Pediatric CNS-isolated hemophagocytic lymphohistiocytosis

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Abstract

Objective

To highlight a novel, treatable syndrome, we report 4 patients with CNS-isolated inflammation associated with familial hemophagocytic lymphohistiocytosis (FHL) gene mutations (CNS-FHL).

Methods

Retrospective chart review.

Results

Patients with CNS-FHL are characterized by chronic inflammation restricted to the CNS that is not attributable to any previously described neuroinflammatory etiology and have germline mutations in known FHL-associated genes with no signs of systemic inflammation. Hematopoietic stem cell transplantation (HCT) can be well tolerated and effective in achieving or maintaining disease remission in patients with CNS-FHL.

Conclusions

Early and accurate diagnosis followed by treatment with HCT can reduce morbidity and mortality in CNS-FHL, a novel, treatable syndrome.

Classification of evidence

This study provides Class IV evidence that HCT is well tolerated and effective in treating CNS-FHL.

MORE ONLINE**→ Class of Evidence**

Criteria for rating
therapeutic and diagnostic
studies

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Glossary

ADEM = acute disseminated encephalomyelitis; **CIS** = clinically isolated syndrome; **CLIPPERS** = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; **FHL** = familial hemophagocytic lymphohistiocytosis; **GVHD** = graft-versus-host disease; **HCT** = hematopoietic cell transplantation; **HLH** = hemophagocytic lymphohistiocytosis; **IVIg** = IV immunoglobulin; **MDEM** = multiphasic ADEM; **NK** = natural killer; **WBC** = white blood cell.

Despite advances in diagnostic capabilities in neuroimmunology, highlighted most dramatically by antineuronal antibody biomarkers, some patients continue to have idiopathic or poorly defined chronic and/or treatment-refractory neuroinflammatory disorders. Neuroinflammatory findings are present in more than half of the patients with hemophagocytic lymphohistiocytosis (HLH).^{1,2} However, systemic inflammation is a fundamental diagnostic component of HLH, which is traditionally characterized by cytokine storm, multi-organ dysfunction, and ultimately death if untreated.³ HLH pathogenesis has been elucidated through the discovery of familial HLH (FHL)-associated genes, which encode proteins required for CD8⁺ lymphocyte and natural killer (NK) cell cytotoxicity. Deficiency in cytotoxic killing results in antigen persistence, leading to the hyperinflammatory state associated with FHL.⁴ The genes most commonly mutated in FHL are *PRF1* (FHL2) and *UNC13D* (FHL3).⁵ Hematopoietic cell transplantation (HCT) is the only definitive cure for FHL.^{6,7}

Although common at diagnosis of systemic HLH, CNS manifestations rarely precede systemic findings.^{1,2} Hemophagocytosis has been found in a brain biopsy of a patient not fulfilling the systemic HLH criteria.⁸ Patients with *PRF1* mutations have been reported with isolated CNS inflammation for weeks to months before therapy initiation^{1,9–12}; 2 such patients underwent HCT.^{9,11} These reports raise, but do not answer, the question as to whether isolated chronic CNS inflammation can occur in the absence of systemic HLH findings.

Here, we describe 4 patients with progressive CNS-isolated inflammation and mutations in FHL-associated genes who never fulfilled the systemic diagnostic criteria for HLH, except for defective NK cell activity reflective of their underlying genetic mutations. The neuropathologic details of 3 of the patients¹³ and HCT outcome details of all 4 patients¹⁴ have been previously reported. HCT was well tolerated in these patients and resulted in arrest of disease progression, highlighted by the lack of development of morbidity in an asymptomatic patient with progressive radiologic neuroinflammatory findings.

Case reports

Baseline characteristics at diagnosis for all patients are described in the table.

Patient 1

The index case presented as a 5-year-old girl with headache, vomiting, mild ataxia, multifocal contrast-enhancing cerebral

and cerebellar T2-hypertense lesions (figure 1, figure 2), and CSF pleocytosis, meeting the diagnostic criteria for a demyelinating clinically isolated syndrome (CIS).¹⁶ Her symptoms and imaging findings responded to high-dose glucocorticoids (methylprednisolone 30 mg/kg IV for 5 days), but returned with steroid tapers despite monthly IV immunoglobulin (IVIg) (1 g/kg/dose). Serial brain MRI identified enhancement patterns reminiscent of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS).¹⁷ Biopsy of a cerebellar lesion identified a mixed chronic inflammatory infiltrate with perivascular inflammation diffusely involving the gray and white matter and leptomeninges (figure 1). Induction treatment with glucocorticoids and cyclophosphamide followed by mycophenolate mofetil per small vessel CNS vasculitis protocol¹⁸ slowed, but did not halt, disease progression. She experienced progressive tremor, ataxia, dysarthria, dysconjugate gaze, and slowed speech and response time. Extensive evaluation including metagenomic next-generation sequencing of CSF and brain tissue was unrevealing for infection. Given her severe symptomatology, worsening course, and prominent T cells on repeat biopsy (left thalamic lesion, data not shown), natalizumab, which inhibits T-cell entry into the CNS, was given under a compassionate use investigational new drug protocol (IND 114796, 150 mg for 4 mg/kg every 4–5 weeks). While on natalizumab, her condition clinically and radiographically improved and then stabilized for 3 years before eventual clinical and radiographic progression. The patient was referred to the Undiagnosed Diseases Program at the NIH,^{19,20} but during the evaluation, she developed rotary nystagmus and worsened ataxia with loss of independent ambulation, partly responsive to high-dose methylprednisolone. Ultimately, CSF immunophenotyping and soluble biomarker analysis²¹ revealed activation of the innate immune system. *PRF1* gene sequencing identified biallelic previously reported, pathogenic mutations 5 years after initial presentation. CSF neopterin was significantly elevated (table). Throughout her course, patient 1 met no systemic HLH criteria except for decreased NK cell activity initially attributed to chronic immunosuppression. Following diagnosis, she received CNS-directed HLH therapy with intrathecal methotrexate and hydrocortisone and systemic dexamethasone with clinical improvement and normalization of the neopterin level before undergoing unrelated donor HCT at age 10 years.

Patient 2

A 6-year-old girl developed vomiting, headache, psychiatric symptoms, and cognitive decline over 3 months and then had focal status epilepticus prompting hospitalization. Additional symptoms noted during the hospitalization included left

Table Characteristics of patients with CNS-FHL

Patient	1	2 (at diagnosis)	3	4	2 (At relapse)
Age at symptom onset (y)	5	6	7	NA	9 (Symptom onset 13 mo posttransplant)
Sex	F	F	F	F	
Age at FHL diagnosis (y)	10	8	13	11	9
Neurologic symptoms					
Ataxia	Y	Y	Y	N	N
Weakness	Y	Y	Y	N	N
Seizure	Y	Y	Y	N	Y
Headache	Y	Y	N	N	Y
Vomiting	Y	Y	N	N	N
Cognitive decline	Y	Y	N	N	N
Other symptoms	Esotropia, nystagmus, tremor, and dysarthria	Dystonia and dysphagia	Diplopia and mood lability	N	Dystonia
Immunotherapy before HLH diagnosis					
Oral steroids	Y	Y	Y	N	
IV steroids	Y	Y	Y	N	
IVIg	Y	Y	Y	N	
Cyclophosphamide	Y	Y	Y	N	
Mycophenolate mofetil	Y	N	Y	N	
Other immunotherapy	Natalizumab	Plasmapheresis	Rituximab and azathioprine	N	
Mutation	<i>PRF1</i> c.452A>T (p.H151L) and c.666C>A (H222Q)	<i>PRF1</i> c.443C>G (p.A148G) and c.666C>A (H222Q)	<i>UNC13D</i> c.2346_2349delGGAG (p.R782fs), c.2588G>A (p.G863D)	<i>UNC13D</i> c.2346_2349delGGAG (p.R782fs), c.2588G>A (p.G863D)	<i>PRF1</i> c.666C>A (H222Q) heterozygous mutation in the first HCT donor
Systemic HLH evaluation ^a	No fever or splenomegaly, WBC 13, Hgb 16.0, Plt 359, ferritin 36.5, fibrinogen 407, and triglycerides 56	No fever or splenomegaly, WBC 22, Hgb 13.6, Plt 423, ferritin 20.8, fibrinogen 443, and triglycerides 99	No fever or splenomegaly, WBC 4.42, Hgb 14.2, Plt 346, ferritin 71.9, fibrinogen 365, and triglycerides 52	No fever or splenomegaly, WBC 7.34, Hgb 13.1, Plt 334, ferritin 31, fibrinogen 242, and triglycerides 124	No fever or splenomegaly, WBC 6.42, Hgb 13.4, Plt 215, ferritin 281.7, fibrinogen 192, and triglycerides 62
Soluble IL-2 receptor (unit/mL, normal <1,100)	265	209	710	647	519

Continued

Table Characteristics of patients with CNS-FHL (*continued*)

Patient	1	2 (at diagnosis)	3	4	2 (At relapse)
NK cell function (lytic units, normal >2.6)	1.7	0.0	Lymphopenia too severe	0.0	0.1
NK cell perforin positivity (normal 73%–91%)	0%	0%	Lymphopenia too severe	Not performed	52%
NK cell CD107a	Not performed	Expression 10% (normal 11–35%)	Lymphopenia too severe	Expression 3% (normal 11–35%)	Not performed
		Mean fluorescence 164 (normal 207–678 MCF)		Mean fluorescence 72 (normal 207–678 MCF)	
%ESR (mm/hr)/CRP (mg/dL)	7/0.17	5/<0.03	12/0.5	7/<0.03	8/0.11
CSF WBC (per microliter)	10	2	10	7	0
CSF neopterin (nmol/L, normal <33)	48	150	24	22	14
Pre-HCT therapy					
Enteral dexamethasone	Y	Y	Y	Y	Y
Intrathecal methotrexate/hydrocortisone	Y	Y	N	N	Y
Duration of follow-up post-HCT (mo)	36	13 mo to relapse	28	25	11 mo
Post-HCT imaging	No new lesions, no enhancement, and diffuse encephalomalacia	No new lesions, no enhancement, and diffuse encephalomalacia until 13 months posttransplant	No new lesions and no enhancement	No new lesions and no enhancement	No new lesions, no enhancement, and diffuse encephalomalacia
Pre- and post-HCT Modified Rankin Scale ¹⁵	4	4	2	0	4

Abbreviations: ESR = erythrocyte sedimentation rate; FHL = familial hemophagocytic lymphohistiocytosis; HCT = hematopoietic cell transplantation; HLH = hemophagocytic lymphohistiocytosis; IVIg = IV immunoglobulin; NA = not applicable; NK = natural killer; N = no; Y = yes.
^a Fever >38.0°C, WBC = white blood cell count ($\times 10^3$ per μL), Hgb = hemoglobin (g/dL), Plt = platelet count ($\times 10^3$ per μL), ferritin (ng/mL), fibrinogen (mg/dL), and triglycerides (mg/dL).

Figure 1 Imaging and histopathologic characteristics of patients with CNS-FHL

FLAIR (row A) and post-contrast T1 (row B) MRI findings for patients before initial diagnosis or at relapse. Note the varied lesion appearance with small multifocal, confluent, and tumefactive lesions. Punctate and curvilinear enhancement resembling CLIPPERS is common to 3 of the 4 patients early in disease. Patient 4 had multifocal small lesions with a single area of enhancement. Avid enhancement was a common feature of new or active lesions. Over time, lesions became confluent, and diffuse atrophy evolved in patients 1 and 2. Representative histopathology (row C) images from prediagnosis or relapse biopsies demonstrating a diffuse mixed chronic inflammatory infiltrate in patient 1, foci of perivascular lymphocytes (arrow) extending into the parenchyma for patient 2 prediagnosis, perivascular (arrow) and parenchymal mixed chronic inflammatory infiltrate with small vessel vasculitis in patient 3, and destructive perivascular (arrow) and parenchymal lymphohistiocytic infiltrate in patient 2 at relapse (magnification: $\times 40$ objective). Post-HCT FLAIR (row D) and post-contrast T1 (row E) MRI images demonstrate resolved enhancement and no development of new lesions for patients 1, 3, and 4 after HCT #1 and for patient 2 after HCT #2. CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; FLAIR = fluid-attenuated inversion recovery; HCT = hematopoietic cell transplantation.

hemiparesis and dystonia. Brain MRI identified contrast-enhancing cerebral and cerebellar white matter T2 hyperintense lesions (figures 1 and 3). She met the criteria for and was diagnosed with acute disseminated encephalomyelitis (ADEM)¹⁶ and received pulse methylprednisolone IV for 3 days and IVIg, followed by tapering daily oral prednisolone with gradual partial improvement. However, 4 months after the seizure, while off immunotherapy, she re-presented with

headache, vomiting, lethargy, worsened motor and language function, and new MRI lesions prompting additional IV methylprednisolone and 5 sessions of plasmapheresis. The presentation now met the criteria for multiphasic ADEM (MDM). She was then treated with 3 doses of monthly IV cyclophosphamide. Over the next 8 months, she had interspersed periods of improvement and worsening, including 2 episodes of status epilepticus. Treatments during this time

Figure 2 Patient 1 MRI evolution over time

(A) Confluent cerebellar FLAIR lesions with punctate, folia, and curvilinear enhancement without SWI change evolved to cerebellar atrophy with confluent nodules of enhancement and associated accumulation of microhemorrhages. Pattern persists posttransplant but without enhancement. (B) Supratentorial multifocal asymmetric small well-circumscribed lesions all with avid enhancement without initial SWI change evolving to confluent FLAIR lesions with punctate and confluent areas of enhancement and SWI change over time leading up to transplant. Imaging remains stable post-transplant. FLAIR = fluid-attenuated inversion recovery; SWI = susceptibility-weighted imaging.

included IV and oral corticosteroids and IVIg. Serial brain MRI showed accumulation of multifocal T2 hyperintense lesions, becoming confluent in the bilateral periventricular white matter, as well as progressive supra- and infra-tentorial atrophy, necrosis, and scattered hemorrhages (figure 3). Nineteen months after her first symptoms, she developed dysphagia and worsened dystonia and was referred to Boston Children's Hospital. Biopsy of a frontal lobe lesion showed perivascular lymphocytic foci with parenchymal extension

Figure 3 Patient 2 MRI evolution over time before relapse

(A) Cerebellar FLAIR lesions with punctate and curvilinear enhancement without SWI change evolved to cerebellar atrophy with confluent nodules of enhancement and associated accumulation of microhemorrhages. Pattern persists posttransplant, but enhancement responded to treatment. (B) Supratentorial multifocal asymmetric lesions with white matter, cortical, deep gray, and insular predilection with initial punctate enhancement evolving to curvilinear cortical enhancement. No initial SWI change evolving to punctate and confluent areas of SWI change consistent with hemorrhage over time leading up to transplant. Posttransplant FLAIR lesions become smaller with further global brain atrophy. FLAIR = fluid-attenuated inversion recovery; SWI = susceptibility-weighted imaging.

(figure 1). CSF neopterin was elevated. Based on imaging similarities to patient 1, reanalysis of previously performed whole-exome sequencing with attention to FHL genes identified biallelic *PRF1* mutations (1 previously reported in FHL2, 1 novel). She met no systemic HLH criteria except for decreased NK cell activity. She received intrathecal methotrexate and hydrocortisone and systemic dexamethasone before undergoing HLA-matched sibling donor HCT at age 9 years.

Patients 3 and 4

Patient 3 presented as a 7-year-old girl with diplopia, right hemiparesis, ataxia, CSF pleocytosis (white blood cell [WBC] count 10/ μ L with 85% lymphocytes), and multifocal brain lesions, including a large brainstem lesion (figure 1), leading to diagnosis of a demyelinating CIS. Symptoms and MRI findings transiently improved with methylprednisolone IV 30 mg/kg/d for 5 days, followed by prednisolone starting at 1 mg/kg/d and tapered over 3 months, but she developed seizures and new contrast-enhancing lesions similar to CLIPPERS (figures 1 and 4) 7 months after initial presentation. Biopsy of a frontal lobe lesion showed extensive

Figure 4 Patient 3 MRI evolution over time

(A) Initial attack and follow-up FLAIR and T1 post-contrast images showing tumefactive brainstem lesions with heterogeneous enhancement pattern. Significant improvement with steroids at 4-month follow-up. (B) Attack 7 months from onset with multifocal FLAIR lesions throughout the brain and spinal cord with punctate, speckled enhancement throughout. (C) Pre- and post-HCT images of the cerebellar involvement with minimal atrophy over time in this patient despite 7 years of disease. FLAIR = fluid-attenuated inversion recovery; HCT = hematopoietic cell transplantation.

vascular, perivascular, and parenchymal mixed inflammatory infiltrates with occasional small vessel vasculitis (figure 1). Despite treatment with a small vessel CNS vasculitis protocol,¹⁸ symptoms including altered mental status and seizures recurred 6 months after glucocorticoid discontinuation while still on mycophenolate mofetil 600 mg/m²/dose twice daily. Over the next 4 years, subsequent treatments (in addition to oral steroids) included infliximab (5 mg/kg/dose at 0, 2, and 6 weeks and every 4 weeks thereafter for 9 months), cyclophosphamide (10 mg/kg/dose every 2 weeks for 3 months), rituximab (3 cycles of 1000 mg $\times$ 2 doses), azathioprine (100 mg twice daily), and IVIg (0.5g/kg every 4 weeks) with periods of improvement, followed by breakthrough clinical and MRI disease activity. Based on our experience with patients 1 and 2, FHL genetic testing 7 years after symptom onset identified biallelic pathogenic mutations in *UNC13D*. Patient 3 met no systemic HLH criteria, although she was too lymphopenic from previous therapy to assess NK cell function, and CSF neopterin was normal. During her course, she had recurrent sinusitis, mildly low IgG and IgA, and elevated gamma delta T cells (up to 19%) while on immunosuppression; these findings were attributed to medication toxicity but may have been related to her *UNC13D* mutations. She received systemic dexamethasone therapy before undergoing unrelated donor HCT at age 14 years.

Patient 4, the asymptomatic sister of patient 3, was found at age 12 years to have the same biallelic *UNC13D* mutations during evaluation as a potential bone marrow donor for her sister. Brain MRI demonstrated multifocal white matter lesions, one of which was contrast enhancing (figure 1). Two of the lesions increased in size over 6 weeks. Neurologic examination was normal. CSF demonstrated pleocytosis (WBC count 7/ μ L, 92% lymphocytes) and oligoclonal bands, but normal CSF neopterin. Laboratory evaluation demonstrated absent NK cell function and decreased CD107a expression. Similar to her sister, she was hypogammaglobulinemic (IgG 482). She met no other systemic HLH criteria. She received oral dexamethasone therapy before undergoing unrelated donor HCT.

Methods

Patients and medical record review

This study was approved by the Boston Children's Hospital and National Human Genome Research Institute Institutional Review Boards. Clinical information was obtained from the medical record.

HLH diagnostic testing and pre-HCT therapy

PRF1 and *UNC13D* gene sequencing was performed at the NIH or Cincinnati Children's Hospital. NK cell functional testing, perforin staining, and CD107a mobilization were performed at Cincinnati Children's Hospital. Intrathecal methotrexate and hydrocortisone and systemic dexamethasone were dosed as previously described,³ with dexamethasone weaned after HCT.

HCT procedure

Reduced-intensity bone marrow conditioning with alemtuzumab, fludarabine, and melphalan⁷ was dosed as previously described. Hematopoietic stem cells were harvested from the donor bone marrow. Graft-versus-host disease (GVHD) prophylaxis included cyclosporine and methylprednisolone. Whole blood and T-cell donor chimerism studies were performed by the American Red Cross using the short tandem repeats-PCR method. Further details of the transplantation process and transplant outcomes are published separately.¹⁴

Data availability

Patient data were obtained from their electronic medical records for this study. All abstracted data are included within the manuscript, table, and figures. If additional details are needed, they can be requested from the corresponding author.

Results

Hematopoietic stem cell transplantation and CNS-FHL disease response

Following HCT, patients 1, 3, and 4 demonstrated normalization of NK cell activity and resolved MRI contrast enhancement, did not develop new brain lesions (figures 1–4) or further neurologic deficits, and had immunosuppressive glucocorticoids discontinued by 3 months post-HCT. Patient 1 had improved cranial nerve function, strength, coordination, and tremor, but continued to have significant physical deficits requiring a wheelchair or 1:1 assistance for ambulation and cognitive deficits with a full-scale IQ of 70. Patient 2 had immunosuppressive glucocorticoids discontinued by 2 months post-HCT. Her dystonia, mental status, and strength improved at 1 year following HCT, but remains wheelchair dependent. Patient 3 had improved diplopia, gait, strength, and seizures, with resolution on levetiracetam. Patient 4 remained neurologically asymptomatic post-HCT. None of the 4 patients experienced graft failure or acute or chronic GVHD. Length of follow-up for all 4 patients ranged from 2 to 3 years posttransplant.

Disease recurrence and second HCT

Thirteen months following HCT, patient 2 experienced seizures, headache, and worsening dystonia. Biopsy of a new frontal lobe white matter enhancing lesion (figure 1) showed a dense, destructive perivascular and parenchymal lymphohistiocytic infiltrate (figure 1). Pathologic evaluation excluded posttransplant lymphoproliferative disorder, and extensive infectious testing was negative. She was diagnosed with relapsed CNS-FHL. Clinical and laboratory findings at relapse are described in the table. She met no systemic HLH criteria except decreased NK cell function. Her NK cell function was decreased despite donor chimerism greater than 46% in whole blood, T cells, and NK cells, which is typically considered adequate. Her sibling donor possessed a monoallelic *PRF1* mutation. Upon relapse, NK cell testing in the donor revealed

absent function, although decreased NK cell function has previously been noted in patients with heterozygous *PRF1* mutations and the significance is uncertain.²² Patient 2 repeated remission induction with systemic dexamethasone and had a stable MRI (not shown) without new enhancement before undergoing second HCT from an unrelated donor using an alternative reduced-intensity bone marrow conditioning regimen of fludarabine, alemtuzumab and busulfan.

Twelve months posttransplant, patient 2 had normal NK cell function and no contrast-enhancing lesions on MRI (figure 1).

Discussion

We describe 4 patients with isolated CNS-FHL, who lacked any systemic HLH manifestations or typical laboratory abnormalities (other than decreased NK cell function), but carried FHL-associated mutations in *PRF1* or *UNC13D*. It is likely that additional genetic modifying factors exist that predispose patients to CNS-isolated disease or that specific neuroinflammatory events lead to CNS involvement without triggering systemic inflammation. We did not identify an infectious trigger in our cohort, including negative testing for Epstein-Barr virus, but we cannot exclude an undetected organism or virus. Further studies will be required to identify the inherited and environmental risk factors for CNS-isolated inflammation.

Our findings of CNS-FHL as a cause of treatment-refractory, isolated neuroinflammation are an important advance in the differential diagnosis of neuroinflammatory disorders. Some notable features may facilitate diagnosis. Patients 1–3 had overlapping symptoms including seizures (3/3), weakness (3/3), ataxia (2/3), cognitive decline (2/3), eye movement abnormalities (2/3), headache (2/3), and vomiting (2/3). Symptoms typically improved with immunotherapy but recurred both during weans and active treatment. Relapses were especially common when corticosteroids were weaned or discontinued. The treatment-refractory and steroid-dependent nature of the symptoms was striking. Some shared imaging characteristics include multifocal T2/fluid-attenuated inversion recovery hyperintense lesions with avid enhancement and accumulation of microhemorrhages evident on susceptibility-weighted imaging. Punctate and curvilinear lesions evolved in the 3 symptomatic patients at times in their illnesses.

In these patients, CNS-FHL mimicked several CNS inflammatory disorders including CLIPPERS, MDEM, and small vessel CNS vasculitis. These diagnoses were made by treating clinicians, and presentations met the diagnostic criteria. The clinical, radiographic, and pathologic features for patient 1 meet proposed CLIPPERS diagnostic criteria.²³ In addition, patients 2 and 3 had radiographic features including homogeneous enhancing nodules and curvilinear and

punctate lesions as seen in CLIPPERS. Patient 2 met the criteria for MDEM¹⁶ early in her course. Some patients with MDEM harbor anti-myelin oligodendrocyte glycoprotein antibodies, which were not clinically available when patient 2 presented, but should now be obtained in patients with MDEM. Patient 3 met the diagnostic criteria for small vessel CNS vasculitis including pathologic confirmation.

As above, there may be clinical and radiographic features that are suggestive of CNS HLH; however, many of these features overlap with other neuroinflammatory disorders. As seen in patients 1 and 2, CNS HLH can be a destructive process with significant morbidity. As such, and in the interest of earlier diagnosis and definitive treatment, we propose that pediatric patients with treatment-refractory or recurrent CNS inflammation of uncertain etiology, including presentations consistent with CLIPPERS, MDEM (especially if anti-myelin oligodendrocyte glycoprotein antibodies are negative), and small vessel CNS vasculitis, undergo genetic testing and NK cell functional testing for FHL. Patients with refractory or recurrent neuroinflammation often require long-term immunomodulatory therapy, which can reduce the yield of a brain biopsy and alter functional testing for FHL; therefore, obtaining functional diagnostic studies before treatment is preferred. NK cell function and FHL genetic testing may eliminate the need for brain biopsy in some patients. Furthermore, our results illustrate the importance of screening siblings of patients with CNS-FHL, as early detection and treatment can limit the development of clinical symptomatology and permanent, potentially devastating neurologic sequelae.

CSF neopterin is associated with CNS involvement of HLH among a broad group of neuroinflammatory disorders.²⁴ Levels were elevated in patients 1 and 2 at diagnosis and were normal following apparent disease control. CSF neopterin may provide a useful biomarker of CNS-FHL disease activity and treatment efficacy.

In addition to the importance of diagnostic clarity and genetic counseling, the diagnosis of CNS-FHL has profound treatment implications. Compared with current primary neuroinflammatory standard-of-care therapies, HCT represents a fundamentally different treatment paradigm: correcting an underlying genetic etiology as opposed to controlling inflammatory disease with chronic immunosuppression. We found that HCT using reduced-intensity conditioning regimens was tolerated by patients with CNS-FHL without engraftment failure or evidence of acute GVHD. Three of the 4 patients achieved CNS-FHL disease control following the first HCT. One patient (patient 2) relapsed in the setting of a heterozygous *PRF1* mutated donor marrow with persistently decreased NK cell function despite adequate donor chimerism, but achieved normal NK cell function and disease control after a second HCT using a different bone marrow donor. These findings underscore the potential importance of screening prospective sibling stem cell donors with genetic and functional testing.

Although all patients in this cohort achieved positive outcomes and are off chronic immunosuppressive therapy, delayed diagnoses resulted in significant disability, especially for patients 1 and 2. Longer-term follow-up is required to assess response durability given reports of CNS-isolated relapses following HCT for systemic HLH.^{25,26} Follow-up will also help clarify optimal post-HCT monitoring protocols, including MRI, CSF, donor chimerism, and NK cell function. These initial results support efforts to pursue early and accurate diagnosis and early treatment with HCT to reduce morbidity and mortality in CNS-FHL, a novel, curable syndrome.

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Disclosure

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Appendix Author contributions

Name	Location	Role	Contribution
Leslie A. Benson, MD	Department of Neurology, Boston Children's Hospital, Boston, MA	Author	Designed and conceptualized the study, acquisition of data, drafted the manuscript, and revised the manuscript for intellectual content
Hojun Li, MD, PhD	Dana-Farber/ Boston Children's Cancer and Blood Disorders Center, Boston, MA	Author	Designed and conceptualized the study, acquisition of data, drafted the manuscript, and revised the manuscript for intellectual content
Lauren A. Henderson, MD	Department of Rheumatology, Boston Children's Hospital, Boston, MA	Author	Acquisition of data and revised the manuscript for intellectual content
Isaac H. Solomon, MD, PhD	Department of Pathology, Boston Children's Hospital, Boston, MA	Author	Acquisition of data and revised the manuscript for intellectual content
Ariane Soldatos, MD, MPH	Undiagnosed Disease Program of the National Institute of Neurologic Disorders and Stroke, Bethesda, MD	Author	Acquisition of data and revised the manuscript for intellectual content
Jennifer Murphy, NP	Undiagnosed Disease Program of the National Institute of Neurologic Disorders and Stroke, Bethesda, MD	Author	Revised the manuscript for intellectual content.

Appendix (continued)

Name	Location	Role	Contribution
Bibiana Bielekova, MD	Undiagnosed Disease Program of the National Institute of Neurologic Disorders and Stroke, Bethesda, MD	Author	Acquisition and interpretation of immunophenotyping data, participation in diagnostic workup, and revised the manuscript for intellectual content
Alyssa L. Kennedy, MD, PhD	Dana-Farber/ Boston Children's Cancer and Blood Disorders Center, Boston, MA	Author	Revised the manuscript for intellectual content.
Michael J. Rivkin, MD	Department of Neurology, Boston Children's Hospital, Boston, MA	Author	Revised the manuscript for intellectual content.
Kimberly J. Davies, MD	Dana-Farber/ Boston Children's Cancer and Blood Disorders Center, Boston, MA	Author	Revised the manuscript for intellectual content.
Amy P. Hsu, BA	Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, Bethesda, MD	Author	Diagnosed and performed genetic testing for patient and revised the manuscript for intellectual content
Steven M. Holland, MD	Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, Bethesda, MD	Author	Care for Patient 1 and revised the manuscript for intellectual content.
William A. Gahl, MD, PhD	National Human Genome Research Institute, Bethesda, MD	Author	Revised the manuscript for intellectual content.
Robert P. Sundel, MD	Department of Rheumatology, Boston Children's Hospital, Boston, MA	Author	Revised the manuscript for intellectual content.
Leslie E. Lehmann, MD	Dana-Farber/ Boston Children's Cancer and Blood Disorders Center, Boston, MA	Author	Revised the manuscript for intellectual content.
Michelle A. Lee, MD, PhD	Division of Hematology, Oncology, and Marrow & Blood Cell Transplantation, Children's Hospital at Montefiore, Bronx, NY	Author	Revised the manuscript for intellectual content.
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Appendix (continued)

Name	Location	Role	Contribution
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Mark P. Gorman, MD	Department of Neurology, Boston Children's Hospital, Boston, MA	Author	Designed and conceptualized the study and revised the manuscript for intellectual content

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