

Case Report

Acute Hemorrhagic Leukoencephalitis Manifesting as Intracerebral Hemorrhage Associated with Herpes Simplex Virus Type I

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Summary

Acute hemorrhagic leukoencephalitis (AHL) is a rare and usually fatal disorder characterized by an acute onset of neurological abnormalities. It may occur in association with a viral illness or vaccination. Radiology and brain biopsy are essential for the diagnosis. We present a case of AHL mimicking or manifesting as intracerebral hemorrhage associated with herpes simplex virus. A 3-year-old boy was admitted to our hospital with cerebral hemorrhage. The findings of cerebrospinal fluid, MRI and electroencephalogram indicated acute hemorrhagic leukoencephalitis associated with herpes simplex virus involving the left parietal cortex (hemorrhage) and the right temporal lobe (encephalitis). The patient received intravenous dexamethasone (1.5 mg/kg/24 h divided q6 (six times a day) for 5 days, tapered slowly to discontinuation over the next 5 days) and aciclovir (15 mg/kg/every 6 h for 14 days). His clinical condition markedly improved, and after 3 weeks he was discharged from the hospital with moderate right hemiparesis. Mild hemiparesis with normal psychometric testing was determined when he was checked 6 months later. AHL remains misdiagnosed as viral encephalitis because it produces different protean clinical forms. Pediatric patients admitted with cerebral hemorrhage and infarct should be evaluated for presence of hemorrhagic encephalitis-causing agents, especially for herpes simplex. Since, as in our case, treatment with corticosteroid and acyclovir markedly improves conditions of herpes simplex-caused AHL, we suggest that early diagnosis and treatment is of importance for the prognosis.

Introduction

Acute hemorrhagic leukoencephalitis (AHL) is a rare catastrophic demyelination disease often preceded by vaccination and common viral infections such as herpes simplex.¹ It remains misdiagnosed as viral encephalitis because of its protean clinical forms. Clinical entity of AHL is characterized by rapid evolution of focal neurological symptoms, notably hemiplegia and aphasia, accompanied by headaches, mental confusion, and fever. The etiology of AHL is still unclear. It has been postulated that viral/bacterial infections might be responsible, directly or through an immune-mediated mechanism, for this acute inflammatory myelinopathy.^{1,2} Infectious agents, including varicella zoster virus (VZV), herpes simplex virus (HSV), human herpes virus-6 (HHV-6),

cytomegalovirus, Epstein–Barr virus, and mycoplasma have been investigated in brain specimens using polymerase chain reaction (PCR), reverse transcriptase (RT)-PCR, serological testing, and immunohistochemistry.^{3,4} It has been suggested that radiology and brain biopsy are essential for the diagnosis.^{1–3}

We present a case of AHL associated with HSV in order to emphasize that early diagnosis and treatment are important for successful recovery in AHL with protean clinical manifestations.

Case Report

A 3-year-old boy was admitted to our hospital with a 10-day history of frontal headache and difficulty in walking. The patient had no antecedent upper respiratory symptoms, cough, diarrhea, pharyngitis, conjunctivitis, arthralgia, rash, or seizure. There was no history of seizure, recent travel, vaccinations, HSV/VZV infection, and hemorrhagic disease. He was reported to have had no contact with tuberculosis patients. The only medication he had taken was

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acetaminophen 5 days prior to admission. He had never received blood products. He had unrelated parents. On physical examination at admission, the patient was found to be thin but well nourished. His temperature was 38.5°C, pulse 120 beat/min, blood pressure 140/95 mmHg, and respiratory rate 36 breaths/min. He was cooperative and oriented. He had at right-sided hemiparesis that moderated right-sides upper and lower extremity weakness. His fundi were normal. Other physical examination findings were normal. The patient was admitted to the intensive care unit.

Laboratory testing performed at admission revealed a peripheral WBC count of 17 700 cells/mm³, with 80 per cent segmental neutrophils, 12 per cent lymphocyte, 6 per cent monocytes, and 2 per cent eosinophils. Measurement of hemoglobin and platelet count, analysis of serum, urinalysis and chest radiography yielded normal results. The erythrocyte sedimentation was 40 mm/h. A cranial CT scan showed left-sides hemorrhagic lesion at the parietal area with surrounding cerebral edema (Fig. 1). Cerebral edema was regressed by administration of mannitol (0.5 g/kg, single dose), and the patient then received intravenous dexamethasone (1.5 mg/kg/24 h divided q6 for 5 days, tapered slowly to discontinuation over the next 5 days) at the intensive care unit.

On the second day of admission, a lumbar puncture was performed; opening pressure was 8 mmHg. There were 450 cells/mm³ WBC (80 per cent segmental neutrophils and 20 per cent lymphocytes) and 170 cells/mm³ RBC in the cerebrospinal fluid (CSF).

Total protein level in the CSF was 148 mg/dl, and the glucose level was 94 mg/dl with simultaneous measurement of blood glucose 125 mg/dl. Other results of infectious, metabolic, hematologic and collagen-vascular (including bacterial/viral; serologic evaluation for acute enterovirus, EBV, influenza viruses, Chlamydia species, *Mycoplasma pneumoniae*, and HIV; Gram staining, the levels of lactate/private in sera) were normal, except for HSV. On the second day of hospitalization, serological testing by ELISA method (TKA-4HD, Italy) for herpes simplex viruses was performed on CSF and serum samples, which yielded positive. CSF and serum IgG levels were found to be 112 Uarb/ml and 200 Uarb/ml, respectively. Serum and CSFIgM were found to be positive (OD450 nm <1.58). The results of other laboratory tests including oligoclonal bands and immunoglobulin G in CSF were normal.

Repeated cranial CT, MRI, and electroencephalogram obtained on the 3rd hospital day showed localized and contrasted hypointensity involving the right temporal lobe (encephalitis) and the left parietal cortex (hemorrhage) (Fig. 2), and EEG displayed sharp and slow wave activity, respectively. Because of the clinical course and results of laboratory examinations, the patient was diagnosed as AHL probably due to HSV. Intravenous acyclovir (15 mg/kg every 6 h for 14 days) was added to the treatment.

Following the patient in our clinic, a marked improvement was observed, and after 3 weeks he was discharged from the hospital with moderate right

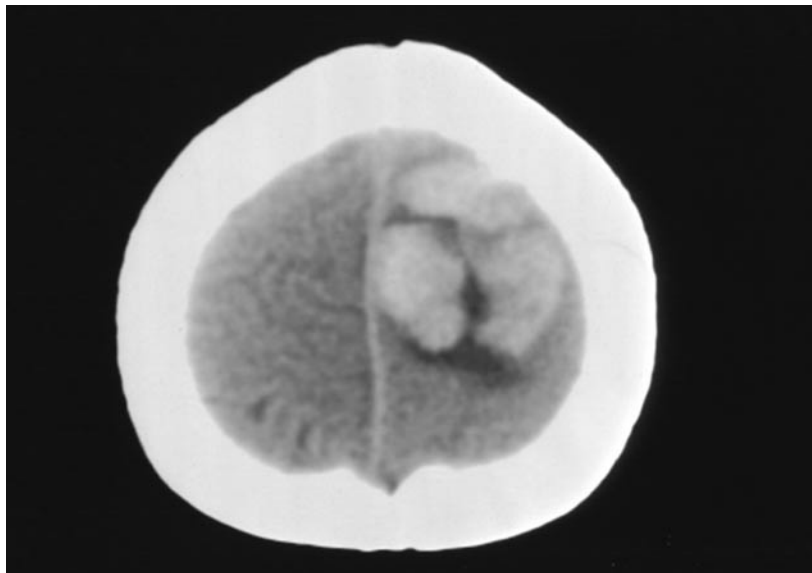


FIG. 1. Noncontrast CT scan shows lobule-shaped high signal intensity (hemorrhage) surrounding peripheral edema at the level of the left parietal area.

hemiparesis. There was mild hemiparesis with normal psychometric testing when a check-up was performed 6 months later.

Discussion

Although the clinical picture of AHL is hardly characteristic and can resemble that of acute viral

encephalitis, the pathological findings are unique. In essence, there is diffuse and necrotizing angiitis of venules and capillaries of cerebral white matter, with hemorrhagic areas around affected blood vessels.¹ AHL may be misdiagnosed with various diseases, which are accompanied by demyelination and hemorrhage, such as acute disseminated encephalomyelitis (ADEM). Indeed, AHL is a variant of ADEM

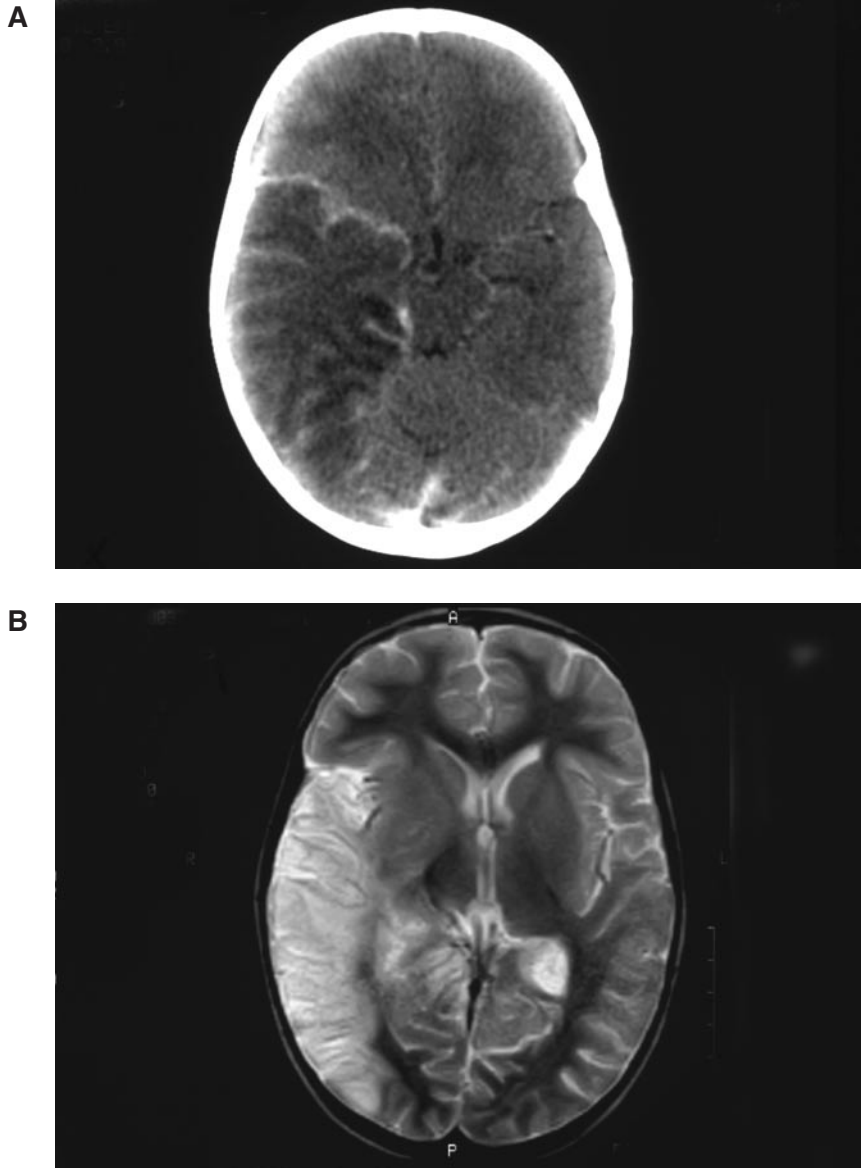


FIG. 2. (A) Axial CT demonstrates localized and contrasted hypointensity involving the right temporal lobe. (B) Axial T2-weighted MRI shows hyperintensity in the same temporal lobe. (C) Coronal T2-weighted MRI shows hyperintensity of the right temporal lobe (encephalitis) and of the left parietal cortex (hemorrhage).

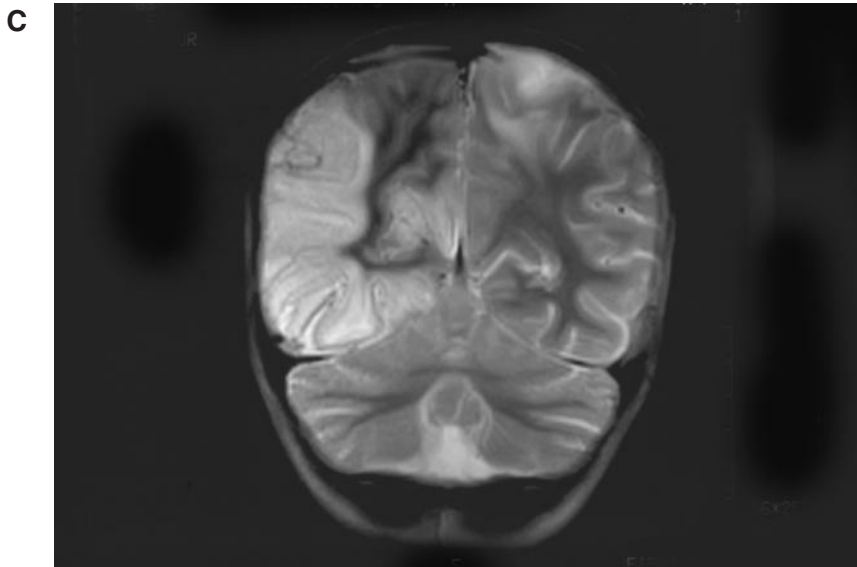


FIG. 2. Continued.

in which the involved regions of brain undergo hemorrhagic necrosis. Imaging findings are similar to those in ADEM except that the lesions are hemorrhagic and have more associated edema and mass effects. Patients often progress rapidly into delirium and coma. Most die within the first few days to a week of onset, and the few survivors have serious neurological sequelae.¹

Patients have survived when treated with various combinations of corticosteroids, immunoglobulin, and cyclophosphamide, with most improvement after plasma exchange.⁵ If the infectious agent has been detected treatment should be based against it. There are studies reporting the effectiveness of corticosteroid in AHL.^{5,6} In the case of Klein, *et al.*,⁵ acyclovir was given initially, but no infectious agent was found and complete recovery was achieved with dexamethazone. Similarly, acyclovir was given as the initial treatment in the case reported by Meilof, *et al.*,⁶ and when no infectious agent was detected treatment was achieved with a high dose of methylprednisolone.

In the present case, a rapid progressive course, striking numbers of leukocytosis in the peripheral blood, elevation of protein and pleocytosis with red blood cell in CSF, cerebral edema and hemorrhagic findings in CT and MRI were found. Moreover, serologic testing for herpes simplex viruses in CSF and serum was positive. In view of all these findings, we thought that it was HSV-associated or accompanied AHL. Similarly, Takeda, *et al.*⁷ detected a hematoma in the right basal ganglia by CT in a 15-year-old girl who presented with meningeal irritation after influenza and who was treated for the AHL

diagnosis. Because of the development of acute stroke and related hemorrhage findings in brain CT, our case was initially evaluated as 'intracerebral hemorrhage'. While laboratory examinations towards this diagnosis were in progress, performing cranial CT, MRI, and EEG on the third day implicated that there was a possible infectious pathology affecting the right temporal lobe. CSF findings revealed herpes encephalitis, and acyclovir was then added to the treatment.

Herpes simplex virus I is able to cause neurological disease, meningitis, encephalitis, meningovascularitis, radiculitis, and acute hemorrhagic leukoencephalitis, potentially involving the entire range of neurological anatomical sites.^{8,9} It has been determined that in AHLs with identified etiology, HSV is among to the most frequently involved virus. Therefore, pediatric patients admitted with cerebral hemorrhage and infarcts should be evaluated in terms of encephalitis-causing infectious agents especially for HSV. Present, as well as emerging, symptoms should be considered in the differential diagnosis. As in our case, in herpes simplex-caused AHL, early diagnosis is very important for the prognosis since significant recovery can be obtained with corticosteroid and acyclovir treatment.

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