Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of excessive immune activation causing widespread inflammation and tissue destruction leading to multi-organ dysfunction and failure. Making the diagnosis of HLH could be quite challenging due to the broad range of presenting symptoms and their lack of specificity. After ruling out considerations for differential diagnoses, recognizing the most common presenting signs and symptoms of HLH, including neurologic dysfunction, and having a high clinical suspicion for HLH in the setting of inflammatory/demyelinating diseases are important for prompt diagnosis and treatment.

**Keywords:** Acute disseminated encephalomyelitis, encephalopathy, familial hemophagocytic lymphohistiocytosis, hemophagocytic lymphohistiocytosis, seizures

**INTRODUCTION**

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hematologic syndrome characterized by the uninhibited activation of immune cells. HLH could occur sporadically or could be acquired genetically. The clinical presentation is typically triggered by infection, autoimmune conditions, or immunosuppression. It tends to present in patients in their infancy or in the early years of life, although it has been known to present at any age. Presentation of HLH can be extremely variable making early diagnosis quite difficult. Without prompt treatment, mortality is extremely high.[1,2] However, with prompt diagnosis and adherence to treatment protocols, median survival is currently 54% at 6.2 years.[3,4]

**Pathogenesis and epidemiology**

In a healthy individual, natural killer (NK) cells and cytotoxic lymphocytes (CTLs) are responsible for inducing cell death in macrophages to maintain homeostasis and prevent excessive activation of inflammatory pathways. Typically, NK cells and CTLs create pores in macrophages, via the protein perforin, through which cytolytic granules, containing proteases such as granzyme B, are delivered causing the macrophages to lyse. In patients with HLH, proteins involved in this process are mutated preventing macrophage lysis from occurring. Without this negative feedback mechanism, the macrophages continue to proliferate producing large amounts of interferon gamma and other cytokines resulting in a massive inflammatory reaction and ultimately, tissue destruction and multi-organ failure. Due to the over-abundance of macrophages, another process termed hemophagocytosis, which is the process by which macrophages phagocytize all blood cells (eventually causing pancytopenia), also occurs within the hematologic system of HLH patients. This process can usually be visualized on lymph node, spleen, liver, and bone marrow biopsies of HLH patients.

HLH is inherited (familial HLH) about 25% of the time, while the remainder of the cases are believed to occur sporadically. Both familial and sporadic HLH cases can be triggered by immune activation or immune suppression. Viral infections, such as Epstein–Barr virus, are the most common trigger.[5] Of note, Kawasaki disease, a childhood autoimmune disorder, has also been reported as a trigger of HLH.

Familial HLH is inherited in an autosomal recessive manner, most often associated with parental consanguinity. Currently, five main loci for the mutated HLH genes are...
known: FHL1 resulting from an unclear genetic defect, FHL2 resulting from a mutated PRF1 gene that codes for perforin, FHL3 resulting from a mutated UNC13D gene that codes for Munc13-4 (protein involved in cytolytic granule maturation), FHL4 resulting from a mutated STX11 gene that codes for syntaxin 11 (protein controlling granule exocytosis), and FHL5 resulting from a mutated STXBP2 gene that codes for Munc18-2 (protein involved in cytotoxic granule release).\cite{10-13}

Although this syndrome can affect patients of any age, HLH is typically seen in children and most frequently occurs prior to 3 months of age.\cite{1} Among the pediatric population, HLH is estimated to affect 1 in 100,000 children.\cite{10} HLH has been reported to affect patients from a multitude of ethnic backgrounds. However, among the adult HLH patient population, about half of the cases were found to have occurred in Japan.\cite{11}

**Case Report**

Our patient, a previously healthy 11-year-old male of Honduran descent, with a past medical history significant for Kawasaki’s disease at age 3, initially presented with complaints of headache and nonbloody, nonbilious emesis for 4 days. Of note, family history was significant for the patient’s younger brother with HLH who had died at the age of 4 years, after presenting with symptoms of fever, pancytopenia, ataxia, and severe neurologic dysfunction, though the family was uncertain of the cause of death and had been unable to provide this information to the patient’s medical team at presentation.

A noncontrast head computed tomography was performed as part of his initial evaluation, which revealed multifocal edematous lesions of the brain. His magnetic resonance imaging (MRI) brain revealed supratentorial multifocal contrast-enhancing white matter lesions involving the bilateral temporal lobes with mild bilateral uncal herniation. Spinal MRI demonstrated multiple T2 hyperintense lesions within the thoracic spinal cord. Clinically, the patient was stable with intact mentation and normal functioning with mild right arm weakness. His electroencephalography (EEG) displayed excess delta waves consistent with diffuse cerebral dysfunction possibly related to toxic or metabolic causes; however, the patient had remained clinically stable and mentally intact. At this time, levetiracetam was initiated – due to the MRI and EEG findings – for seizure prophylaxis.

The patient then had a lumbar puncture (LP) and his cerebrospinal fluid (CSF) analysis revealed white blood cells 6/cubic mm (98% lymphocytes), red blood cell (RBC) 1/ cubic mm, glucose 74 mg/dL and protein 55 mg/dL (slightly elevated). There was no growth on CSF cultures, and the CSF was negative for Lyme disease, cryptococcal antigen, viral encephalitis panel, oligoclonal bands, Venereal Disease Research Laboratory, herpes simplex virus, beta-human chorionic gonadotropin, and alpha-fetoprotein. Bone marrow biopsy revealed no signs of malignancy. Though his initial symptoms of headache and emesis improved, the patient was noted to have become extremely anxious and agitated. Given the negative bone marrow biopsy and presence of white matter lesions on MRI brain, the patient was started on intravenous (IV) methylprednisolone for a presumed diagnosis of acute disseminated encephalomyelitis (ADEM). Over the course of the next several days, the patient’s anxiety and agitation progressed to severely disorganized thought processes and psychosis. When levetiracetam and steroids were stopped, his mental status had returned to normal, and he was discharged with neurology clinic follow-up.

However, he was re-admitted for headache and emesis in 2 weeks. Repeat brain MRI showed a significant increase in the number and size of white matter lesions. Several changes in the brain vasculature on MRI brain were concerning for vasculitis, including primary angiitis of the central nervous system (CNS) or neoplastic vasculitis. Spine MRI showed T2 hyperintense lesions of the cervical and thoracic spine, possibly indicative of ADEM, transverse myelitis, or vasculitis. At this point, additional imaging of the vasculature with magnetic resonance angiography was performed and normal vasculature was seen, essentially ruling out vasculitis. HLH studies including soluble CD25 (interleukin [IL]-2 receptor), NK function, perforin, and genotyping were sent to Cincinnati Children’s Hospital. His symptoms resolved again and he was discharged. He traveled outside the US to visit his home country for a couple of weeks after discharge from the hospital.

He was re-admitted again after 1 month with fever, body aches, headache, emesis, and diarrhea, at which time his laboratory work indicated that the patient had developed pancytopenia. He also had new-onset altered mental status with a rising ferritin level at 1029 ng/dL. His repeat EEG monitoring (video-EEG) prompted by the change in patient’s mental status revealed subclinical status epilepticus, for which the patient was treated with lorazepam, fosphenytoin, and levetiracetam. Bone marrow studies and other diagnostic tests were repeated and indicated no signs of malignancy. The patient was started on etoposide, dexamethasone, and broad-spectrum antibiotics for the treatment of presumed HLH as specified by the HLH treatment protocol. Due to worsening of seizure frequency with the development of status epilepticus, the patient was placed on a pentobarbital drip with the goal of burst
suppression pattern on EEG, and continuous renal replacement therapy was initiated as a result of the patient’s declining renal function. IL-2 receptor studies returned indicating extremely high levels consistent with a diagnosis of HLH. Additional HLH studies indicated minimal to absent NK cell activity, increased perforin, and granzyme B mean channel fluorescence in the NK cells, an increased percent of CD8 and NK cells expressing perforin. The genetic testing had revealed a mutation in Munc13-4, confirming familial HLH. After considerable effort, it was later discovered that this was the same genetic mutation that his deceased brother’s genetic testing had revealed. Two days later, the patient was successfully weaned off pentobarbital and started on phenobarbital at which point, he began to show signs of improvement from his prior comatose state. Gradually, the patient’s mental status and neurological examination improved over the next few days.

In concordance with the HLH protocol, the next phase of intrathecal HLH treatment with methotrexate was initiated. Due to a lack of improvement in the disease-marker laboratory results, etoposide was discontinued and the patient was initiated on a second-line HLH therapy, anti-thymocyte globulin (ATG), and methylprednisolone for 5 days. A repeat bone marrow biopsy revealed persistent pancytopenia consistent with HLH. The patient’s ferritin and other inflammatory markers continued to trend upward and the patient continued to improve. He was eventually discharged home with outpatient hematology-oncology and neurology follow-ups for continued HLH and seizure treatments, respectively.

**Clinical presentation**

HLH is a disease of multi-organ dysfunction that can have an extremely varied and nonspecific presentation. Fever, hepatosplenomegaly, lymphadenopathy, neurologic involvement, and or rash are common manifestations. High serum ferritin levels, pancytopenia, elevated liver function tests (LFTs), elevated D-dimer, hypertriglyceridemia, and hypofibrinogenemia are common laboratory abnormalities in patients with HLH.

According to the HLH-94 study (a set of treatment guidelines created by the Histiocyte Society in 1994), up to 33% of HLH cases have neurologic features. In some HLH cases, neurologic dysfunction has been the primary presenting feature of the illness. Neurologic symptoms of HLH include, but are not limited to, irritability, seizures, ataxia, cranial nerve palsies, hemiplegia/tetraplegia, mental status change, and/or encephalitis. CSF studies may show elevated protein levels and/or pleocytosis, and hypodense/necrotic areas have been observed on MRI of the brain.

Respiratory distress/failure requiring artificial ventilation, hypotension requiring vasopressors, and renal dysfunction requiring dialysis have all been recorded in HLH syndrome. Bleeding due to coagulation dysfunction and/or thrombocytopenia is also common, requiring transfusions.

**Diagnostic criteria**

The diagnostic criteria for HLH, determined by the subsequent HLH-2004 trial, are as follows:

- Confirmation of an HLH-associated genetic mutation
  - In children, the mutation must be either homozygous or compound heterozygous
  - In adults, a heterozygous mutation is sufficient if their clinical presentation is consistent with that of HLH.

- The presence of at least five of the eight of the following features:
  - Fever ≥38.5°C
  - Splenomegaly
  - Peripheral blood cytopenia
  - Hypertriglyceridemia and/or hypofibrinogenemia
  - Hemophagocytosis in bone marrow, spleen, lymph node, or liver
  - Low or absent NK cell activity
  - Ferritin >500 ng/mL
  - Elevated soluble CD25 (soluble IL-2 receptor alpha) two standard deviations above age-adjusted laboratory-specific norms.

**Management**

Prompt diagnosis and treatment of HLH is critical for patient survival. If the diagnosis of HLH is high on the differential, treatment should not be delayed despite pending test results or failure to meet all five of the eight required diagnostic criteria. Treatment of HLH is typically based on the HLH-94 treatment protocol that has increased the life expectancy of a patient with HLH from months to years. In 2004, the HLH-2004 treatment protocol was created, but many of the recommendations have not yet been implemented into clinical use due to the fact that the results of the trial are not currently available.

Under the HLH-94 guidelines, patients are to be treated for 8 weeks with an induction therapy, consisting of dexamethasone and etoposide. During the initial 8 weeks, etoposide should be given twice weekly for the first 2 weeks and then once weekly for the next 6 weeks. Etoposide is given at a dose of 150 mg/m² for adults and 5 mg/kg for children under 10 kg. For patients with renal dysfunction, these doses can be adjusted based on creatinine clearance. Dexamethasone is also given for the first 8 weeks. It can be given either orally or intravenously.
at a dose of 10 mg/m² daily for weeks 1 and 2, 5 mg/m² daily for weeks 3 and 4, 2.5 mg/m² for weeks 5 and 6, 1.25 mg/m² for week 7, and then tapered to 0 during week 8. In patients who require continued therapy after week 8, the HLH-94 protocol calls for 10 mg/m² pulses of dexamethasone for every 3 days along with continued weekly treatment with etoposide. After 8 weeks, patients with sporadic HLH can stop therapy unless their disease is persistent or if relapse occurs. In patients with familial or persistent HLH, the guidelines recommend a maintenance phase in which dexamethasone is given in pulses along with weekly etoposide treatments and cyclosporine (with a target trough of 200 mcg/L) until an allogeneic hematopoietic cell transplantation (HCT) can be performed. The protocol also recommends that intrathecal methotrexate can be administered weekly in HLH patients with CNS involvement.

Although the HLH-94 protocol also calls for the addition of cyclosporine after week 8, its use is not recommended due to the association between cyclosporine use and the development of posterior reversible encephalopathy syndrome (PRES) in HLH patients. PRES is a condition in which vasogenic cerebral edema of the posterior cerebral hemispheres occurs causing headache, seizures, mental status change, and/or vision loss.

For patients with neurologic symptoms, abnormal CSF findings, or pathologic findings on brain MRI, HLH-94 recommends that intrathecal methotrexate should be added to the treatment regimen. This therapy can be initiated as soon as any coagulopathy and/or thrombocytopenia is controlled to the point at which LP can be safely performed. The intrathecal methotrexate should be administered weekly at dosages, which are dependent on the patient’s age.

Several alternative HLH therapies also exist. One retrospective report analyzed 38 patients with familial HLH who received ATG therapy. The ATG was administered along with methylprednisolone over 5 consecutive days. After the 5 days, the methylprednisolone was tapered. Twenty-eight of the 38 patients received ATG as their first-line therapy along with intrathecal methotrexate, corticosteroids, and maintenance-phase cyclosporine. Due to incomplete response, 6 of these 28 patients required a second course of ATG. The remaining ten patients received ATG as a second-line therapy after other preceding therapies failed. One of these ten patients required a second course of ATG. Overall, 26 (73%) of the 38 patients were put into remission, 9 (24%) had a partial response to treatment, and 1 had no response.

Ultimately, for patients with familial HLH, HLH with hematologic malignancy, and persistent HLH, HCT is essential for long-term survival. HLA typing and the search for an HCT donor should be initiated shortly after diagnosis. Potential donors within the family should be tested to ensure they are not carrying HLH gene mutations. The goal is to achieve remission in all HLH patients prior to HCT to reduce morbidity and mortality associated with the therapy. In preparation for HCT, the patient must first undergo a myeloablative, nonmyeloablative, or reduced intensity-conditioning (RIC) regimen. Recent data suggest that RIC regimens, using alemtuzumab, fludarabine, and melphalan, may lead to increased survival and less complications when compared to other methods.

In addition to the HLH-specific therapies outlined above, these patients also require a multitude of supportive care therapies. RBC and platelet transfusions are often provided to maintain a specified hemoglobin level and an adequate platelet count. If a patient is having bleeding issues, fresh frozen plasma and/or cryoprecipitate can be given. HLH patients are also extremely susceptible to infection and thus, should be placed on neutropenic precautions as well as prophylactic antimicrobials (i.e., trimethoprim-sulfamethoxazole and fluconazole). IV immune globulin is also frequently utilized in these patients. Hypertension or hypotension must be managed with proper medications. In addition, many HLH patients require dialysis due to failing renal function.

To determine the effectiveness of the therapy, clinical and disease-specific HLH markers need to be evaluated on a regular basis. Clinical markers that should be evaluated daily include physical examination findings, a complete blood count (CBC) with differential, coagulation studies, renal function, electrolytes, and LFTs. CSF analysis should be performed at the time of the weekly intrathecal methotrexate therapy. Serum ferritin levels, which should be evaluated daily, and lymphocyte and cytokine markers, which should be evaluated weekly, are disease-specific markers. These markers are useful in determining whether or not the patient is responding appropriately to therapy.

For those who do achieve remission after induction therapy or for those who successfully receive HCT, these patients need to be closely monitored for signs of disease recurrence or relapse. Frequent follow-ups are required, especially during the 1st year of remission, and need to include a thorough physical examination, CBC with differential, LFTs, fibrinogen and D-dimer levels, and serum ferritin levels. In addition, steps should be taken to educate the patient’s family about the disease and to provide them with access to genetic counseling/testing.
**DISCUSSION**

The initial presentation and the lack of symptom specificity contribute to the challenges that physicians face in diagnosing this disease. In cases with no prior HLH family history or limited family history, physicians must be able to recognize the most common signs and symptoms of HLH clinically. HLH should be considered in cases involving fever of unknown origin and multi-organ dysfunction, especially in infants and young children. Clinical changes such as hepatosplenomegaly, lymphadenopathy, rash, and/or neurologic dysfunction are all common features seen in HLH. Exceedingly high ferritin levels, which are rarely seen outside of the setting of iron overload syndromes, should serve as a red flag in cases of undetermined diagnosis. Cytopenias, elevated LFTs, and coagulation dysfunction are other clues that a diagnosis of HLH may be on the differential.

Neurologic dysfunction may be a predominant feature of HLH. Neurologic symptoms such as seizures, ataxia, cranial nerve palsies, hemiplegia/tetraplegia, mental status change, and/or encephalitis are present in up to one-third of the diagnosed cases of HLH and thus, should raise suspicion of this diagnosis. In addition, HLH patients may have CSF abnormalities, including elevated protein levels, and/or demyelinated, necrotic lesions on MRI brain.

Several other diseases and disorders have symptomatology quite similar to that of HLH. Among them are drug reaction with eosinophilia and systemic symptoms, Kawasaki disease, autoimmune lymphoproliferative syndrome, cytaphagic histiocytic panniculitis, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome. When any of these diagnoses are on the differential, HLH should also be considered.

When neurologic dysfunction is the predominant feature of the disease, differential diagnosis such as ADEM is often considered first. However, within the pediatric population, the incidence of ADEM is actually reported to be lower than that of HLH. According to one review, the incidence of ADEM in the state of California is 0.4/100,000 per year.[27] Meanwhile, a different report reviewed the incidence of HLH to be as high as 1/100,000 per year in the state of Texas.[10] Like HLH, ADEM is typically triggered by infection causing autoimmune dysfunction in genetically susceptible individuals. In ADEM, demyelination of the CNS takes place resulting in fever, headache, vomiting, encephalitis, and a broad range of neurological deficits.[12,28] As with HLH, hemiparesis, cerebellar ataxia, and cranial neuropathies are also commonly observed ADEM symptoms.[28] White matter lesions are demonstrated on T2-weighted images and fluid-attenuated inversion recovery sequences, and pleocytosis and/or elevated protein may be seen on CSF studies.[30,31] Unlike HLH, however, ADEM patients often undergo a complete recovery within 2–4 weeks of symptom onset. Moreover, patients with ADEM will not have the multi-organ dysfunction seen in HLH patients. In addition, findings such as splenomegaly, peripheral blood cytopenias, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis, and elevated serum ferritin levels would be left unexplained by a diagnosis of ADEM.

**CONCLUSIONS**

Prompt diagnosis and treatment are very important for the overall well-being and survival of HLH patients. However, this can only be achieved if HLH is first suspected. Physicians need to be able to recognize the signs and symptoms commonly seen in HLH and actively pursue this diagnosis in the cases of undiagnosed febrile illness with multi-organ dysfunction. HLH should also be explored in pediatric cases of acute-onset neurologic symptoms and in cases of suspected ADEM. In cases where the diagnosis of HLH is highly suspected, diagnostic criteria have not yet been met, treatment should be initiated and HLH-specific markers should be pursued simultaneously. HLH poses a diagnostic dilemma in neurological disorders because of the similarity of imaging and initial clinical findings to ADEM, but with a comprehensive investigation of other organ systems and close follow-up after the initial presentation, the dilemma could be appropriately addressed.

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**Conflicts of interest**

There are no conflicts of interest.

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