BRIEF COMMUNICATION

Primary Adult-Onset Hemophagocytic Lymphohistiocytosis with Neurologic Presentation

Cormac Southam, Jennifer Grossman, Chris Hahn

ABSTRACT: Hemophagocytic lymphohistiocytosis (HLH) is a rare immune deregulatory disorder that predominantly presents in children. Here we describe three patients with adult-onset primary HLH whose initial presentations were characterized by neurological features, and we review the literature of published cases. These cases ranged in age from 17 to 30 and presented with a variety of neurological symptoms. One of our cases demonstrated numerous microhemorrhages on MR brain. This is the first published case of adult-onset HLH presenting with cerebral microhemorrhages. In addition, literature review identified five additional patients with isolated central nervous system presentation of primary HLH.

RÉSUMÉ : Étude de cas de lymphohistiocytose hémophagocytaire primaire apparus chez des adultes présentant des symptômes neurologiques. La lymphohistiocytose hémophagocytaire (LHH) est un trouble rare de la dysrégulation immunitaire qui se manifeste principalement chez les enfants. Nous voulons décrire ici les cas de trois patients chez qui une LHH primaire est apparue à l'âge adulte et qui ont tout d'abord présenté des symptômes neurologiques. Nous avons aussi passé en revue les publications portant sur de tels cas. Les patients visés étaient âgés de 17 à 30 ans et présentaient une variété de symptômes neurologiques. L'un d'entre eux montrait par exemple de nombreuses microhémorragies observées lors d'examens d'IRM. Il s'agit là du premier cas publié d'apparition de la LHH chez un adulte donnant à voir des microhémorragies cérébrales. De plus, une revue de la littérature a permis d'identifier cinq autres patients atteints de LHH primaire limitée à leur système nerveux central (SNC).

Keywords: Autoimmune disease, CNS inflammation, Genetics, Hemorrhage – cerebral, Immunology, Magnetic resonance imaging, Neuroimmunology, Neuroinflammation

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Hemophagocytic lymphohistiocytosis (HLH) is an immune dysregulatory disorder. Secondary HLH is most commonly associated with infections, malignancies, or rheumatologic disorders. Primary HLH is genetic in origin with most cases occurring in children and curative treatment involving hematopoietic stem cell transplant (HSCT).[1] Documented adult cases are uncommon.[2,3] Here we report three cases of primary HLH presenting with central nervous system (CNS) involvement in adults.

The first patient was a 17-year-old male reported previously with a focus on genetics.[4] He presented with 2 weeks of fever and respiratory symptoms before developing slurred speech and impaired balance. Brain magnetic resonance imaging (MRI) showed patchy T2 hyperintensities in the parietal lobes (Figure 1), pons, and midbrain. Lumbar puncture was nonspecific. CBC revealed neutropenia and thrombocytopenia and bone marrow biopsy showed a nonspecific increase in macrophages. The patient was discharged without a definite diagnosis.

Six months later, he presented with new diplopia and right-sided weakness. Repeat MRI showed new hyperintensity of the abducens nerve as well as discrete lesions in the thalami and internal capsules. CSF WBC was increased with prominence of T-cells on flow cytometry. He was pancytopenic with markedly elevated ferritin and hepatosplenomegaly. Whole exome sequencing was performed for suspicion of an immunodysregulatory disorder and demonstrated compound heterozygous mutations in the RAB27A gene. This was felt to be consistent with Griscelli syndrome type 2,[4] causing CNS HLH, despite the absence of albinism. He received dexamethasone that resulted in improvement of his CNS symptoms and cytopenias and subsequently started on cyclosporine to prevent a flare of presumed HLH. In spite of this, he developed profound thrombocytopenia causing refractory epistaxis and hematuria. He had 2 allogeneic stem cell transplants from unrelated donors. The first transplant failed to engraft and was complicated by infection. The second transplant was done 6 weeks later but he died shortly thereafter with autopsy showing persistent HLH.

The second patient was a 22-year-old female who presented with limb numbness and diplopia. MRI showed T2 hyperintensities in the cerebellar hemispheres and vermis as well as in the subcortical and periventricular white matter (Figure 1). Ferritin was mildly elevated; she was thrombocytopenic, and ultrasound

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showed splenomegaly. Diagnosis remained unclear after extensive investigations including CSF sampling.

The patient was stable for 2 years without treatment before developing subacute hemiparesis and incoordination. Repeat MRI revealed progression of cerebellar hyperintensities with new leptomeningeal involvement. A 2-month trial of oral prednisone yielded little symptomatic improvement, and she was monitored for disease progression without further active treatment.

One year later, she presented to hospital with high-grade fevers and fatigue. She was found to be pancytopenic with hemophagocytes noted on her bone marrow biopsy. Ferritin and serum soluble interleukin-2 receptor levels were markedly elevated and abdominal ultrasound revealed hepatosplenomegaly with ascites. Repeat MRI showed worsening leptomeningeal disease. Work-up for secondary causes of HLH was negative, and genetic testing revealed compound heterozygous mutations in the STXBP2 gene consistent with primary HLH.[5] She received an abridged version of the HLH-1994 protocol and continued on maintenance cyclosporine monotherapy as she declined HSCT. She remained in remission for 2.5 years. She then developed worsening ataxia, headache, and tremor. MR showed interval progression in left frontal lobe and cerebellar lesions (Figure 1). She was treated again with the HLH-1994 protocol, including intrathecal methotrexate. Her symptoms improved markedly, and she was discharged home. Unfortunately, she was admitted to hospital shortly thereafter with bacterial sepsis and invasive fungal infection and passed away from infectious complications.

The third patient was a 30-year-old male who presented with sudden left-sided weakness and dysarthria. He had a history of mild hypertension treated with nifedipine. CT scan showed intraparenchymal hemorrhage involving the midbrain and thalamus. MR additionally visualized innumerable foci of intraparenchymal microhemorrhage throughout the infra and supratentorial compartments with a posterior fossa and midbrain predominance (Figure 2).

Cerebral angiogram was normal without features of vasculitis. Ferritin was not initially tested but was found to be elevated 3 months later without clear cause. At discharge, the stroke etiology was attributed to hypertension.

Three years later, the patient presented with cough and shortness of breath, progressing to fever, pancytopenia, and hyperferritinemia. Bone marrow biopsy showed increased histocytes with hemophagocytosis. Genetic workup revealed two mutations in PRF1. Abdominal imaging showed borderline splenomegaly. MRI brain showed significant increase in burden of microhemorrhages and multiple T2 hyperintensities in the supratentorial white matter. Primary HLH was diagnosed, and treatment was initiated using the HLH-2004 protocol.[1] There was initial improvement, but his cytopenias persisted and treatment was re-escalated as he became febrile and his ferritin increased again. He was temporarily treated with rituximab and maintained on cyclosporine. However, his cyclosporine was discontinued several months later when he developed multiple infectious complications.

Over the subsequent years, his cognitive capacity declined along with his imaging profile, with the latter exhibiting an increasing burden of edema and microhemorrhages both infra and supratentorially. He passed away shortly thereafter.

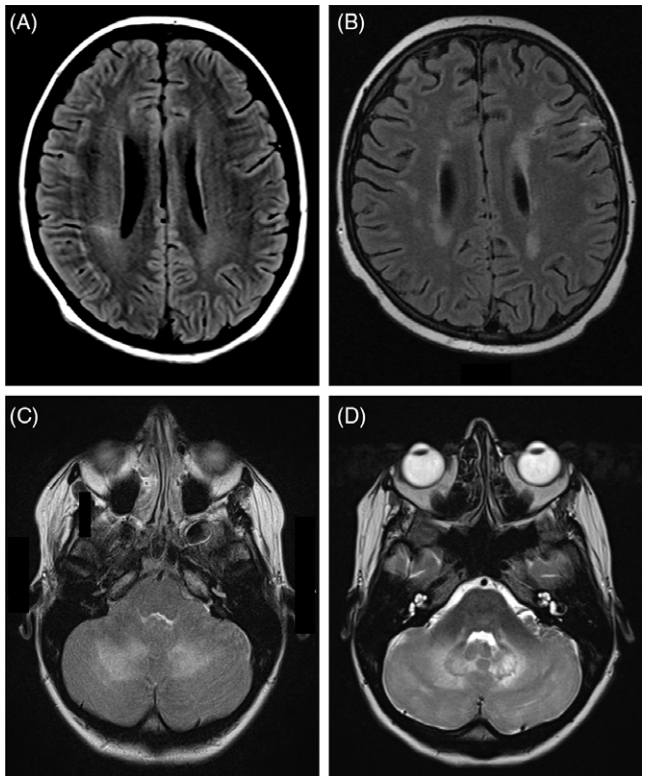

Figure 1: *(A) Axial MR brain FLAIR sequence from patient one at time of initial presentation demonstrating bilateral hyperintensities in the centrum semiovale of the parietal lobes. (B) Post-gadolinium axial MR brain FLAIR sequence from patient one 14 months after initial presentation demonstrating progression of bilateral supratentorial white matter hyperintensities and left frontal lobe encephalomalacia at site of previous brain biopsy. (C) T2-weighted MR brain from patient two at time of initial presentation showing bilateral cerebellar hemisphere white matter hyperintensity with local mass effect and relative sparing of the cerebellar peduncles. (D) T2-weighted MR brain from patient two approximately 7 years after initial presentation showing progression of the bilateral cerebellar white matter hyperintensities, now with prominent involvement of the bilateral dentate nuclei.*

HLH is a rare disorder with an estimated prevalence of 1.2 cases per 1,000,000 with an age of onset of less than 36 months in more than eighty percent of cases.[2] The pathogenesis is a persistent overactivation of the immune system, specifically of macrophages and T lymphocytes, leading to infiltration of organs including the CNS.[5] Imaging findings are nonspecific and include diffuse leptomeningeal and perivascular enhancement and T2 hyperintense lesions in the cerebral white matter.[6]

All three patients we report had primary late-onset HLH. CNS involvement is less common in adults than in children in both forms of HLH and occurs in ˜10% of patients at any point.[7] Literature review identified 5 other adult patients with isolated CNS presentation of primary HLH. All patients were between 18 and 28 years, seizures were common, and imaging findings typically involved the periventricular and subcortical white matter (Table 1).

Our three patients had a variety of clinical and imaging findings. However, the patients' PRF1, STXBP2, and RAB27A mutations are all implicated in the PRF1 cytotoxic pathway, which functions in lymphocytic regulation.[5] Notably, the oldest patient in our study and more than half of those previously

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Table 1: Clinical, laboratory, imaging, and genetic characteristics of all eight patients, including three patients identified in this report, with adult-onset primary HLH identified in literature search. Normal range of ferritin 13–375 μg/l. Gene mutations known to be pathogenic unless otherwise specified

Paper reference	Age at onset	Sex	Presenting symptoms neurological?	Initial neurologic symptoms	Subsequent neurologic symptoms	Peak ferritin measurement (μg/l)	CSF findings	Initial imaging findings	Genetic findings
8	20	Male	Yes	Painless visual loss, headache, and decreased visual acuity	Generalized tonic clonic seizure	Not reported	Pleocytosis and increased protein	T2 hyperintensities in parieto-occipital cortex, corpus callosum, dorsal pons, and cerebellar hemispheres	Homozygous variant in PRF1 gene
9	24	Female	No	Seizures and decreased level of consciousness	–	~5000	–	Extensive T2 hyperintensities throughout the periventricular and subcortical white matter	Homozygous mutation in PRF1 gene
7	28	Male	Unknown	Seizures	–	Not reported	Elevated opening pressure, pleocytosis, and increased protein	Diffuse white matter T2 hyperintensities	Heterozygous missense mutation in PRF1 gene and homozygous missense mutation in SH2D1A gene
10	18	Male	Unknown	Ataxia	–	Not reported	Pleocytosis	–	Munc13–4 gene mutation
3	20	Male	No	Status epilepticus	–	Not reported	Elevated opening pressure	T2 hyperintensities in the bilateral frontotemporal lobes and occipital dorsal thalamus	c.172T > C (p.S58P) heterozygous missense mutation in MAP2K1 gene
Southam, Grossman, & Hahn, 2021	17	Male	Yes	Dysarthria and ataxia	Diplopia and hemiplegia	>8000	Pleocytosis and increased protein	Patchy T2 hyperintensities jn parietal lobes, midbrain, and pons	c.400_401delAA (p. Lys134Glufs*2) and c.74T > G (p. Val25Gly) compound heterozygous mutations in RAB27A gene
Southam, Grossman, & Hahn, 2021	22	Female	Yes	Diplopia and hemianesthesia	Ataxia and tremor	15,567	Pleocytosis and increased protein	T2 hyperintensities in cerebellar hemispheres, vermis, and supratentorial white matter	c.1247–1G > C canonical splicing mutation and c.1621G > A (p.G541S) mutation, both in the STXBP2 gene
Southam, Grossman, & Hahn, 2021	30	Male	Yes	Dysarthria and hemiplegia	Cognitive decline	56,252	–	Intraparenchymal hemorrhage involving unilateral thalamus and midbrain and innumerable microhemorrhages	c.133G > A (p. Gly45Arg) and c.586C > T (p. His190Tyr) variant of unknown significance mutation both in the PRF1 gene

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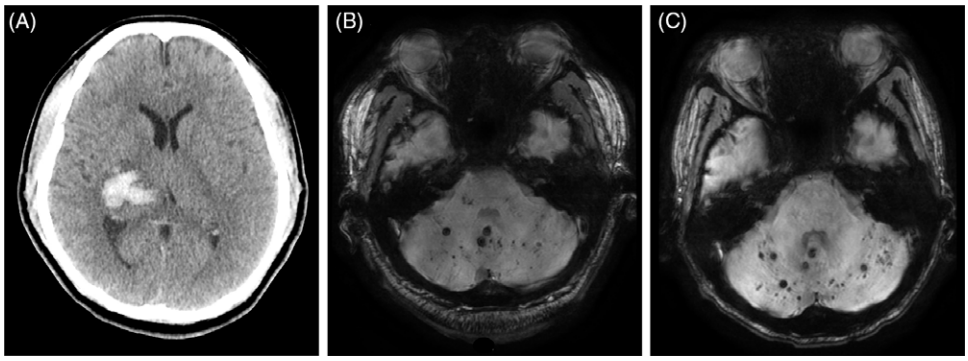

Figure 2: *(A) Dry axial CT head showing intraparenchymal hemorrhage involving the right thalamus and posterior limb of the internal capsule. (B) Susceptibility weighted imaging MR brain without contrast performed on initial presentation showing diffuse multifocal cerebellar and pontine microhemorrhages. (C) Subsequent susceptibility weighted imaging MR brain without contrast performed 5 years after initial presentation showing progression of posterior fossa microhemorrhages.*

reported had PRF1 mutations. In this case series, we also report the first case of CNS microhemorrhages associated with HLH in an adult. This finding has previously been seen in pediatric patients,[6] but the etiology remains unclear.

In conclusion, primary HLH is a rare cause of isolated CNS disease in adults. The diagnosis should be suspected in patients with progressive neurologic symptoms and atypical white matter lesions with otherwise negative work-up, especially with marked elevation in ferritin or hematologic abnormalities. Additionally, HLH is a rare cause of widespread microhemorrhages although more typical etiologies must be ruled out first. Genetic testing can assist in the diagnosis.

Conflicts of interest

Dr. Hahn reports personal fees from Akcea and personal fees from Alnylam, outside the submitted work. Dr. Southam and Dr. Grossman report no conflicts of interest.

Statement of authorship

CS drafted the manuscript and created the figures and table. JG and CH assisted in the drafting and editing of the manuscript.

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