Imaging Spectrum of Neurological Manifestations of Hemophagocytic Lymphohistiocytosis in Pediatrics: A Case Series

Geethapriya Sivaramalingam1  Afeya VK1  Bagyam Raghavan1  Jayaraj Govindaraj1

1 Department of Radiology, Apollo Speciality Hospital, Chennai, Tamil Nadu, India

Address for correspondence Afeya VK, DNB (Radiodiagnosis), Department of Radiology, Apollo Cancer Institutes, Padma Complex, Anna Salai, Chennai 600035, Tamil Nadu, India (e-mail: afiyaaf@gmail.com).

Abstract
Hemophagocytic lymphohistiocytosis (HLH) is an uncommon condition, which can result either from a primary genetic abnormality affecting children or secondary to various conditions like malignancy or infection predominantly in adults. HLH is associated with immune dysregulation, resulting in an uncontrolled overproduction and infiltration of lymphocytes and histiocytes. The infiltration predominantly involves liver, spleen, lymph nodes, and central nervous system. Neuroimaging features on magnetic resonance imaging are highly nonspecific and variable. The most typical findings include periventricular white matter hyperintensities and diffuse atrophy. Ring or nodular enhancing or nonenhancing focal parenchymal lesions may be seen. Here, we present three pediatric cases of primary HLH with a wide spectrum of imaging findings involving cerebral and cerebellar cortex, white matter, deep gray matter, and brain stem. The findings in these patients range from small nonenhancing hemorrhagic lesions and enhancing small lesions to ill-defined mass with mass effect and midline shift. Lesions in deep gray matter including thalamus, basal ganglia, and also brain stem in HLH are rarely described in literature. Early diagnosis of HLH and timely management can improve the course of the disease.

Keywords
► hemophagocytic lymphohistiocytosis
► neuroimaging
► pediatric

Introduction
Hemophagocytic lymphohistiocytosis (HLH) is a rare, nonmalignant, life-threatening disorder, due to excessive immune system activation. HLH typically affects infants and young children, though it may affect any age group. HLH commonly affects the liver, spleen, lymph nodes, bone marrow, lungs, and central nervous system (CNS); while it very rarely affects musculoskeletal system and skin. Approximately 30% of patients with HLH show neurological abnormalities.1

This case series includes three pediatric patients with primary HLH, who presented with CNS manifestations, which were confirmed by genetic analysis and HLH 2004 criteria.

Case 1
A 6-year-old boy presented with recurrent fever, hepatosplenomegaly, pancytopenia, and bone marrow aspiration showing significant hemophagocytosis (►Figs. 1–3). HLH genetic testing showed familial HLH. Magnetic resonance imaging (MRI) brain showed CNS involvement and was treated with etoposide and intrathecal methotrexate. After 3 months of treatment, allogeneic hematopoietic stem cell transplantation (HSCT) was done. Pre-HSCT workup MRI showed regression of most of the findings. Six months post-HSCT follow-up MRI showed further regression of the lesions.
Case 2

A 7-year-old boy presented with history of multiple episodes of fever, infections, refractory seizures, pancytopenia, and hepatosplenomegaly (Fig. 4). Genetic testing showed RAB27 gene mutation; thus, diagnosis of Griscelli syndrome-type 2 was made. Cerebrospinal fluid (CSF) analysis showed few lymphocytes. MRI brain was performed to evaluate CNS involvement of HLH. The patient underwent HSCT and improved symptomatically.

Case 3

A 6-year-old girl, a diagnosed case of congenital HLH with STX mutation, underwent MRI as a part of a pre-HSCT workup (Figs. 5 and 6). The girl underwent haploidentical HSCT and later presented with fever, pansinusitis, and sepsis on day 15 post-HSCT. Invasive fungal sinusitis was diagnosed and MRI brain with orbits was performed.

Discussion

HLH is a multisystem disorder with aggressive proliferation of activated macrophages and histiocytes, commonly affecting the CNS. CNS imaging findings in HLH may mimic other disease entities and can be a diagnostic challenge. In our study, we had a wide spectrum of neuroimaging findings (Table 1).

Pathophysiology

HLH is characterized by uncontrolled activation of macrophages, which accumulates in tissues and leads to organ damage by excessive production of cytokines. Primary HLH is
Fig. 3 Case 1: (IA) Initial magnetic resonance imaging (MRI) showing restricted diffusion in subcortical U fibers of bilateral frontal, parietal and occipital cortices, (IB) Pre-hematopoietic stem cell transplantation (HSCT) MRI showing regression of the same, (IC) MRI post 6 months HSCT showing resolution of the same. (IIA) Initial MRI showing normal ventricles, sylvian fissures, cortical sulci and cisternal spaces, (IIB) Pre-HSCT MRI and (IIC) MRI post 6 months HSCT showing minimal dilatation of all ventricles, sylvian fissures, cortical sulci and cisternal spaces. (IIIA) Initial MRI showing increased signal intensity on T2-weighted and fluid-attenuated inversion recovery imaging in periventricular white matter of bilateral cerebral hemispheres. (IIIB), Pre-HSCT MRI and (IIIC) MRI post 6 months HSCT showing regression of the same. (IVA) Initial MRI showing hemorrhagic lesion in left cerebellum (white arrow), (IVB) Pre-HSCT MRI and (IVC) MRI post 6 months HSCT showing further regression of the same.
an autosomal recessive condition with defective genes involved in cytotoxic granule exocytosis. Primary HLH can be associated with immunodeficiency syndromes like Griscelli syndrome type-2, Chediak–Higashi syndrome, Hermansky–Pudlak syndrome type-2, and X-linked proliferative syndrome type-2.2 Secondary HLH is associated with infection, malignancy, rheumatologic, or iatrogenic (transplantation, immune suppression, immune activation).3

Neuropathological stages of HLH consist of three stages correlating with the severity of the disease and the amount of lymphocytic and histiocytic infiltration.4 Stage 1 is leptomeningeal infiltration. Stage 2 is additional involvement of the adjacent brain parenchyma with perivascular infiltrations. Stage 3 is the final stage of massive parenchymal infiltration with demyelination, parenchymal necrosis, and calcification.

**Clinical Features**
The most common presentation includes fever, pancytopenia, and hepatosplenomegaly. The most commonly affected systems include hematologic, hepatic (hepatitis, coagulopathy), central nervous (seizures, altered mental status), and pulmonary (Table 2).

**Diagnostic Criteria**
The diagnosis of HLH is based on the presence of molecular diagnosis of an HLH gene mutation or by the presence of 5 of 8 criteria from the HLH-2004 trial (Table 3).5

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**Fig. 4** Case 2: (A) Axial T2 and (B) axial fluid-attenuated inversion recovery (FLAIR), (C) and (D) axial postcontrast T1, (E) coronal postcontrast T1, and (F) sagittal postcontrast T1 showing ill-defined heterogeneous lesions involving bilateral fronto-parieto-occipital cortices, bilateral subcortical, and deep periventricular white matter, bilateral basal ganglia, corona radiata and centrum semiovale, pons, brain stem, and right cerebellum (white arrow). The lesions appear heterointense on T2 and FLAIR images. No signal loss is seen on gradient imaging (not shown here). On contrast administration nodular enhancement is seen. No mass effect or midline shift is seen. (G) Axial T1W T1-weighted (T1W), (H) axial T2W, and (I) axial FLAIR showing cystic encephalomalacia with gliosis, volume loss, and cortical laminar necrosis in bilateral temporal gyri.
Imaging Features
There are no imaging guidelines in HLH and the workup depends on clinical presentation. It is recommended to perform CSF studies and MRI brain even in patients without CNS symptoms. Abnormal imaging findings are seen in patients with HLH, who have no CSF abnormalities or neurologic symptoms.

The most common imaging finding is diffuse cerebral atrophy. Other findings are white matter lesions, demyelination, increased T2 hyperintensity in white matter, and
Table 1  Comparison showing typical neuroimaging features described in literature and the findings in our study

<table>
<thead>
<tr>
<th>Neuroimaging features of HLH described in literature</th>
<th>Finding in case 1</th>
<th>Finding in case 2</th>
<th>Finding in case 3</th>
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<tbody>
<tr>
<td>Diffuse cerebral atrophy</td>
<td>Diffuse cerebral atrophy</td>
<td>Diffuse cerebral atrophy</td>
<td>Diffuse cerebral atrophy</td>
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<tr>
<td>Diffuse white matter edema</td>
<td>Diffuse white matter edema</td>
<td>Diffuse white matter edema</td>
<td>Diffuse white matter edema</td>
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<tr>
<td>Rim/nodular enhancing or nonenhancing white matter and cortical lesions</td>
<td>Nonenhancing white matter and cortical lesions</td>
<td>Nodular enhancing white matter and cortical lesions</td>
<td>Rim enhancing white matter and cortical lesion</td>
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<tr>
<td>Deep gray matter lesions</td>
<td>–</td>
<td>Deep gray matter lesions</td>
<td>–</td>
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<tr>
<td>Leptomeningeal enhancement</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hemorrhage, calcification or necrosis</td>
<td>Hemorrhage</td>
<td>Necrosis, cystic encephalomalacia, cortical laminar necrosis</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Subdural collections</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Perineural and perivascular enhancement</td>
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Abbreviation: HLH, hemophagocytic lymphohistiocytosis.

Table 2  Imaging features of HLH involving various systems

<table>
<thead>
<tr>
<th>CNS</th>
<th>Pulmonary</th>
<th>Abdomen</th>
<th>Musculoskeletal</th>
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<tr>
<td>Diffuse cerebral atrophy</td>
<td>Alveolar or interstitial infiltrates</td>
<td>Hepatosplenomegaly</td>
<td>Periosteal new bone formation</td>
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<tr>
<td>White matter lesions and demyelination</td>
<td>Pleural effusion</td>
<td>Hepatic steatosis</td>
<td>Healing fractures</td>
</tr>
<tr>
<td>Cortical and subcortical lesions with or without variable nodular or ring enhancement</td>
<td>Peribronchial thickening</td>
<td>Ascites</td>
<td>Osteonecrosis</td>
</tr>
<tr>
<td>Hemorrhage, calcification, necrosis</td>
<td>Centrilobular nodules</td>
<td>Gallbladder wall thickening, periportal echogenicity</td>
<td>–</td>
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<tr>
<td>Diffuse brain edema</td>
<td>Consolidation</td>
<td>Nephromegaly, increased cortical echogenicity</td>
<td>–</td>
</tr>
<tr>
<td>Subdural collections</td>
<td>Ground glass opacities</td>
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Abbreviations: CNS, central nervous system; HLH, hemophagocytic lymphohistiocytosis.

Table 3  Clinical criteria from the HLH-2004 trial for diagnosis of HLH

1. Fever (≥38.5°C)
2. Splenomegaly
3. Cytopenia (at least 2 of 3: hemoglobin <9 g/dL, platelets <100,000/μL, absolute neutrophil count <1,000/μL)
4. Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL)
5. Hyperferritinemia (ferritin >500 ng/mL, although it is usually >3,000 ng/mL)
6. Elevated soluble CD25 (IL-2 receptor α, two standard deviations above age-adjusted norms)
7. Low or absent natural killer cell activity (cytotoxicity assay)
8. Hemophagocytosis in bone marrow, spleen, lymph node, or liver

Abbreviations: HLH, hemophagocytic lymphohistiocytosis; IL-2, interleukin-2.

Focal lesions in cortical and subcortical regions with variable nodular or ring enhancement or leptomeningeal enhancement. Patchy areas of T2 hyperintensity involving white matter represent patchy distribution of histiocytes infiltrating brain tissue. Inflammation may be seen along the spinal roots or cranial nerves showing enhancement. T2
hypointense parenchymal lesions are also described in the literature which was assumed to be caused by calcifications or hemorrhage. Restricted diffusion with low apparent diffusion coefficient values may be seen, which suggests active inflammation in the brain. Subdural collections may also be seen.

Various differential diagnoses are meningoencephalitis like aspergillosis and tumors with diffuse brain involvement (lymphoma, leukemia). The differential diagnosis for hemorrhagic lesions involving deep gray matter includes acute necrotizing encephalopathy (ANE) and acute hemorrhagic encephalomyelitis (AHEM). ANE typically involves bilateral thalami with necrosis and hemorrhage being the predominant findings. AHEM is a rare and severe form of acute disseminated encephalomyelitis in which variable involvement of the central gray matter is seen in addition to tumefactive white matter lesions.

**Conclusion**

The most common neuroimaging manifestation of HLH is multifocal parenchymal lesions and atrophy. Though MRI findings of HLH are nonspecific, it helps in evaluating the CNS involvement and extent of the disease in a diagnosed case of HLH and for follow-up.

**Funding**

None.

**Conflict of Interest**

None declared.

**References**