Acute hemorrhagic leukoencephalitis (AHLE) is a rare, fulminant CNS demyelinating condition usually diagnosed at autopsy. We report the clinical, laboratory, radiographic, and pathologic features of the first nonfatal case of pediatric AHLE confirmed by brain biopsy. Pathologic diagnosis of this condition may be critical to exclude more-common processes and to expedite the decision to administer high-dose corticosteroid therapy, which is potentially lifesaving.

Case report. A 10-year-old, previously healthy Filipino girl was admitted to Children’s Hospital and Health Center, San Diego, California, in October 1999 with a 2-day history of fever, right-sided frontal headache, abdominal pain, and vomiting. One day before admission to the hospital, she had become progressively lethargic. On the day of admission, she became photophobic and stated that she could not see her mother, who brought the child to the hospital immediately on noting a rightward gaze deviation.

The patient had no antecedent upper respiratory symptoms, cough, diarrhea, pharyngitis, conjunctivitis, arthralgia, or rash. There was no history of recent travel or vaccinations. A 3-year-old sibling had a resolving febrile illness without localizing signs, the onset of which was concomitant with the onset of the patient’s symptoms. There were no other ill contacts or contact with any person with tuberculosis. The patient had been bitten by a mosquito on the same day that she developed symptoms, but she denied previous mosquito or other insect bites, including tick bites. There was no exposure to domestic or wild animals, including bats, skunks, and raccoons. She had visited a local department store 3 months before the onset of the illness, where she observed but did not touch caged parakeets. She frequently swam in a chlorinated municipal pool but had not swum in freshwater lakes or rivers.

The only medication she had taken recently was acetaminophen, 10 mg/kg every 4–6 h, 1 day before admission. Her medical history was unremarkable, and immunizations were up to date. She had a history of wild-type varicella-zoster virus (VZV) infection 3 years earlier and of intermittent cold sores (but none recently). She had never received blood products.

On physical examination at admission, the patient was found to be thin but well nourished. She had a Glasgow coma score of 14. Her temperature was 39.4°C; pulse, 90 beats/min; blood pressure, 130/70 mm Hg; and respiratory rate, 18 breaths/min. Examination of the patient’s head and neck revealed subtle meningismus. Her fundi were normal. Her pupils were unequal in size (right pupil, 3 mm in diameter; left pupil, 5 mm) but reactive. Results of examination of the chest were unremarkable. She had no hepatosplenomegaly, lymphadenopathy, or rash. She had persistent rightward gaze deviation and inability to move her eyes leftward beyond midline, limitation of inferior gaze, and moderate left-sided and mild right-sided upper and lower extremity weakness. Reflexes were normal, except for equivocal plantar extensor responses bilaterally.

A cranial CT scan without contrast showed severe right-sided cerebral edema with a midline shift and mild left-sided edema. MRI revealed extensive deep and subcortical white-matter changes in the right hemisphere and posterior left hemisphere (figure 1). Laboratory testing performed at admission revealed a peripheral WBC count of 16.0 cells/µL, with 75% segmented neutrophils, 13% bands, 8% lymphocytes, 4% monocytes, and 0% eosinophils. Measurement of hemoglobin and platelet count, analysis of serum, urinalysis, and chest radiography yielded normal results. The erythrocyte sedimentation rate (ESR) was 98 mm/h.

After the patient was admitted to the intensive care unit, control of intracranial pressure (ICP) was achieved through intubation, hyperventilation, and administration of mannitol, hypertonic saline [1], and thiopental. A lumbar puncture was performed. Opening pressure was 6 mm Hg, and closing pressure was 5 mm Hg. The CSF had 275 WBCs/µL, with 75% segmented neutrophils, 2% bands, 8% lymphocytes (with reactive lymphocytes seen), 7% monocytes, and 377 RBCs/µL.
The total protein level in the CSF was 160 mg/dL, and the glucose level was 79 mg/dL.

An electroencephalogram obtained on the second hospital day showed delta-wave activity that was consistent with diffuse, severe encephalopathy. Intermittent sharp contoured forms were demonstrated bitemporally, with a right-sided predominance observed on a second recording. Despite maximal medical treatment to control ICP, the patient developed a herniation syndrome with increasingly asymmetric and sluggishly reactive pupils. ICP of 20–30 mm Hg was measured via a transduced external ventricular drain placed shortly after admission, and a second CT scan showed severe, worsened right-sided cerebral edema. The patient was taken to the operating room, where a partial right decompressive hemicraniectomy was performed \[2\] and a right temporal brain biopsy specimen was obtained.

The biopsy specimen included an adequate portion of cerebral cortex, with multiple large arteries and arterioles. Perivascular hemorrhagic necrosis with subacute inflammation in the subcortical white matter was a predominant finding. Patchy demyelination was evident in these foci, with an inflammatory infiltrate principally composed of neutrophils and foamy histiocytes. Individual neurons were normal in distribution and histologic appearance. There was no evidence of neoplasia, thrombosis, granulomas, abscess, vasculitis, fungi, parasites, or intranuclear or intracytoplasmic viral inclusions (figure 2).

The patient initially received vancomycin, ceftriaxone, and acyclovir. Antituberculous chemotherapy (isoniazid, rifampin, and pyrizinamide) and fluconazole were added until the results of CSF acid-fast bacillus smears, PCR for *Mycobacterium tuberculosis* complex, testing for cryptococcal antigen, and serologic testing for coccidioidomycosis were found to be negative. Bacterial, fungal, and mycobacterial cultures of blood, CSF, and brain tissue and viral cultures of samples from the nasopharynx and rectum and of CSF and brain tissue were negative. PCR testing for enteroviruses (EVs) and herpes simplex viruses (HSV) performed on CSF samples yielded negative results (Rapid Diagnostic Laboratory, Children’s Hospital and Health Center). In addition, consensus sequence PCR testing of CSF samples for human herpesviruses (HSV 1 and 2, cytomegalovirus, VZV, Epstein-Barr virus [EBV], and human herpesvirus 6) yielded negative results (California State Public Health Laboratory, Berkeley). Serologic evaluation for acute EV, HSV, VZV, EBV, influenza viruses A and B, St. Louis encephalitis and western equine encephalitis viruses, *Bartonella henselae*, *Chlamydia* species, *Mycoplasma pneumoniae*, and HIV infection had negative results. Rabies fluorescent antibody testing of 6 slides of brain tissue also yielded negative results (San Diego County Public Health Laboratory).

On the sixth day of hospitalization, after negative results of testing for acute infection and histopathologic examination of brain tissue were obtained, the patient was treated with dexamethasone, 4 mg/kg/day iv in divided doses administered every 6 h (with a subsequent gradual intravenous dexamethasone taper that lasted 5 weeks), and 2 doses of intravenous immunoglobulin (IVIG), 2 mg/kg followed by 1 mg/kg 24 h later. The patient’s ICP normalized after 72 h, and medical ICP ther-
apy was gradually decreased over the course of the following week. CSF pleocytosis resolved by the 14th hospital day. Weekly neuroimaging revealed slowly decreasing white-matter edema in both hemispheres and evolving encephalomalacia and atrophy over the course of the following 6 weeks. The patient had a protracted but relatively uneventful convalescence. She was discharged after 3 months of hospitalization (including 5 weeks of rehabilitation) with mild to moderate residual left-sided weakness, left lower quadrantanopsia, and left spatial neglect of moderate degree. At almost 2 years after admission, she had only a subtle decline in cognitive skills and continued in the same school grade but with mildly decreased aptitude for some subjects, particularly mathematics.

**Discussion.** This 10-year-old child is the fourth reported pediatric survivor of AHLE and the only survivor with pathologic confirmation of the diagnosis. Aggressive medical and surgical control of ICP, along with immunomodulatory therapy, led to a good outcome of this usually fatal condition.

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**Figure 2.** A, Punctate, ring-shaped foci of perivascular hemorrhage and edema localized to cerebral white matter. Thromboemboli, viral cytopathologic effects, foreign cells, abscesses, and granulomas are not seen. (Original magnification, ×200.) B, Accentuation of perivascular hemorrhage and edema, with scattered infiltrating polymorphonuclear leukocytes (vertical arrowheads), foamy macrophages (horizontal arrows), and rare hemosiderin-laden macrophages. Scattered individual glial cell necrosis is evident. (Original magnification, ×400.)
Table 1. Clinical, laboratory, and radiographic features and options for treatment of acute disseminated encephalomyelitis (ADEM) and acute hemorrhagic leukoencephalitis (AHLE).

<table>
<thead>
<tr>
<th>Feature</th>
<th>ADEM cases</th>
<th>AHLE cases</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidly progressive and fatal disease, (n/N)%</td>
<td>1/39 (3)</td>
<td>6/10 (60)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>WBC count in CSF, median cells/(\mu)L (range)</td>
<td>15 (0–340)</td>
<td>145 (2–11,900)</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>Total protein level in CSF, median mg/dL (range)</td>
<td>32 (14–672)</td>
<td>115 (12–1290)</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>Elevation of CSF opening pressure or ICP, (n/N)%</td>
<td>3/39 (8)</td>
<td>5/7 (71)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Peripheral WBC count, median cells/(\mu)L (range)</td>
<td>13,000 (3300–28,100)</td>
<td>17,000 (15,000–40,000)</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>CT results</td>
<td>Normal or WM hypodensities</td>
<td>Edema (often asymmetric)</td>
<td></td>
</tr>
<tr>
<td>MRI (T2/FLAIR) results</td>
<td>Diffuse subcortical WM changes</td>
<td>Diffuse WM changes</td>
<td></td>
</tr>
<tr>
<td>Pathologic features</td>
<td>Focal demyelination, perivascular PMNL infiltrates, macrophages, hemorrhage absent</td>
<td>Focal demyelination, perivascular PMNL infiltrates, focal perivascular WM hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Methylprednisolone and dexamethasone</td>
<td>Dexamethasone</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. FLAIR, fluid-attenuated inversion recovery; ICP, intracranial pressure; PMNL, polymorphonuclear leukocytes; WM, white matter. ADEM data are from J. A. D. Leake, S. Albani, A. S. Kao, M. O. Senac, M. P. Nespeca, A. D. Paulino, E. R. Quintela, M. H. Sawyer, and J. S. Bradley, unpublished data; AHLE data are from [10].

In 1941, Hurst [3] described 2 adult patients who developed acute encephalopathy with focal neurologic signs after respiratory illness. The first patient was a housewife who died <2 days after developing headache, aphasia, and right-sided hemiparesis, and the second patient was a munitions worker who died <1 week after developing confusion, aphasia, and seizures and entering a coma. The pathologic lesions seen in the 2 patients were similar and were characterized by edema; hemorrhagic lesions of the white matter, primarily limited to 1 cerebral hemisphere; perivascular polymorphonuclear infiltrates; demyelination; necrosis; and fibrin deposition in and around blood vessels [3].

Since Hurst’s first description, <100 adult [4–9] and 10 pediatric [10, 11] cases of AHLE have been reported. Of 7 pediatric cases confirmed by histologic testing, all were fatal, and all nonfatal cases were diagnosed on clinical and radiographic grounds alone. In the only published review of pediatric cases, the age range of the patients was 2–19 years, and death usually occurred within hours to days after the onset of neurologic symptoms [10].

It is widely hypothesized that AHLE represents the rare, severe extreme of a spectrum of CNS demyelinating diseases, which includes the more common pediatric condition acute disseminated encephalomyelitis (ADEM) [10, 12]. Many similarities exist between AHLE and ADEM. Both are commonly preceded by upper respiratory infections or by HSV, EBV, rubella, measles, mumps, or influenzavirus infection or vaccination. Although many infectious and vaccine antecedents have been associated with both conditions, an active search for such causes is often unrevealing, as it was with our patient. Despite these similarities, there are epidemiologic, clinical, laboratory, and pathologic distinctions between the 2 conditions (table 1). Whereas ADEM is more commonly diagnosed in children, AHLE is seen most frequently among young adults. AHLE may be disproportionately common among persons of Asian and/or Pacific Island ancestry, as in our Filipino patient, but ADEM does not more commonly affect persons of any particular ethnicity. Further differentiation between the 2 entities is suggested by certain laboratory findings: in patients with ADEM, CSF cell counts and total protein levels are usually normal or mildly elevated, with a lymphocytic predominance, whereas in patients with AHLE, the CSF often has a more pronounced pleocytosis, with a polymorphonuclear predominance. A higher peripheral polymorphonuclear leukocytosis is also seen in association with the latter condition. The ESR is usually normal to moderately elevated in patients with ADEM, but in those with AHLE, the ESR is often high. CSF opening pressure is likely to be normal during ADEM but elevated early in the course of AHLE. CSF pleocytosis with neutrophils and increased opening pressure may prompt concern about bacterial meningitis, but asymmetric white-matter changes are very rarely seen in association with bacterial, fungal, or other infections and should lead one to consider AHLE. Hemorrhage is not seen in patients with ADEM, and unilateral neurologic findings and hemispheric edema are rare. Finally, AHLE is usually fatal, whereas full recovery is the rule for patients with ADEM (J. A. D. Leake, unpublished data).
Although no prospective evaluation of corticosteroid therapy or IVIG has been performed for either AHLE or ADEM, both therapies were used in our patient after active viral infection had been excluded as a cause. High-dose corticosteroid therapy was used in all 3 of the nonfatal pediatric cases that have been reported elsewhere and in none of the fatal cases [10]. It may be of value to administer corticosteroids early to acutely deteriorating patients with white-matter disease whose evaluation suggests the presence of a nonviral cause. It is biologically plausible that corticosteroids attenuate the autoreactive lymphocyte responses that play a key pathologic role in CNS demyelinating conditions in humans and animals (Leake et al., unpublished data) [13–16]. In addition to aggressive medical and surgical management of increased ICP, immunomodulatory therapy may be lifesaving when it is rapidly initiated, which strongly underscores the need for prompt diagnosis of AHLE. Prospective, comparative investigation of the efficacy of anti-inflammatory therapy in treatment of AHLE and ADEM is needed.

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References