic-related immune disorder.[1] Based on different pathogenic genes and copy number variations (CNV), FHL is divided into various types, including FHL1 (9q21.3–22), FHL2 (*PRF1*), FHL3 (*UNC13D*), FHL4 (*STX11)*, and FHL5 (*STXBP2*). According to the 2004 diagnostic criteria, involvement of the central nervous system (CNS) can be the primary clinical feature of FHL.[2] Pathophysiological process of CNS involvement in FHL is not well understood. It was hypothesized that peripheral cytokines storm impairs blood-brain barrier and drives CNS inflammatory response. While another opinion considered that inflammatory storm caused by abnormal activation of immune cell originates within central nervous system because of cases of CNS-isolated FHL.[3] As depicted by Blincoe et al,[4] CNS-isolated FHL is rare, but exists. The scarcity of reported cases brings challenges to the recognition of clinical features and early initiation of proper therapies. Misdiagnosis of CNS inflammatory diseases occurs when the clinical presentation, neuroimaging features, and biopsy findings are ambiguous. As FHL is a genetic-related disease, next-generation sequencing can be a powerful tool for disclosing the distinction between atypical neuroinflammatory diseases and the

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phenotype-genotype relationship of FHL, providing a better piece of evidence for therapeutic strategies. Here, we describe and discuss in detail a case of FHL with CNS-isolated presentations due to likely pathogenic variants of *UNC13D* and perform a literature review of CNS-isolated FHL3 for better understanding.

Case Presentation

A 13-year-old Chinese female from a non-consanguineous family presented with central nervous system manifestations at the age of 10 years. She presented with headache, visual problems, vomiting, and altered mental status without fever. Physical examination revealed an altered level of consciousness (Glasgow Coma Scale score of 9), normal muscle tone, and a bilateral positive Babinski sign. The liver and spleen were both normal in size. Brain magnetic resonance imaging (MRI) revealed widespread white matter lesions across the cerebrum (Figure 1A). The patient was then diagnosed with immune-related encephalitis. The patient responded to immediate treatment with intravenous immunoglobulin (IVIG, 2 g/kg), intravenous methylprednisolone (IVMP, 30 mg/kg over 3 days), and oral prednisolone (2 mg/kg/d) which was gradually decreased. It took her three days to become fully conscious and three months for almost normalization of the brain MRI.

Following tapering of oral prednisolone for nearly six months, her symptoms recurred. The patient presented with diplopia, an abnormal gait, and shaky hands. Brain lesions on MRI expanded to the medulla oblongata and the cervical spinal cord (Figure 1B). Neither positron emission tomography (PET)/computerized tomography (CT) of the whole body nor bone marrow aspiration could detect anything indicative of the tumor. She achieved a second complete remission in terms of both symptoms and CNS imaging after receiving IVIG and IVMP followed by oral prednisolone. Nevertheless, the patient relapsed seven months later when the oral prednisolone dose was tapered. Thereafter, the patient responded only partially to immunotherapy (either a combination of IVIG and IVMP, followed by prednisolone or other immunosuppressants, including azathioprine and mycophenolate mofetil). The MRI lesions showed a parallel dynamic of fluctuation, mirroring the onset and remission of clinical symptoms. Interestingly, some of the lesions were close and

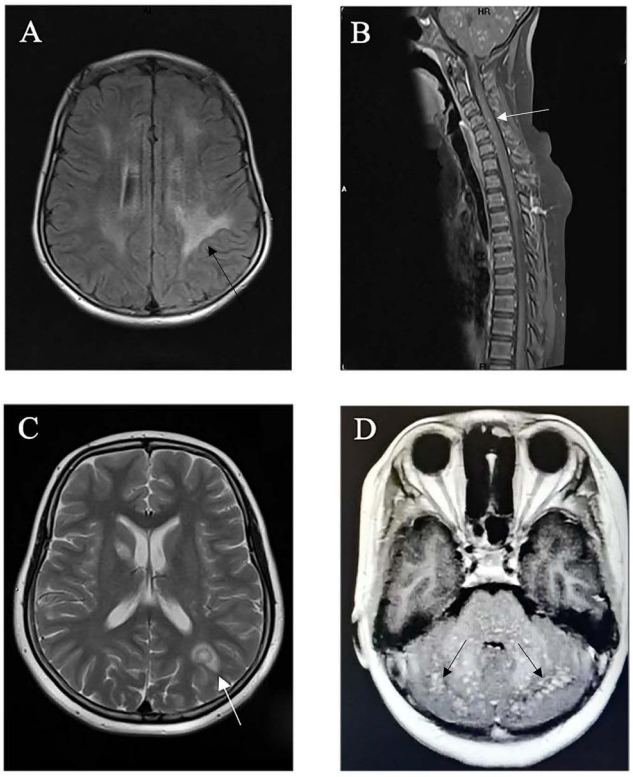

Figure 1 Brain images of the patient before and after HSCT. (**A**–**D**) Brain images before HSCT. (**A**) Widespread white matter lesions across the cerebrum (black arrow). (**B**) Lesions expanding to medulla oblongata and cervical spinal cord (white arrow). (**C**) Tumefactive lesions (white arrow). (**D**) CLIPPERS-like lesions (black arrow).

perpendicular to the lateral ventricles, whereas others appeared as tumefactive lesions that misled us to the diagnosis of multiple sclerosis (MS) (Figure 1C). A diagnosis of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) was also considered because of the presence of persistent subacute pontocerebellar dysfunction and homogenous gadolinium-enhancing nodules in the pons and cerebellum improved by corticosteroids (Figure 1D).

Routine blood examination results were normal during the disease course, with no pancytopenia, hypertriglyceridemia, or hypofibrinogenemia. Rheumatological diseases and tumors were excluded from related tests. Serous Epstein-Barr virus (EBV) DNA copies detected by polymerase chain reaction were negative and herpes simplex virus (HSV)-1-IgG was positive. The predominant cells in the cerebrospinal fluid (CSF) were leukocytes (14×10^6/L). A CSF examination revealed no oligoclonal bands. Blood and cerebrospinal fluid examinations were negative for antibodies related to autoimmune encephalitis and inflammatory demyelinating diseases. Bone marrow aspiration revealed no hemophagocytes. Approximately three years after the onset of the disease, when the lesions on MRI appeared to be out of control by the routine immunotherapies mentioned above, a brain biopsy was performed. Neuropathology of the brain biopsy showed that vessels were surrounded by numerous lymphocytes, in particular T cells, as well as a few macrophages, together with astrogliosis and a Ki-67 index of 10%, suggesting possible lymphoproliferative diseases (Figure 2). Whole-exome sequencing revealed inherited parental homozygous variants of *UNC13D* (c.2588G>A, p.G863D), which were confirmed by Sanger sequencing (Figure 3). The predictive value of PolyPhen-2 was 1.000 (probably damaging) and the combined annotation dependent depletion (CADD) score was 25.8. The minor allele frequencies for *UNC13D* (c.2588G>A) were 0.0002907 and 0.003710 in the East Asian population. According to American College of Medical Genetics and Genomics (ACMG) guidelines, this inherited homozygous variant was considered likely pathogenic (PM2 +PM3+PP3). Reduced CD107a expression in natural killer (NK) cells was detected (Δ2.27%, reference range > 10%) using flow cytometry, indicating the incapability of degranulation (Figure 4). Therefore, CNS-isolated FHL was final diagnosis of this patient.

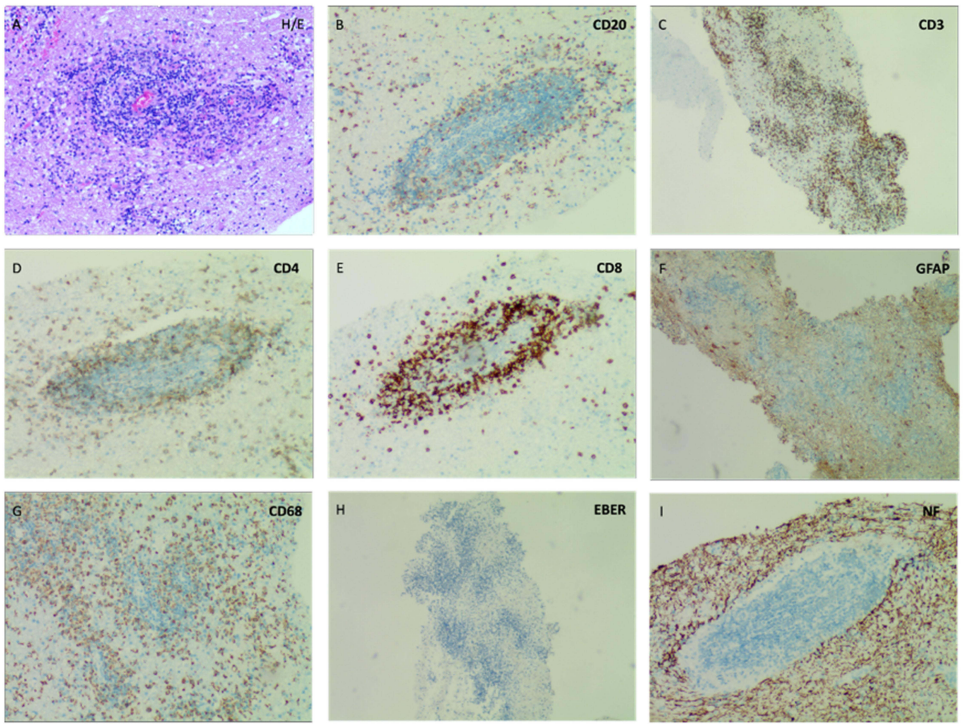

Figure 2 Neuropathology of the patient. (**A**) Brain biopsy showed perivascular lymphocytic inflammation. (**B**–**I**) Immunohistochemistry results: (**B**) CD20 staining demonstrated scattered B lymphocytes, (**C**–**E**) Intense T lymphocytes infiltration, (**F** and **G**) Glial fibrillary acidic protein (GFAP) and CD68 unveiled reactisuppl ve astrogliosis and microgliosis, (**H**) Negative in situ hybridization of Epstein-Barr virus early RNA-1 (EBER) pointed to no sign of EBV infection, and (**I**) Nerve fiber (NF) stanning showed intact preserved axon. H/E = hematoxylin and eosin. Magnification: ×40 objective.

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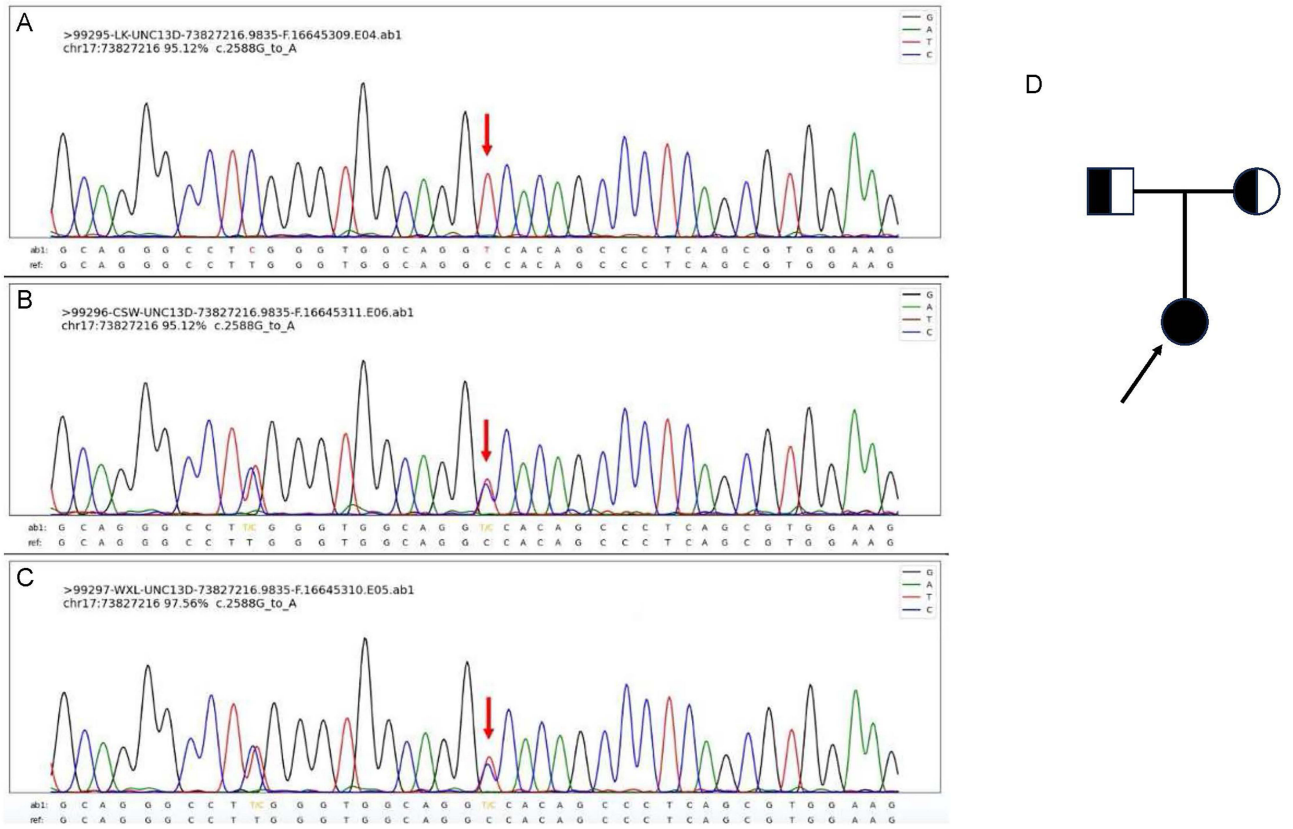

Figure 3 Sanger sequencing and family map of the patient. (**A**–**C**) Sanger sequencing demonstrated inherited homozygous variants of *UNC13D* gene (c.2588G>A, p.G863D). (**A**) Sanger sequencing of proband. (**B**) Sanger sequencing of mother of proband. (**C**) Sanger sequencing of father of proband. Red arrows indicate changes of nucleotide. (**D**) Family map of the patient. Black arrow indicates proband. The parents are asymptomatic carriers of the point mutation.

Allogeneic hematopoietic stem cell transplantation (HSCT) was performed four months after the final diagnosis, and hematopoietic stem cells were obtained from a matched unrelated donor. Conditioning included thiotepa, etoposide, busulfan, cyclophosphamide (CTX), and anti-thymocyte globulin. After HSCT, cyclosporine A(CsA) and methotrexate (MTX) were administered for graft-versus-host (GVHD) and CsA was tapered within six months. During follow-up 4 months post-HSCT, the patient showed dramatic relief from CNS symptoms, with a chimerism index of 99.85%. The latest brain MRI showed fewer lesions (Figure 5A–5D). Unfortunately, the patient had pancreatitis at the last follow-up, and whether this was a post-HSCT complication and/or protopathy remains unknown.

Literature Review

Table 1 summarized clinical characteristics, treatment and outcome of patients with isolated central nervous system FHL3. Five patients with a CNS-isolated FHL3 were included. The age of onset ranged from seven to 31 years. Three of them were female and one was male. Two patients were from Europe (United Kingdom and Germany), two patients came from United States and the rest one was Chinese. The median time from onset to diagnosis was 36 (6–72) months. Possible hotspot variant sites were c.2588G>A (3/10) and c.2346_2349del (3/10). Possible triggers include the Epstein-Barr virus and herpes simplex virus. The predominant CNS presentations were headaches (3/5), seizures (3/5), diplopia/double vision (3/5), and gait abnormality/ataxia/imbalance (3/5). MRI revealed multifocal lesions in the cerebrum (5/5), brainstem (3/5), spinal cord (3/5), and cerebellum (2/5). No specific patterns were found in the CSF, which was comprised of elevated leukocytes, neopterin, and positive oligoclonal bands. Three patients underwent biopsy, and neuropathology revealed T-cell-predominant lymphocytic infiltration (3/3). Functional tests revealed reduced CD107a expression in four patients (4/4). Two patients developed systemic hemophagocytic lymphohistiocytosis, while the other two did not until the last follow-up visit. All patients were diagnosed with acute/chronic neuroinflammatory disease and

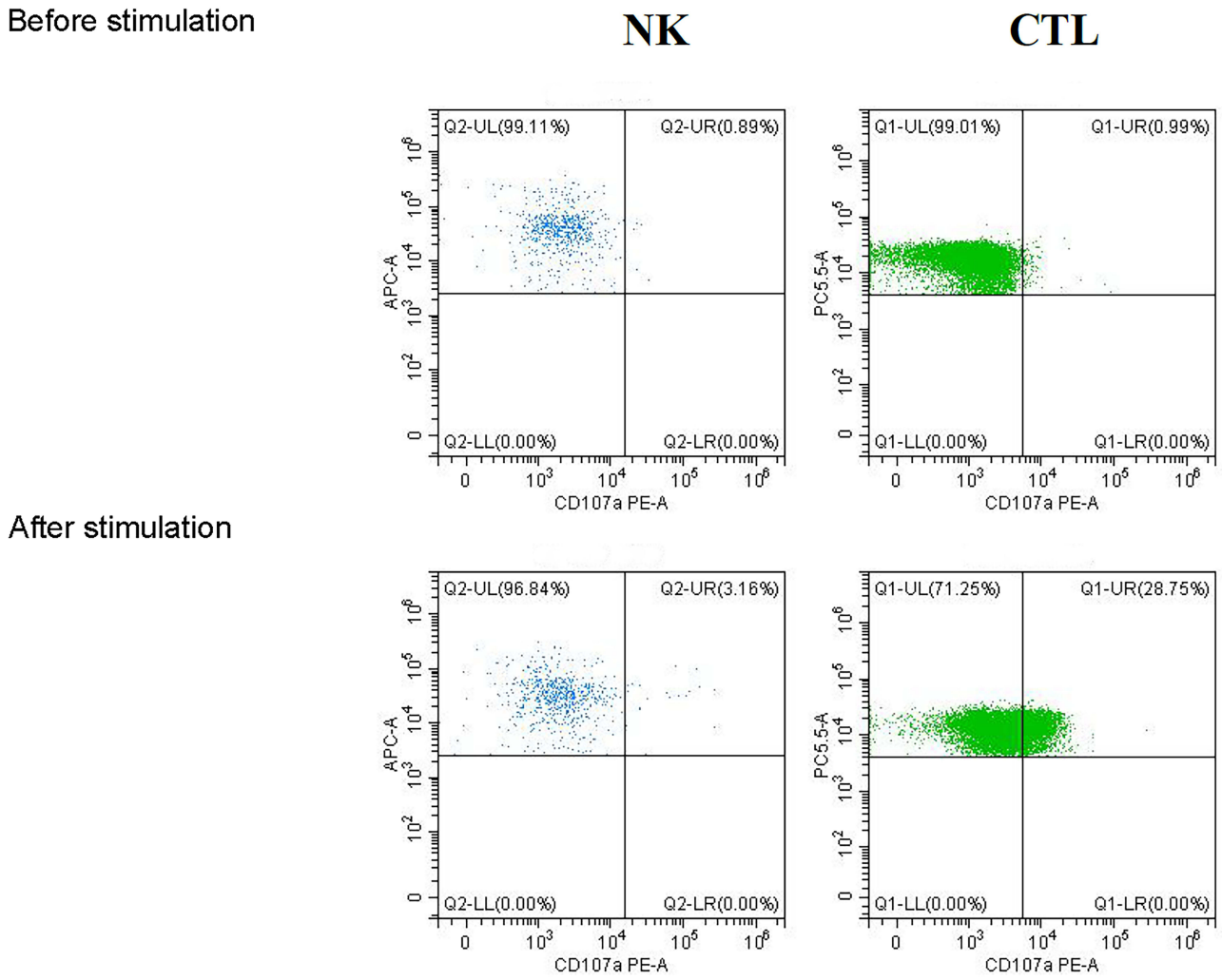

Figure 4 Flow cytometry of CD107a expression in natural killer (NK) cells and cytotoxic T cell (CTL) before and after stimulation.

three of them were considered to have CLIPPERS. Steroids (5/5) were the most used immunotherapy, followed by IVIG (4/5). Other immunosuppressive medications included rituximab, infliximab, mycophenolate mofetil, azathioprine, cyclosporine A, and cyclophosphamide. Three patients showed clinical and radiological improvements, but all of them relapsed. Four patients underwent HSCT and all achieved good outcomes. One patient died of systemic hemophagocytic lymphohistiocytosis.

Discussion

Herein, we report a rare case of FHL3 presenting with isolated neuroinflammatory features without systemic manifestations, even when combined with previous reported cases.[5–10] We also summarized the clinical characteristics of CNS-isolated FHL3 for better understanding.

The main symptoms include headache, seizures, diplopia, and ataxia. These nonspecific CNS symptoms cannot be directly diagnosed. Misdiagnosis can be further maximized by using a combination of brain MRI findings. In general, brain lesions on MRI of CNS-isolated FHL can spread symmetrically or asymmetrically across the cerebrum, cerebellum, brainstem, and spine, especially in the cerebrum and cerebellum,[4] which are nonspecific features compared with other CNS inflammatory demyelinating diseases. In our case, MRI lesions once resembled those of MS along with tumefactive lesions,[11] but they did not completely meet the 2017 revisions of the McDonald criteria.[12] The diagnosis of CLIPPERS

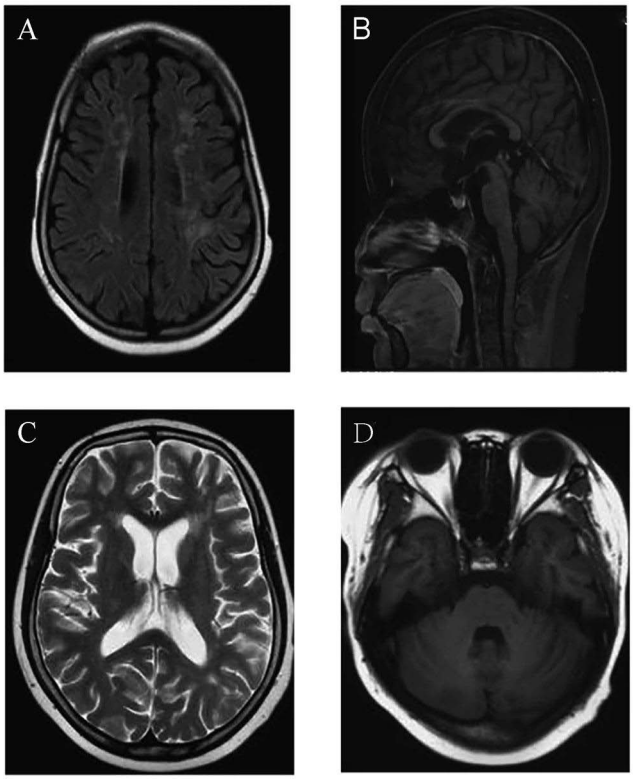

Figure 5 Brain images after four months of HSCT. After HSCT, lesions gradually disappeared (**A**–**D**).

was also considered in three patients, given the homogenous gadolinium-enhancing nodules in the pons and cerebellums.[8,13]

Since FHL still adheres to the 2004 diagnostic criteria,[2] and CNS involvement was not diagnosed by pathology, neuropathology is rare for CNS-isolated FHL. Therefore, specific mechanism is not well understood. In our case, perivascular lymphocyte infiltration was observed as previous reports.[6,8] It was inferred that abnormal activation of immune cells in the brain triggered by infectious or non-infectious factors, especially NK cells and T cells, led to cytokines storm.[3,4]

The cerebral pathology of CNS-isolated FHL3 includes T lymphocyte infiltration, similar to CLIPPERS.[4,13] It has also been reported that patients who were diagnosed with FHL using genetic tools shared parallel characteristics of neuropathology with CLIPPERS.[8] Indeed, our patient presented with CLIPPERS-like syndrome in terms of clinical, imaging, and pathological characteristics. Recent studies have shown that some previously diagnosed CLIPPERS cases were CNS-isolated FHL,[14,15] indicating that the incidence of this rare CNS-isolated FHL entity might be underestimated.

When FHL is suspected, the cytotoxicity of NK cells and cytotoxic T lymphocytes should be tested, which is one of the criteria outlined in the 2004 guideline.[2] With the development of tests for FHL, perforin for FHL2 and CD107a for FHL3, FHL4, and FHL5 have been widely used because of their high sensitivity and specificity.[16,17] Given that the pathogenicity of variants is sometimes uncertain, functional tests can provide more evidence, which is also highlighted in ACMG guideline.[18] Although the homozygous variants of c.2588G>A in *UNC13D* have been confirmed as pathological causes of systematic FHL,[19] whose pathogenicity has been further proven by functional analysis of CD107a expression, they have never been reported as the culprits of CNS-isolated FHL. In this case, we confirmed the inability of degranulation of NK cells within the same variant by CD107a expression in CNS-isolated FHL. However, the reason why the same variant leads to different parts of the involvement remains unknown. One possible reason might be that systemic inflammation in our case was already suppressed by continuous immunotherapy.

Notably, based on available evidence, the variant site of c.2588G>A in *UNC13D* seems to be more frequent in the East Asian population.[20] However, it is still evident enough to prove the pathogenicity according to ACMG guidelines

Table 1 Literature Review of Isolated Central Nervous System FHL3

	Case1[7]	Case2[8,9]	Case3[4,5]	Case4[10]	Case5 (Our Case)
Age of onset	14y	7y	31y	12y	10y
Gender	Female	Female	NA	Male	Female
Country/region	United Kingdom	United States	Germany	United States	China
Time from onset to diagnosis	16m	72m	36m	6m	39m
Possible trigger	Epstein-Barr virus	NA	Epstein-Barr virus	NA	Herpes simplex virus
Genetic test	*UNC13D* c.C817T, c.G1241T	*UNC13D* c.2346_2349delGGAG, c.2588G>A	*UNC13D* c.1820G>C, c.2346_2349del	*UNC13D* c.2346_2349del, c.887C>T	*UNC13D* c.2588G>A, c.2588G>A
CNS presentations	Headache, right-sided convergent squint, dysarthria, gait abnormality, difficulty in motor, hyperesthesia, generalized seizure, VI cranial nerve palsy, papilledema, decreased power in limbs, absent reflexes	Diplopia, right hemiparesis, imbalance, clumsiness, seizure, mood lability	Paresthesia left arm, left-sided hemiparesis, seizure	Headache, ataxia, double vision, vomiting, seizures	Headache, visual problems, vomiting and altered mental status, diplopia, abnormal gait, shaky hands
CNS MRI	Leptomeningeal enhancement and generalized white matter lesions, mid–cervical cord contrast-enhancing lesions	Multiple enhancing lesions in brain, brainstem, and spinal cord, most prominent in pons	Multiple cerebral lesions, vasculitis	Multiple lesions involving in the cerebrum, posterior fossa, cerebellum, and brainstem	Widespread lesions across the cerebrum, brain stem, cerebellum and spinal cord; tumefactive lesions, CLIPPERS-like lesions
CSF tests	Positive oligoclonal bands	CSF pleiocytosis	CSF cell count 84×10^6/L, protein 791mg/dL	Mildly elevated neopterin	Slightly elevated leukocytes
Brain biopsy	NA	Diffuse lymphocytic infiltration of parenchyma, perivascular and small vessel walls. Predominant CD3-positive T cells	NA	T-cell infiltration	Perivascular lymphocytic infiltration. Predominant T cells
Functional test	Decreased CD107a	NA	Decreased CD107a	Decreased CD107a	Decreased CD107a
Systemic HLH	Yes, thirteen months after CNS presentations	NA	Yes, three years after CNS presentations	No	No
Considered neurological diagnoses	Unclassified neuroinflammatory disease	Demyelinating clinically isolated syndrome, CLIPPERS	Encephalitis, cerebral vasculitis	Demyelinating disorder, CLIPPERS	Immune-related encephalitis, multiple sclerosis, CLIPPERS
Treatment	IVIG, IVMP with tapering prednisolone, RTX, MMF	High-dose glucocorticoids, infliximab, RTX, azathioprine, IVIG	Steroids, cyclosporine A, cyclophosphamide, MMF	High-dose steroids, IVIG, DXM, prednisone, mycophenolate	IVIG, IVMP, azathioprine, MMF
Response to immunotherapy	Brain imaging and symptoms improved, but relapsed	NA	Not improved	Symptoms and MRI improved and relapsed	Symptoms and MRI improved and relapsed
HSCT	Yes	Yes	No	Yes	Yes
Outcome	Good outcome	Good outcome	Poor outcome (Dead)	Good outcome	Good outcome

Abbreviations: Y, year; M, months; NA, not available; CNS, central nervous system; MRI, magnetic resonance image; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CSF, cerebrospinal fluid; IVIG, intravenous immunoglobin; IVMP, intravenous methylprednisolone; RTX, rituximab; MMF, mycophenolate mofetil; DXM, dexamethasone.

and appearance in CNS-isolated FHL in other populations, except for East Asian.[8] It is noteworthy that the sibling of the proband showed no phenotype, whereas both the sibling and the proband showed a decrease in cytotoxic degranulation. However, we are still attempting to determine the reasons for this discrepancy. In our case, the EBV-DNA test result was negative, whereas the HSV-1-IgG was positive. We speculate that this is because missense variants are associated with moderately preserved cytotoxicity and can be triggered by pathogens such as EBV and Herpes simplex virus[21,22] for a short time or constantly. Another frequent variant was c.2346_2349del, which led to premature termination of translation, and was considered pathogenic variant.[10]

HSCT is necessary for CNS hemophagocytic lymphohistiocytosis. Summarized cases of CNS-isolated FHL demonstrated a higher rate of improvement and lower rate of mortality.[4] Patients with FHL with CNS involvement and FHL3 tended to have worse outcomes.[23] Prompt HSCT can increase overall survival and reduce neurological sequelae.

Conclusion

We report a patient with a homozygous variant of *UNC13D* (c.2588G>A, p.G863D), which has never been reported in CNS-isolated FHL, and review related cases that enriched the phenotypes and genotypes. Nonspecific CNS symptoms and brain MRI of CNS-isolated FHL simulate some neuroinflammatory diseases, especially CLIPPERS, and whole-exome sequencing and functional analysis can aid in distinguishing between them. HSCT might be an effective therapeutic strategy.

Patient's Perspective

The patient and her guardians suggested that genetic tests are necessary when diagnosis is ambiguous.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the both corresponding authors on reasonable request.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki, and was approved by the Institutional Ethics Committee of Xiangya Hospital Central South University. Institutional Ethics Committee of Xiangya Hospital Central South University approved publication of this study when informed consent from guardians was obtained.

Consent to Participate

Informed consent was signed by parents of the patient and parents of the patient agreed to participate.

Consent for Publication

Parents of the patient have signed informed consent and agreed on publication of the images in all figures.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; Have drafted or written, or substantially revised or critically reviewed the article; Have agreed on the journal to which the article will be submitted; Reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage; Agree to take responsibility and be accountable for the contents of the article.

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Disclosure

All authors claimed no conflicts of interest.

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