

Hemophagocytic Lymphohistiocytosis Masquerading as Child Abuse: Presentation of Three Cases and Review of Central Nervous System Findings in Hemophagocytic Lymphohistiocytosis

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ABSTRACT. Hemophagocytic lymphohistiocytosis (HLH) is a rare disease resulting from abnormal proliferation of histiocytes in tissues and organs. Although the disease generally presents with systemic symptoms such as pancytopenia, coagulopathy, and organomegaly, HLH may also present with central nervous system (CNS) manifestations. CNS events can range from irritability to encephalopathy and coma. Retinal and intracranial hemorrhages are among the neuropathologic findings in these children. Patients who present with CNS findings may have symptoms that mimic those of inflicted injury. These children are at risk, therefore, for misdiagnosis as victims of child abuse. Such an error causes not only unnecessary additional trauma to the family but also, more important, a delay in initiating effective therapy. We present 3 cases of children with HLH who initially came to medical attention with neurologic findings, all suspected to be victims of child abuse. Subsequent laboratory evaluations, however, were consistent with the diagnosis of HLH. No additional evidence of child abuse was obtained, and the charges eventually were dropped. Two of the 3 children died from their disease shortly after presentation; the third is surviving with no evidence of HLH several months after allogeneic bone marrow transplantation. Although the diagnosis of child abuse certainly is all too common, clinicians need to be diligent and informed to avoid assigning this label erroneously. Several laboratory findings of HLH may alert physicians to the possibility of this diagnosis. The timely diagnosis of and institution of therapy for HLH may reduce ultimate morbidity and mortality. *Pediatrics* 2003;111:e636–e640. URL: <http://www.pediatrics.org/cgi/content/full/111/5/e636>; *child abuse, hemophagocytic lymphohistiocytosis.*

ABBREVIATIONS. HLH, hemophagocytic lymphohistiocytosis; CNS, central nervous system; ED, emergency department; PT, prothrombin time; PTT, partial thromboplastin time; CT, computed tomography.

Hemophagocytic lymphohistiocytosis (HLH), a rare disorder primarily of childhood, typically presents with fever, hepatosplenomegaly, lymphadenopathy, and sometimes vague or dramatic central nervous system (CNS) dysfunction.

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Supporting laboratory evidence includes cytopenias, elevated liver enzymes and hyperbilirubinemia, coagulopathy, hypertriglyceridemia, hyperferritinemia, and hypofibrinogenemia.¹ When untreated, the disease is uniformly fatal. Optimal therapy consists of cytotoxic and immunosuppressive chemotherapy with the HLH-94 protocol.² A bone marrow transplant, given a suitable donor, provides the greatest chance for a cure in very young children or in those with the familial form of HLH.

Although some cases are thought to be associated with virus infection, others manifest a familial inheritance pattern, and a large percentage of cases have no definable cause. Because of the relative rarity of the disorder as well as unfamiliarity on the part of physicians, the diagnosis can be elusive even with a classic presentation.

We report 3 cases of patients who received a diagnosis of HLH after an atypical presentation involving CNS events initially suspected to be evidence of child abuse. It is hoped that an increased awareness of HLH by primary care and emergency department (ED) physicians will lead to prompt initiation of proper therapy and avoidance of inappropriate accusations of child abuse.

CASE REPORTS

Case 1

A Vietnamese boy was born at 35 weeks' gestation to a 23-year-old Gravida 2 Para 1 mother by cesarean section performed because of preterm labor. The pregnancy was otherwise uncomplicated, and the child's birth weight was 2926 g (6 lb 7 oz) with Apgar scores of 9/9. After a brief hospitalization to rule out sepsis (maternal group B streptococcus status unknown), the patient was discharged in good condition with the mother. The family history was remarkable for consanguinity of the maternal great-grandparents, a maternal uncle who died at 3 years of age in Vietnam of unexplained "internal bleeding," and retinitis pigmentosa in the mother. The patient's older sibling is healthy. On the 11th day of life, the infant began to refuse feedings and cry inconsolably. After several hours, the mother noticed that the infant was cold and blue, so he was rushed to a local hospital ED where he was found to have profound hypothermia and acidosis.

In the ED, the patient had a temperature of 89°F (32°C) and pH of 6.9. His weight had decreased to 2200 g. Laboratory test abnormalities, aside from acidosis, included a shortened prothrombin time (PT), prolonged partial thromboplastin time (PTT), and slightly elevated alanine aminotransferase (Table 1). He received appropriate resuscitation and was transferred to the neonatal intensive care unit. The patient developed seizure activity that was controlled with Phenobarbital and a sepsis evaluation was negative. A computed tomography (CT) scan of his head revealed moderate left-sided subdural hemorrhage with cerebral edema and mass shift (Fig 1). An electroencephalogram was likewise abnormal, consistent with diffuse encephalopathy. Ophthalmic

TABLE 1. Summary of Clinical and Laboratory Findings

Laboratory Data (Normal Values)	Case 1 Initial	Case 1 HLH Diagnosis (3 Months Later)	Case 2	Case 3
Seizure	X		X	X
Retinal hemorrhages	X		X	
Intracranial hemorrhage	X		X	
Brain edema	X			X
Hepatosplenomegaly		X		X
Abnormal skeletal findings				X
Hemophagocytosis		X	X	X
WBC ($5-19.5 \times 10^3/\mu\text{L}$)	16.1	5.21	16.6	6.19
ANC ($1-8.5 \times 10^3/\mu\text{L}$)	9.36	0.250	10.9	2.17
Platelets ($150-450 \times 10^3/\mu\text{L}$)	246	27	544	51
Hemoglobin (9.5–14.1 gm/dL)	11.6	9	7.3	12.5
Ferritin (20–236 ng/mL)	ND	19 923	ND	20 286
Triglycerides (20–150 mg/dL)	105	136	194	66
PT/PTT (10.5–14.5/21–34 s)	9.3/39.8	22.9/146	22/46	16/81
AST (20–60 U/L)	ND	363	363	719
ALT (6–50 U/L)	54	377	414	161
Bilirubin (mg/dL; unconjugated/ conjugated; <0.35/<1.0)		0/9.4	1.6/0	0.6/1.3

WBC indicates white blood cells; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ND, not done.

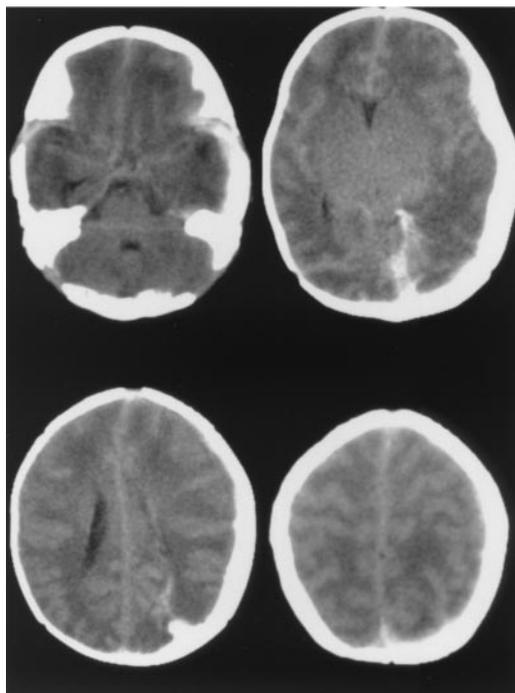


Fig 1. CT of brain without contrast. Extra-axial hemorrhage of the left temporal, frontal, occipital, and parietal regions. Diffuse subarachnoid hemorrhage in the basilar cisterns and along the tentorium on the left and posterior interhemispheric falx, as well as focal hemorrhages in the cortex and subcortex of the left occipital parietal lobe. Diffuse brain edema is also present.

examination revealed bilateral predominately peripheral perivascular retinal hemorrhages with peripheral retinal necrosis compatible with an infectious cause versus shaken infant syndrome.

The composite findings of subdural hemorrhage, failure to thrive, and retinal hemorrhages resulted in the diagnosis of shaken infant syndrome. The patient and his older sibling were placed under child protective custody.

Approximately 2 months after a prolonged hospitalization for malabsorption, the patient became febrile and was placed on antibiotics. Cultures of the blood and cerebrospinal fluid were negative. During the next 7 days the patient developed massive hepatosplenomegaly resulting in respiratory compromise. He also had a coagulopathy (PT 22.9 seconds/PTT 146.5 seconds) and

pancytopenia with an absolute neutrophil nadir of $250/\mu\text{L}$, platelet count $<27\,000/\mu\text{L}$, and hemoglobin of 9 g/dL (90 g/L). Liver function studies were abnormal with mild unconjugated hyperbilirubinemia and ferritin of 19 923 ng/mL. A bone marrow biopsy and aspirate revealed hemophagocytosis confirming diagnosis of HLH. The patient was treated on the HLH-94 protocol with dexamethasone, VP-16, and cyclosporine and improved dramatically over the next several weeks. Approximately 6 months after diagnosis, he underwent a bone marrow transplant and is cured of the HLH. Because of the diagnosis of HLH with its CNS manifestations, the diagnosis of shaken infant syndrome was removed. The patient and sibling were returned to parental custody after a social services investigation failed to find other evidence of child abuse.

Case 2

A 4-month-old white boy had a 2-day history of fussiness, difficulty sleeping, a small amount of bleeding from his nares, and an ecchymoses on his chest (possibly from mild trauma by a sibling). On the evening before his death, the child fed poorly, had a fever of 100.6°F, and had a high-pitched cry. He was found pale, yellow, and cold by his mother and taken to a community hospital with apparent seizures. A head CT showed a subdural and intraparenchymal bleeding with no skull fracture and a unilateral enlarged pupil. Radiologic examinations of the abdomen and skeleton revealed no intra-abdominal trauma or fractures. He was transferred to a tertiary medical center, where bilateral retinal hemorrhages and the chest ecchymoses were noted. Throughout the medical records were comments that the brain and eye findings were the result of inflicted injury. He had no lymphadenopathy or enlargement of the liver or spleen. In the tertiary medical center, laboratory evaluations showed anemia hemoglobin of 8.8 g/dL (80 g/L), normal white blood cell count ($9000/\mu\text{L}$), and platelet count ($544\,000/\mu\text{L}$), but elevated liver function tests alanine aminotransferase 363 U/L ($6.1\ \mu\text{kat/L}$), aspartate aminotransferase 414 U/L ($6.9\ \mu\text{kat/L}$), lactate dehydrogenase 1305 U/L ($21.7\ \mu\text{kat/L}$), PT (20 seconds), PTT (46 seconds), and elevated triglycerides of 194 mg/dL ($2.2\ \text{mmol/L}$). He had a craniotomy to evacuate the subdural bleed and vigorous support with transfused red cells, platelets, fresh-frozen plasma, and ventilatory assistance. Despite these interventions, he died ~36 hours after presenting to the community hospital.

An autopsy showed focal hemophagocytic histiocytic infiltrate consistent with HLH in the leptomeninges and the subdural hemorrhage (Fig 2A). Within the bilateral retinal hemorrhages and perioptic sclera were hemophagocytic histiocytes (Fig 2B). The bone marrow, lymph nodes, and spleen did not have lymphohistiocytic infiltrates. There was no family history of consanguinity or possible HLH.

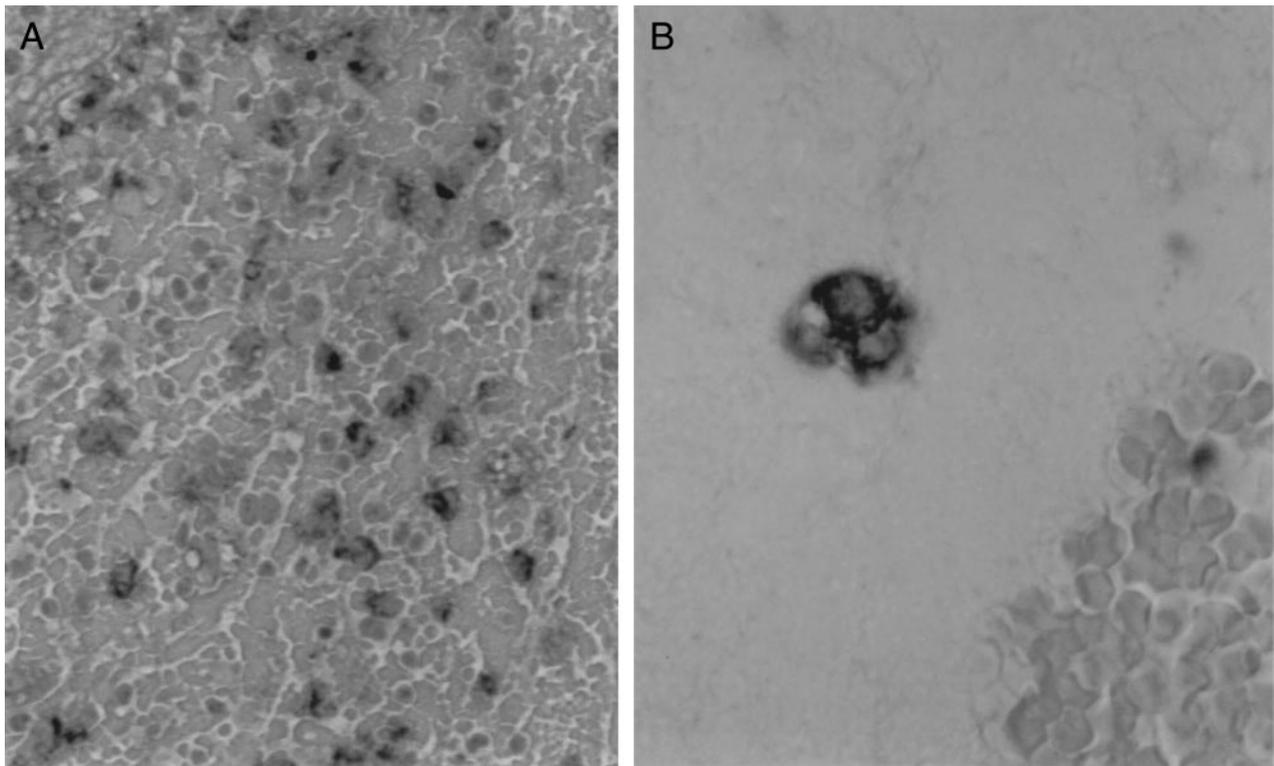


Fig 2. A, Wright-Geimsa–stained section of the subdural hemorrhage in patient 2 with many CD68 positive (brown) macrophages present. B, Higher power view of a CD68-positive macrophage from the retinal hemorrhage demonstrating hemophagocytosis.

Case 3

A 7-week-old male Nigerian infant was found unresponsive and asystolic in his child care center. The emergency medical service resuscitated him but noted that the pupils were fixed and dilated and his liver was 3 cm below the costal margin. On arrival at the Texas Children’s Hospital ED, his pH was 7.12 and he had a platelet count of 51 000/ μ L, a prolonged PTT, and elevated liver enzymes (Table 1). A noncontrast brain CT showed no hemorrhage or skull fracture, but hypodense areas of both posterior temporal and parietal lobes were indeterminate for infarct or edema versus white matter immaturity. A skeletal survey demonstrated periosteal new bone of the left humeral midshaft and mild cortical irregularity of the left medial tibial cortex for which a traumatic cause could not be excluded (Fig 3). Periosteal new bone formation of the medial right tibia seemed to be physiologic. Ventilatory support, fluid resuscitation, transfusions of hemoglobin and platelets, plus infusions of fresh-frozen plasma corrected some of these abnormalities. The patient had multiple seizures. Repeat noncontrast brain CT performed 2 days after admission revealed severe brain edema without herniation or bleed and extensive areas of hypodensity in the deep gray nuclei. Because of the suspicion of HLH, a serum ferritin was drawn and found to be 20 286 ng/mL. A bone marrow aspirate was diagnostic of HLH, and treatment was initiated with dexamethasone and VP-16 after obtaining informed consent from the parents. No family history of consanguinity or possible HLH was determined. Unfortunately, this child’s neurologic condition continued to deteriorate and the parents agreed to withdrawal of life support. Permission for a postmortem examination was declined.

DISCUSSION

The preceding case reports illustrate that HLH can present with symptoms similar to child abuse and that clinicians may have significant difficulty diagnosing HLH, especially when the presentation is atypical. In the first 2 cases, an older sibling was removed from parental custody because of the suspicion of abuse, causing additional stress and trauma

for the family. Although not always part of the classic presentation for HLH, CNS events have been previously described by numerous authors as occurring in 20% to 100% of HLH patients.^{3–5} Patients may present with primarily CNS findings and be treated for presumed infectious encephalitis before the correct diagnosis is made.⁶ Those with meningeal symptoms receive a diagnosis, on the average, in the first 7 months of life, and those with other neurologic symptoms receive a diagnosis by 16 months of life. Reported CNS symptoms include hypo- or hypertonia, opisthotonus, irregularities of heart rate or respirations, seizures, ataxia, cranial nerve findings, and other nonspecific signs of raised intracranial pressure.³ Frequently described radiologic manifestations include abnormal leptomeningeal enhancement, focal necrosis with parenchymal volume loss, and atrophy.^{4,5} The leptomeninges are infiltrated by lymphocytes and histiocytes, associated with a sterile CSF lymphocytosis and elevated protein levels.⁴ With more extensive involvement, the perivascular spaces are infiltrated with astrocytic and microglial cell proliferation affecting the white matter most extensively. Areas of necrosis and focal or diffuse demyelination may follow. Henter and Nennesmo’s⁴ report of 23 patients revealed focal hemorrhage in the leptomeninges of 1 patient and of the basal ganglia in another. Although Haddad et al⁵ did not specifically describe hemorrhages in their patients, 2 were found to have subdural space dilation. The unenhanced CT (Fig 2A) of the Haddad paper showed a subdural effusion that had similar imaging characteristics of the hemorrhage seen in our patient



Fig 3. The left humerus has periosteal new bone reaction, not typical of a physiologic reaction, and trauma was suspected according to the radiology report. Anteroposterior films of the tibia show an irregularity of the medial cortex on the left suspicious for traumatic reaction and periosteal new bone formation on the medial aspect of the right tibia (arrows).

1 (Fig 1). Cases 1 and 2 in our report probably represent the extreme result of tissue necrosis and blood vessel destruction caused by the perivascular infiltrations of lymphocytes and macrophages. The hemorrhages were facilitated by the coagulopathy manifested by the prolonged PTTs in all 3 patients.

Ocular findings, prominent in our first and second cases, have also been described.⁷⁻¹¹ Liao and Thompson¹⁰ described a case of a teenage boy who presented with fever and visual disturbances. On examination, he was found to have scattered flame hemorrhages, which subsequently resolved as the patient was treated for HLH. Autopsy evaluations have identified lymphohistiocytic infiltration of the optic nerve, iris, choroids, and perivascular structures in other patients.⁷⁻⁹ Retinal hemorrhages, often considered 1 of the hallmarks of shaken infant syndrome, were misleading in the cases presented here. Our first patient presented with several findings characteristic of abuse but were most likely from CNS HLH. The child protective services department cleared the family of the abuse charges after a thorough investigation and realization of the HLH diagnosis as well as the fact that the child continued to require hospitalization for symptoms (diarrhea) that could not be linked to abuse. Thus, the weight of evidence greatly diminishes the probability that this was shaken infant syndrome in addition to HLH.

The third case presents a picture of HLH that often creates suspicion as an abuse case in pediatric EDs, with the sudden lack of responsiveness and subse-

quent asystole in an otherwise healthy child. Given the nonspecific periosteal elevation of the humerus and cortical irregularity of the tibia, nonaccidental trauma could not be excluded. A possible explanation in this case, however, is periosteal elevation as a result of marrow infiltration. Had the treating physicians not been aware of HLH and appropriately explored it as an alternative explanation for the child's condition, the family or child care center may well have had to face a murder charge.

Hepatosplenomegaly in 2 of the cases and abnormal laboratory findings in all 3 at the time of presentation could have alerted clinicians to an underlying systemic illness (see Table 1). Striking elevation of the PTT was present in all 3 patients on initial presentation. Two had markedly elevated liver enzymes (patients 2 and 3). One patient was anemic and another was thrombocytopenic. It is known that patients with severe brain injury may have disseminated intravascular coagulation and elevations of the PT or PTT.¹² Patients reported in that series, however, had traumatic injuries primarily from automobile accidents and penetrating or blunt trauma, not shaken infant syndrome. Likewise hepatosplenomegaly, cytopenias, abnormal liver function tests, and electroencephalogram findings of diffuse encephalopathy are not usual findings in child abuse. One might suspect a coincident viral infection in some instances of cytopenias. However, the constellation of hepatosplenomegaly, CNS abnormalities, and the above noted laboratory findings should alert a clinician to the possibility that HLH could be the correct diagnosis.

It is imperative that clinicians be aware of HLH in all of its manifestations because HLH can be confused with other diagnoses besides child abuse, including hepatitis, fever of unknown origin, and sepsis.¹³ Screening for HLH with a complete blood count, liver function tests, triglyceride level, and serum ferritin levels as well as possibly bone marrow aspiration and biopsy can be accomplished in a relatively easy and expedient manner, even in a critically ill child. The infiltrating features of CNS lesions in HLH are easily seen by T2-weighted or fluid-attenuated inversion recovery MRI images and thus can further differentiate HLH from child abuse. Subsequent institution of appropriate therapy can be life saving. Although child abuse is unfortunately a more common entity than HLH, the false accusation of this can be devastating for a family. Heightened clinical awareness and basic laboratory evaluations may help prevent such an error when HLH is the cause of unusual CNS abnormalities in young children.

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