Acute Hemorrhagic Leukoencephalitis: A Cause of Acute Brainstem Dysfunction

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ABSTRACT: A 37-year-old female physician was admitted to the hospital with severe headache, facial and hand paresthesias, dysarthria, and ataxia. Neurologic examination disclosed signs of brain stem dysfunction. There was rapid neurologic deterioration, and she died in 28 hours. Postmortem studies showed the characteristic features of acute hemorrhagic leukoencephalitis.

Acute hemorrhagic leukoencephalitis (AHE) was first described by Hurst1; Crawford2 and Lander³ subsequently reported similar findings. It has been called acute hemorrhagic encephalitis,4 acute necrotizing hemorrhagic encephalopathy,5 and hemorrhagic immunemediated encephalomyelitis.6 It is a rare but usually fatal demyelinating disorder ordinarily diagnosed at autopsy. Preceding conditions may include a recent viral illness, vaccination, surgery, and pneumonia. We describe the case of a patient in whom signs of an acute brain stem lesion developed, initially suggesting a basilar artery thrombosis. Prompt treatment with dexamethasone was begun 4 hours after admission and, subsequent to additional diagnostic studies, high-dose methylprednisolone therapy was initiated. However, there was inexorable neurologic deterioration, and death occurred 28 hours after admission.

CASE REPORT

A 37-year-old female physician came to the emergency department at St. Luke's Episcopal Hospital because of the sudden onset of severe headache 4 hours previously. She also complained of numbness and tingling of the left face, tongue, and hand, slurred speech, clumsiness, and an unsteady gait. For the previous 3 weeks, she had had occasional episodes of numbness and tingling of the left hand lasting between 1 and 2 hours. Friends reported that she had complained of headache and upper respiratory symptoms for several days before the onset of the acute illness.

Past medical history was remarkable for asthma and acne. She did not smoke or drink. She used acetaminophen for her headaches.

General physical examination disclosed a mildly obese black woman in moderate distress. Blood pressure was 160/90 mm Hg, the heart rate was 100/min and regular, and she was afebrile. A general physical examination yielded normal results. Abnormal neurologic findings included errors in performing simple calculations, reversals of five-letter words, and remembering only two of three words after 5 minutes had elapsed. The right pupil was 3 mm and nonreactive, and the left was 2.5 mm with a 2+/4 reaction. There was paresis of upward gaze and abduction of left eye. The left nasolabial fold was slightly flattened, and there was no gag reflex. There were impaired rapid alternating movements in the upper extremities and decreased foot tapping that was more severe on the left than on the right. She had finger-to-nose dysmetria, on the left greater than on the right, and a left Babinski's sign. Results of an emergency computed tomographic (CT) scan of the brain were normal except for slight radiolucency in the brain stem (Fig 1). Lumbar puncture disclosed an opening pressure of 230 mm; clear, colorless fluid was obtained. Analysis of the fluid yielded the following values: protein, 66 mg/dL; glucose, 64 mg/dL; and white blood cell count, 69/mm³ (97% neutrophils, 3% monocytes). There were 12 red blood cells; Gram's stain showed no organisms. There were no oligoclonal bands, and the IgG index was elevated at 0.81. Fungal stains and acid-fast bacilli smears showed no organisms. Testing for cryptococcal antigen yielded negative results. A complete blood count disclosed a hematocrit of 37% and a white blood cell count of 11,100/mm3 with 86% neutrophils. Blood chemistry studies showed the following values: sodium, 136 mEq/L; potassium, 3.6 mEq/L; chloride, 98 mEq/L; bicarbonate, 29 mEq/L; creatinine, 0.8 mg/dL; blood urea nitrogen, 6 mg/dL; glucose, 137 mg/dL; lactate dehydrogenase, 240 U/L; serum protein, 9 g/dL; and cholesterol 142 mg/dL. Urinalysis yielded normal results, and results of a urine drug screen were negative. A chest roentgenogram yielded normal results. An electrocardiogram revealed left atrial enlargement.

A second CT scan of the brain (Fig 2) obtained approximately 7 hours after admission, showed radiolucency of the thalamus, increasing radiolucency of the brain stem, an enlarged midbrain, and hydrocephalus. Cerebral angiography done 1 hour later disclosed normal vessels. There was good visualization of the posterior circulation, and there were no angiographic signs to indicate uncal or tonsillar herniation.

Treatment with heparin was begun on admission after the first CT scan and cerebrospinal fluid studies. Four hours

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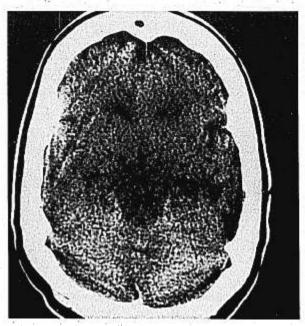


FIGURE 1. Noncontrast CT scan section at midbrain level shows slightly decreased attenuation in midbrain, which may be minimally enlarged.

after admission, the patient's pupils became fixed and dilated, but she was still able to follow simple commands and attempted to speak. Treatment was begun with dexamethasone, 10 mg intravenously, and mannitol, 50 g intravenously and then 25 g every 6 hours. Within the hour, respiratory distress was noted, and the patient was prophylactically intubated and placed on hyperventilation. Therapy with cefazolin, 1 g intravenously every 6 hours, was begun. When the angiograms and second CT scan were completed, approximately 7 hours after admission, therapy with methylprednisolone, 500 mg every 12 hours intravenously, was begun, and the heparin was discontinued. There was no response to these measures, and ventriculostomy was done 14 hours after admission. Twenty-eight hours after admission, the patient had no sign of brain function and had died.

Gross examination of the brain showed symmetrical but swollen cerebral hemispheres. The leptomeninges were minimally thickened and opacified, with focal clouding over the brain stem. The subarachnoid space was free of blood or exudate. The optic chiasm, brain stem, and cerebellum were severely softened, swollen, and shifted to the left. Serial coronal sections of the cerebral hemispheres revealed demarcation between the gray and white matter; the white matter was edematous, discolored, and softened. The corpus callosum was unremarkable. The components of the basal ganglia were demarcated from each other but congested; they also contained petechial hemorrhages. The internal capsule was softened, edematous, and congested. The ventricles were greatly reduced in size. Sections of brain stem and cerebellum showed diffuse petechial hemorrhages and softening in the white matter.

Microscopic examination showed an impressive infiltration of neutrophils throughout the white matter structures, including the internal capsule, optic chiasm, brain stem, and cerebellar peduncles (Fig 3). Mixed with the neutrophils was a variable number of macrophages. Lymphocytes and plasma cells were present but rare. Ball and ring hemorrhages, extravasation of red cells, and deposition of fibrin were noted in almost all white matter structures except the corpus callosum (Fig 4). Myelin destruction was not prominent, although



FIGURE 2. CT scan done 10 hours later shows grossly enlarged midbrain with obliteration of peri-mesencephalic cistern. Obvious low attenuation is now also present in midbrain. No hemorrhage is recognized by CT. There is ventricular dilatation due to obstructive hydrocephalus related to aqueductal compression.

it was present in some perivascular regions. Neuronal necrosis was limited primarily to the brain stem.

DISCUSSION

AHE is heralded by premonitory symptoms that usually occur a few days to a few weeks before onset of the acute illness. Some of these include signs of an upper respiratory infection, headache, seizures, malaise, fever, and vomiting.8 Antecedent events or illnesses may include surgery, vaccinations, Mycoplasma sp infections, measles, and varicella infections. The acute symptoms of AHE are typically fever, malaise, and headache, followed by a rapid progression of multifocal neurologic signs. The cerebral white matter is commonly affected first. Seizures, confusion, aphasia, hemiparesis, and cranial nerve deficits have been found. Rarely, myelopathy occurs. Usually, there is a progressive decline in the level of consciousness that leads to coma. The white blood cell count may be elevated, with a left shift. Cerebrospinal fluid pressure and protein level are elevated, and there is usually a pleocytosis, mainly of neutrophils. A lymphocytosis develops after a few days if the patient survives. Of interest is the absence of red blood cells. 10 The glucose level is normal. Results of the CT scan may be abnormal, revealing hypodense areas in the white matter. 11 Magnetic resonance imaging studies have not been reported in biopsy-proven AHE. The typical clinical course is a rapid decline of neurologic function, with death occurring within days of onset of the illness. There are reports of spon-

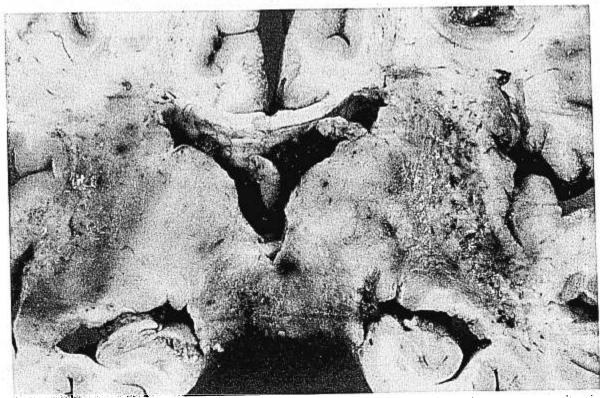


FIGURE 3. Serial coronal sections showing demarcation between gray and white matter. White matter is edematous, discolored, and softened. Note severe involvement of internal capsule and rostral mesencephalon.

taneous recovery, but only in one instance was a biopsy done confirming the suspected diagnosis¹²;

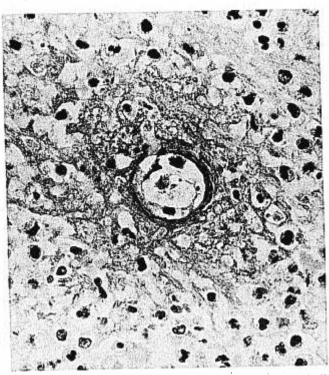


FIGURE 4. Microscopic section showing necrosis of blood vessel walls with deposition of fibrin as prominent feature. (H & E, oil immersion, \times 1,000)

this patient was treated with plasmapheresis, steroids, and cyclophosphamide.

Our patient had a 3-week history of episodes of numbness and tingling of the left hand before onset of the acute illness. Early signs of brain stem, especially midbrain, dysfunction then developed, with paralysis of upward gaze and poorly reactive pupils. Eventually, the pupils became dilated and fixed, but mentation was preserved. The patient followed commands and spoke, although she was severely dysarthric. Virtually all of her initial neurologic signs were consistent with brain stem disease. The lone exceptions were occasional errors with calculations and reversing five-letter words. Vascular disease in the basilar artery distribution was initially suspected. The mild cerebrospinal fluid pleocytosis made the diagnosis less likely, but angiography was required to exclude the presence of vascular disease. Treatment with 10 mg of dexamethasone was initiated 4 hours after admission, and high-dose methylprednisolone therapy (500 mg every 12 hours) was begun 3 hours later. This treatment was given because of a suspected diagnosis of an acute demyelinating disorder. A biopsy was not considered because both the clinical and CT findings indicated a brain stem disorder. The patient died despite a ventriculostomy done to treat developing hydrocephalus.

COMMENT

AHE mainly affects the cerebral white matter, commonly after an upper respiratory infection of several days' duration. There are usually signs of bilateral cerebral dysfunction, although unilateral symptoms often predominate. The CT scan shows hypodense areas despite the hemorrhagic element, which is often quite marked. Herpes simplex encephalitis is a major differential diagnosis when involvement is primarily cerebral.

Our patient sought treatment with focal brain stem symptoms suggesting vascular disease in the vertebrobasilar distribution. The CT scan findings supported that diagnosis. Normal results on angiography practically excluded vascular disease. Prompt steroid therapy was ineffective. The recent report of recovery after treatment with plasmapheresis is encouraging. Perhaps early combination therapy with plasmapheresis, steroids, and cyclophosphamide is essential in improving the recovery rate. 12

References

- Hurst EW: Acute hemorrhagic leukoencephalitis: a previously undefined entity. Med J Aust 1941; 2:1-6
- Crawford T: Acute hemorrhagic leukoencephalitis. J Clin Pathol 1954; 7:1-9
- Lander H: Acute hemorrhagic leukoencephalitis. Australas Ann Med 1958; 7:55-68
- Strümpell A: Uber primäre acute Encephalitis. Deutsche Archives Klinical Med 1891; 47:53-84
- Adams RD, Cammermeyer J, Denny-Brown D: Acute necrotizing hemorrhagic encephalopathy. J Neurolpathol Exp Neurol 1949; 8-1-99
- Johnson KP, Wolinsky JS, Ginsberg AH: Immune mediated syndromes of the nervous system related to virus infection. Handbook of Clinical Neurology. Klawans HL (ed). New York, North-Holland, Vol 34, 1978, pp 391-434
- 7. Byers RK: Acute hemorrhagic leukoencephalitis: report of three cases and review of the literature. *Pediatrics* 1975; 56:727-735
- Geerts Y, Dehaene I, Lammons M: Acute hemorrhagic leukoencephalitis. Acta Neurol Belg 1991; 91:201-211
- Gosztonyi G: Acute hemorrhagic leukoencephalitis (Hurst's disease). Handbook of Clinical Neurology. Vinken PJ, Brun GW (eds). Amsterdam, Elsevier Science Publishers, Vol 3, 1978, pp 587-604
- Beham PO, Moore MJ, Lamarche JB: Acute necrotizing hemorrhagic encephalopathy. Postgrad Med 1973; 54:154-160
- Suchowersky O, Sweeny VP, Berry K, et al: Acute hemorrhagic leukoencephalopathy. a clinical, pathological and radiological correlation. Can J Neurol Sci. 1982; 10:63-67
- Scales D, Greer M: Acute hemorrhagic leukoencephalitis. a successful recovery. Arch Neurol 1991; 48:1086-1088