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Clinical Observation

Acute Hemorrhagic Leukoencephalopathy: Pathological Features and Cerebrospinal Fluid Cytokine Profiles

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ABSTRACT

Background: Acute hemorrhagic leukoencephalopathy is a rare encephalopathy of unknown etiology, causing fulminant, hemorrhagic central nervous system demyelination with high mortality. It is unclear whether acute hemorrhagic leukoencephalopathy is an entirely distinct entity from acute disseminated encephalomyelitis.
Patients and Methods: We report two patients with rapidly progressive neurological illness resulting in raised intracranial pressure and coma, with biopsy-proven acute hemorrhagic leukoencephalopathy (perivascular hemorrhages and demyelination, predominantly neutrophil infiltrates).
Results: Acute cerebrospinal fluid showed pronounced T cell-associated cytokine elevation (interleukins 6, 8, and 17A) and CCL2 or CCL3, higher than in patients with acute disseminated encephalomyelitis, but no B cell-associated cytokine elevation.
Conclusion: Improved understanding of the immune process may provide rationale for use of anti-cytokine biologic agents.

Introduction

Acute hemorrhagic leukoencephalopathy (AHLE) is a rare severe form of brain inflammation with hyperacute presentation, inflammatory neuroimaging features, mass effect, and high mortality. The pathophysiology is not well understood, and different mechanisms have been implicated including postinfective inflammation.[1-3] Histology shows inflammatory infiltration of vessels and parenchyma (neutrophils, lymphocytes) with hemorrhage, pathologically distinguishing AHLE from acute disseminated encephalomyelitis (ADEM).[4] Despite this, AHLE is often considered part of the ADEM spectrum. We report clinical presentation, response to therapies, and cerebrospinal fluid (CSF) cytokine studies in two children with pathologically proven AHLE and compare them with those of ADEM controls.

Materials and methods

Ethical approval was obtained. For CSF cytokine analysis method (Multiplex), genetic testing, and pathology method, see Supplementary Material.

Declarations of interest: none.

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Patient descriptions

Patient 1

This 15-year-old boy presented with 24 hours of fever, headaches, photophobia and vomiting, no meningism, right homonymous hemianopia, and normal mental status.

Magnetic resonance imaging (MRI) demonstrated a focal mass lesion (left parieto-occipital region, corpus callosum). Glioma and tumefactive demyelination were considered (Fig 1A and B). Investigations revealed neutrophilia, increased platelets and C-reactive protein, and normal antinuclear antibodies, rheumatoid factor, and complement 3 and 4. CSF showed pleocytosis (3960 white cells/mm^3, polymorphs 85%, and mononuclears 15%), raised red cells (350 cells/mm^3), protein (4900 mg/dL), increased lactate (5.6 mmol/L), no malignant cells, and no oligoclonal bands or myelin oligodentrocyte glycoprotein/neuromyelitis optica antibodies in the serum. Cytokines or chemokines were obtained from initial CSF samples stored at −20°C. Mycoplasma IgM serology was positive; polymerase chain reaction was positive in pharyngeal aspirate and negative in CSF.

Rapid deterioration occurred following presentation, with decreased level of consciousness, unequal pupils, and upper motor neuron signs requiring intensive care management for raised intracranial pressure (ICP), including intubation and osmotic therapies. Dexamethasone was given 36 hours after initial presentation (10 mg, then 4 mg every six hours). Repeat computed tomography (CT) showed marked progression of edema, obstructive hydrocephalus, and left uncal herniation. Intravenous methylprednisolone (1 g daily) was started at 48 hours. Progressive signs of raised ICP (episodes of pupillary change, hypertension) were noted. Further progression of cerebral edema was noted on CT, and an external ventricular shunt was inserted (ICP 15 to 30 cmH_2O despite medical management). Further CT revealed worsening cerebral edema with increasing mass effect, so a left parieto-occipital decompressive craniectomy with durotomy was performed and a brain biopsy was obtained.

Brain biopsy (Fig 2A and B) showed perivascular inflammatory infiltrate (predominantly neutrophils), fibrinoid necrosis of small vessels, hemorrhage, and perivascular demyelination. Histopathological diagnosis was compatible with AHLE. The patient received five days of therapeutic plasma exchange (TPE) followed by intravenous immunoglobulin (IVIG).

Ongoing raised ICP caused secondary diabetes insipidus despite maximal medical and surgical management. MRI of the brain (day 10) showed marked progression of white matter disease and associated mass effect (Fig 1C–F). Given extensive bilateral brain and brainstem involvement, the patient was extubated and died shortly thereafter.

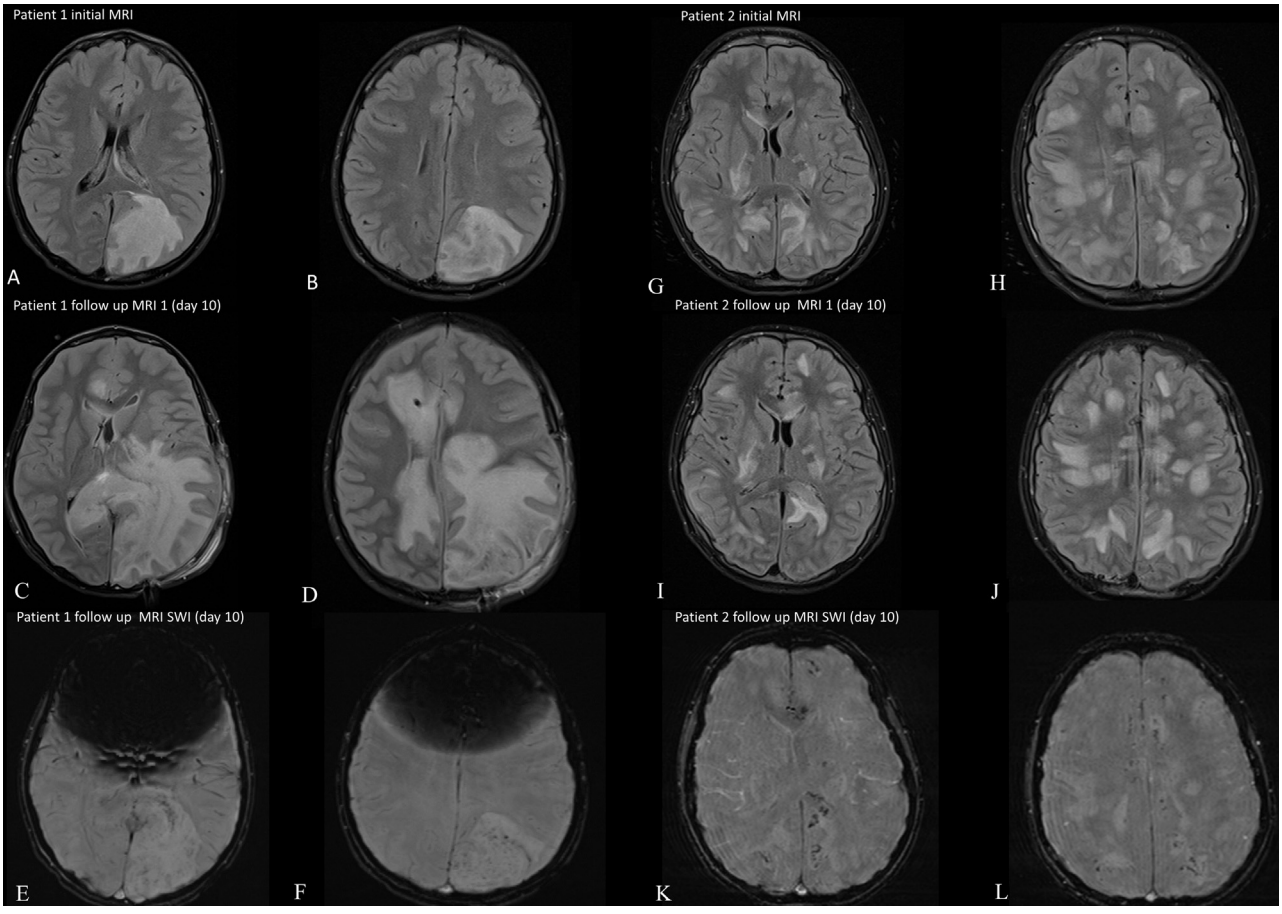

FIGURE 1. Neuroimaging. (A and B) Patient 1 magnetic resonance fluid-attenuated inversion recovery (FLAIR) axial imaging on presentation shows left occipital hyperintensity with some extension into the corpus callosum consistent with cerebral edema. (C and D) Patient 1 magnetic resonance FLAIR axial imaging on day 10 of admission shows extensive high-FLAIR-signal white matter disease involving both cerebral hemispheres (left greater than right), with associated mass effect and progression over time. (E and F) Patient 1 magnetic resonance susceptibility-weighted axial imaging on day 10 shows multiple hypodensities compatible with hemorrhages, associated with the white matter lesion. Note significant frontal artifact. (G and H) Patient 2 magnetic resonance FLAIR axial imaging on neurological presentation shows extensive supratentorial, multifocal, symmetric cerebral white matter hyperintensities. (I and J) Patient 2 magnetic resonance FLAIR axial imaging day 10 following neurological presentation shows mild progression with extensive supratentorial, multifocal, symmetric cerebral white matter hyperintensities. (K and L) Patient 2 magnetic resonance susceptibility-weighted axial imaging on day 10 following neurological presentation shows extensive hypodensities compatible with hemorrhages, associated with most white matter lesions.

The complement factor I gene was sequenced (patient and parents), and no mutations were found.

Patient 2

This 14-year-old boy presented after one week of fever, night sweats, headaches, generalized myalgia, but no neurological concerns.

Laboratory testing showed increased white blood cell count (neutrophilia, monocytosis), raised erythrocyte sedimentation rate (91 mm/hr), decreased platelet count, elevated antinuclear antibodies titers (160 U, normal less than 40), and positive lupus anticoagulant, but all other markers were normal, including serum myelin oligodentrocyte glycoprotein antibodies. Infection screens were negative.

Progressive muscle-pain-limiting mobilization was followed by drowsiness and encephalopathy. MRI revealed extensive supratentorial, multifocal, symmetric white matter changes (bilateral thalamic, upper midbrain), restricted diffusion, and elevated lactate, suggestive of AHLE (Fig 1G and H).

Within 24 hours steroids (methylprednisolone 1 g intravenously) and IVIG (2 g/kg; two days) were commenced.

Encephalopathy and right abducens paresis worsened. Repeat MRI revealed mild extension of white matter changes and evidence of hemorrhage on susceptibility-weighted imaging (Fig 1I–L). An external ventricular shunt was inserted (ICP 15 to 60 cm H_2O) and brain biopsy performed. White matter small vessels showed fibrinoid necrosis, perivascular neutrophil or mononuclear infiltration, demyelination, and hemorrhage consistent with AHLE (Fig 2B). CSF confirmed hemorrhage, raised white cell count (11/mm^3, polymorphs 32%; mononuclears 68%) and protein (3400 mg/dL) and negative oligoclonal bands. CSF samples were obtained for cytokine assessment. TPE was started on day 15 (five days), IVIG was repeated, cyclophosphamide (750 mg/m^2) was given, and oral steroids continued. Dramatic improvement was achieved (alertness, memory, motor function). Rehabilitation process was followed by discharge home by week six (steroid tapering over three months). Assessments at 10 weeks showed normal motor and cognitive function, neurological examination, and school attendance with no observable deficits.

CSF findings

Patients with AHLE were compared with 20 noninflammatory neurological controls (used to generate normative reference ranges) and 16 children with ADEM.[5] Patient 1 showed elevation of

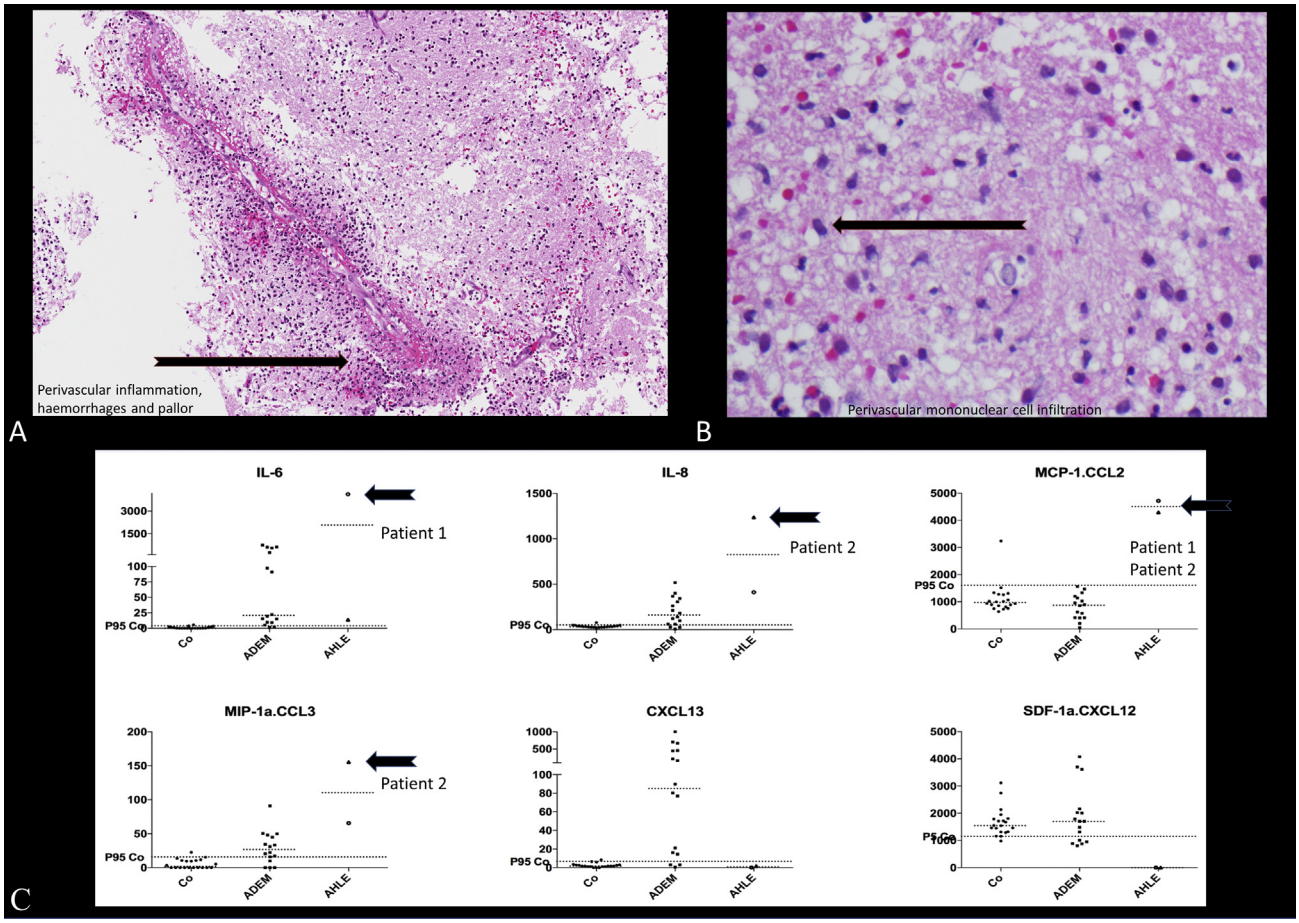

FIGURE 2. (A) Patient 1. Brain biopsy showing an inflammatory process, most severe around vessels with milder inflammation in the intervening cerebral tissue. There are perivascular hemorrhages and perivascular pallor, which was shown to be demyelination on myelin stains (not shown). (B) Patient 2: Brain biopsy at higher power showing necrosis with fibrinoid change of a small vessel. There is surrounding inflammation with neutrophilic nuclear dust and mononuclear cell infiltration. There is perivascular pallor, which was shown to be demyelination on myelin stains (not shown). (C) Comparison of CSF cytokine/chemokine concentrations between patients 1 and 2 having AHLE, patients with acute disseminated encephalomyelitis (ADEM) (n = 16), and controls (Co, n = 20). Interleukin (IL)-6, IL-8, CCL2, and CCL3 are elevated in patients with AHLE compared with controls. B cell-related cytokines (CXCL 13, CXCL 12,) are normal in patients with AHLE (comparable to controls), whereas these are elevated in the patients with ADEM. AHLE Patient 1 is presented as a circle; AHLE Patient 2 is presented as a triangle. The controls were 20 children with noninflammatory neurological disease, as follows: cerebral palsy (n = 8) (kernicterus [2], extreme prematurity [1], placental insufficiency [1], unknown cause [4]), neurotransmitter disorders (n = 4) (dopa-responsive dystonia [3] and 6PTPS deficiency [1]), monogenic movement disorders (n = 6), stereotypy (n = 1), and congenital myasthenic syndrome (n = 1). Cerebrospinal fluid was analyzed in controls as part of the routine evaluation for the patients with underlying etiology. The color version of this figure is available in the online edition.

Th1- (tumor necrosis factor-α, interferon-γ, CXCL9, CXCL10, and CXCL11), Th2- (interleukin [IL]-4, IL-13, CCL17), Treg- (IL-10), Th17-associated (IL-17A, IL-6, IL-8, granulocyte-colony stimulating factor, IL-23), and other cytokines and chemokines (interferon-α, CXCL1, CCL2, CCL3, CCL4, and IL-1receptor antagonist [IL-1ra]) compared with controls; tumor necrosis factor-α, IL-8, CCL2, and CCL3 were elevated in Patient 2. Unlike ADEM, both patients with AHLE showed lack of B cell chemokine elevation. Elevated cytokine and chemokines are presented in Fig 2, and all others in Supplementary Fig 1 according to Th1, Th2, Treg, Th17, B cell, and other associations.

Discussion

Despite similar clinical presentations and investigation findings, the rate of progression, response to therapy, and ultimate outcome were very different in our two patients. Both had radiological features of AHLE (diffusion restriction, hemorrhagic complication) and similar pathologic features. Patient 1 had mainly unilateral complicated demyelination, progressively raised ICP, and secondary complications despite aggressive immune therapy and sadly died. Patient 2 had more protracted prodrome and neurological presentation; received high-dose steroids within 24 hours followed by TPE, IVIG, and cyclophosphamide; and showed good response to therapy. Although there were similarities between our patients, there were key differences such as evidence of mycoplasma pneumonia in Patient 1, highlighting the fact AHLE is likely a heterogeneous syndrome. Our literature review of AHLE reflects the common presentation with raised ICP requiring surgical management, and a mortality of 56%, although there may be reporting bias in these published cases (Supplementary Table 1).

Pathogenesis of AHLE is postulated to be immune mediated and complex.[2,3] Both cellular and humoral immune mechanisms likely contribute to the phenotype, possibly modulated by the nature of preceding infections and patient factors (including genetics). Recently, biallelic changes were found in complement factor 1 in two unrelated patients with recurrent AHLE responsive to IL-1ras,[6] which are postulated to slow neutrophil recruitment and complement protein production.

There are no previous studies of CSF cytokines in patients with AHLE. Our patients showed significantly elevated CSF cytokines obtained within 48 hours of neurological symptoms, mainly IL-6, IL-17A (patient 1), and IL-8 (patient 2). Patient 1 had overall higher cytokine levels and a more severe course. The B cell cytokines were normal in both, in contrast to patients with ADEM (particularly if positive anti-myelin oligodentrocyte glycoprotein antibodies).[5] Interestingly, CCL2, CCL3, and CCL4 were higher in patients with AHLE compared with those with ADEM. These CCL chemokines are "chemoattractants" involved in recruiting lymphocytes, neutrophils, and other innate immune cells to sites of inflammation. Overall, these findings (strongly elevated Th-associated and chemoattractant, normal B cell chemokines) point to a T cell and innate process, not a B cell- or autoantibody-associated process in AHLE.[7]

The severity of cytokine response (cytokine storm) especially in patient 1 (significant elevation of Th1, Th2, Teg, IL-6) underlines the severity of inflammation in patients with AHLE and possibly explains the concerning prognosis.

There is increasing interest in tocilizumab (IL-6ra), which has been used in some inflammatory neurological states.[8] In uncontrolled studies, patients with autoimmune encephalitis and neuromyelitis optica who failed to respond to rituximab have successfully been managed with tocilizumab. Tocilizumab could be theoretically useful in AHLE based on our finding, although its efficiency has not been tested in hyperacute setting.[9,10] In comparison, IL-8 is a neutrophil chemotactic polypeptide that has been associated with worse outcomes in traumatic brain injury and meningitis.[11] Both IL-6 and IL-8 have been shown to be secreted by microglia coincubated with macrophages, suggesting their role in the first response of the innate immune system and chemotaxis[12,13] and differentiation and effects of Th17 cells.[14]

Historically all patients presenting with AHLE died, until early steroid treatment (day 2-8) was found to be effective in some[1,2] but not all patients.[3,4] High-dose steroids have been used safely early in some patients with AHLE, and it has been argued that differential diagnoses like bacterial or viral meningitis or encephalitis and malignancy should not be absolute contraindications to potentially life-saving therapies. TPE is usually considered in individuals with severe ADEM with poor response to immunosuppression (removal of presumed pathogenic autoantibodies or other immune factors). Addition of TPE to immunomodulatory treatments for non-responders can lead to neurological improvement in published cases of ADEM.[15] Our second patient improved significantly after TPE, whereas patient 1 did not improve. Aggressive surgical interventions (decompressive craniotomy) have been successfully implemented in conjunction with immunosuppressive therapy.

Although targeted approaches such as IL-ras are appealing in the context of neuroinflammation, our report emphasizes that AHLE is immunologically complex with pathologic involvement of multiple cell types and broad cytokine elevation. Immunomodulating therapies with rapid onset and broad effects (e.g., corticosteroids, TPE, cyclophosphamide) may be preferable until we can determine the predominant pathways involved in AHLE immunopathology. A rapid diagnostic approach (imaging, brain biopsy, CSF cytokines) could help in decision making and aggressive therapy.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2019.06.013.

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