Case Report

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Acute hemorrhagic leukoencephalopathy: a case report and literature review

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Introduction and importance: Acute hemorrhagic leukoencephalopathy (AHLE) is a rare and devastating condition that can present with various neurological symptoms. The predisposing and initiating factors of AHLE are not fully understood. AHLE has a high morbidity and significant mortality rates, however, our case presents a surviving young girl.

Case presentation: Thirteen years old previously healthy girl was referred to the emergency department due to drowsiness, preceded by an upper respiratory infection 10 days earlier. Firstly, she was treated empirical with antiviral medication (Acyclovir) directed to herpes simplex virus and intravenous (IV) methylprednisolone pulses. When she did not respond well, intravenous immunoglobulin was administrated, which helped with the end-result diagnosis based on clinical and imaging findings.

Clinical discussion: AHLE is a fatal rare demyelinating disease characterized by an acute rapidly progressive fulminant inflammation of the white matter, it is usually misdiagnosed due to being a diagnosis of exclusion, and the much more common other diseases, including infectious encephalitis, meningitis, fulminant multiple sclerosis, other causes of acute disseminated encephalomyelitis. Different types of CNS infiltrates, such as neutrophils in AHLE and lymphocytes in acute disseminated encephalomyelitis, do not support the idea of differentiating the two diseases. The process of differentiating between these two diseases relies mostly on laboratory and imaging findings, which are well demonstrated in this case report.

Conclusion: The authors conclude this report by highlighting the dearth in published knowledge about this disease, and encouraging further studies be conducted about this topic.

Keywords: case report, demyelinating, encephalopathy, hemorrhagic

Introduction

Acute hemorrhagic leukoencephalopathy (AHLE) is a rare and life-threatening condition that can present with many neurological symptoms, including seizures, altered consciousness, and focal deficits. According to a study, AHLE is an uncommon disease, and cases are often misdiagnosed[1]. Diagnosing AHLE is very challenging due to its many differential diagnoses, including viral encephalitis, ischemic stroke, multiple sclerosis, and other autoimmune conditions.

The predisposing and initiating factors of AHLE are not fully understood; however, it is suggested that viral infections, such as influenza and Epstein–Barr virus, may play an important role in the development of the disease[2]. In some reported cases, the use of certain medications, such as immune-modulatory therapies (interferon-α and nivolumab), were also implicated[3].

AHLE has a high morbidity and significant mortality rates. Additionally, older patients may not respond well to the recommended treatment. So that, the disease outcomes are much worse as the patient's age increases[4]. It is also noteworthy to state that the highest population diagnosed with this disease, along being rare even in this epidemiology, belongs to the older patients, patients with comorbid conditions, and terminally ill patients[4], adding to this case report even more complexity and value[5].

Given that AHLE is a rare entity, there are only a few published studies on the disease. Researchers suggest the need for further research to expand the knowledge of the disease's pathophysiology, etiology, and treatment options[6].

This work has been reported in line with Surgical CAse Report (SCARE) criteria[7].

Case presentation

A previously well 13-year-old girl was referred to the emergency department with altered consciousness, drowsiness, and seizures. She had suffered from an upper respiratory infection along with fever and headache 10 days prior to the onset of these symptoms.

She was intubated and placed on mechanical ventilation due to her persistent altered consciousness and seizures. On examination, she could respond to pain and had symmetric, reactive

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pupils. The deep tendon reflexes were brisk, and the Babinski sign was evident.

Initial laboratory results are shown in Table 1.

Cerebrospinal fluid (CSF) was collected and analysis was normal, as seen in Table 2.

Further testing of the CSF culture was negative. Also, using a PCR test revealed negative results for the herpes simplex virus.

On admission, computed tomography (CT) scan of the brain showed no abnormal findings. After 48 h follow-up, a CT scan showed widespread and symmetric areas of reduced density in the brain, affecting both the surface layer and the underlying white matter, without any evidence of bleeding (Fig. 1).

Phenytoin and leviteracetam were given to control the seizures, along with pain relief. Additionally, ceftriaxone and acyclovir were started as the primary suspicion was herpetic meningoencephalopathy[8].

Based on these findings the patient was given methylprednisolone pulses 30 mg/kg/24 h for 5 days, along with prednisolone for a period of 2 weeks[9].

During this time, the patient developed episodes of high intracranial pressure (bradycardia, high blood pressure, and mydriasis) and experienced seizures. As a result, glucose, electrolyte levels, and sedation were closely monitored, and the patient's analgesia and sedation drugs were titrated to a higher dosage. Intravenous fluids containing 3% sodium chloride were administered[10]. Despite these measures, there were no signs of neurological improvement over the 2-week period.

To address the ongoing neurological concerns, intravenous immune globulin (IVIG) was administered at a dose of 1 g/kg/24 h for 2 days, in concordance with previous midazolam and fentanyl. Following this treatment approach, the patient's neurological signs improved, including response to pain, signs of regaining consciousness (opening eyes), and she was able to be gradually taken off the ventilator.

After weening off the ventilator, the patient experienced difficulty with speech (dysarthria) and abnormal movements (dyskinesia).

A MRI of the brain revealed hyper intense lesions with sign of hemorrhage in the temporal lobes, as well as high signal intensity in the frontal lobes, as shown in Figures 2, 3.

Based on the clinical signs, symptoms, and findings on the MRI, the patient was diagnosed with AHLE[11].

Clinical discussion

AHLE is a fatal rare demyelinating disease characterized by an acute rapidly progressive fulminant inflammation of the white matter. It is usually preceded by an infectious illness such as upper respiratory infections. The course is usually short and ends with disability or death[6].

Table 1

Arterial blood gas analysis and blood chemistry workup

PH: 7.45	PCO_2: 26 mmHg	HCO3: 18.7 mmol/l	Glucose: 110 mg/dl
Na: 142 meq/l	K: 4.2 meq/l	Total Ca: 9.5 mg/dl	Cl: 115 meq/l
Mg: 2 mg/dl	WBC: 15 380 70%N/25%l	Hb : 11 g/dl	Platelets: $188 \times 10^3/\mu l$
MCV: 84 fl	Cr: 0.6 mg/dl	Urea: 30 mg/dl	CRP: 3 mg/dl
ESR: 60 mm/h	O_2Sat: 99%		

HIGHLIGHTS

- Acute hemorrhagic leukoencephalopathy (AHLE) is a rare, and life-threatening condition with long-lasting morbid neurological symptoms.
- AHLE diagnosis is often misleading due to its many differential diagnoses, including viral encephalitis, ischemic stroke, multiple sclerosis, and other autoimmune conditions.
- AHLE has high morbidity and mortality rates.
- The case discussed in this study involves a patient with AHLE who was discharged from the ventilator.
- Despite the severity of AHLE, this patient had minimal remnant neurologic deficits.

Fever, headache, fatigue, nausea, neck stiffness, vomiting, seizures, or coma are common symptoms in patients diagnosed with AHLE. Untreated patients have a very high mortality rate[12].

Considering clinical and imaging findings, the differential diagnosis of this disease is infectious encephalitis, meningitis, fulminant multiple sclerosis, and other causes of ADEM[13].

Infectious encephalitis and meningitis are similar to AHLE as they are both usually preceded by an infectious disease, Nonetheless, as can be observed in our patient, no infectious organism is isolated from the CSF. Furthermore, imaging findings are not indicative of suppurative-enhancing diffuse edematous lesions[10]. Fever, leukocytosis, and CSF features, which were seen in our patient, are not compatible with the diagnosis of acute fulminant multiple sclerosis. The combination of clinical observations and diagnostic imaging (no focal enhancing lesions, rather a diffuse edema) strongly supported the exclusion of multiple sclerosis from our list of potential diagnoses[14].

AHLE is regarded as the most severe subtype of ADEM, both of them shares many features[15]. they are usually preceded by infections. However, different types of CNS infiltrates, such as neutrophils in AHLE and lymphocytes in ADEM, do not support differentiation of the two diseases[12]. Further differentiation between the two 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[12]. In our case, the CSF analysis and opening pressure were normal. 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[12].

Distinguishing the two with MRI is difficult. White matter lesions in both diseases can be caused by edema and inflammation at first, and then by axonal loss and demyelination later on[13].

ADEM has less cerebral edema, smaller lesions, and rare hemorrhage[15]. In addition, AHLE presents more acutely and has larger and more edematous lesions with features of hemorrhage[10].

Table 2

Cerebrospinal fluid analysis

Total protein: 40 mg/100 ml	Glucose: 65 mg/100 ml	White blood cell count: 3/μl

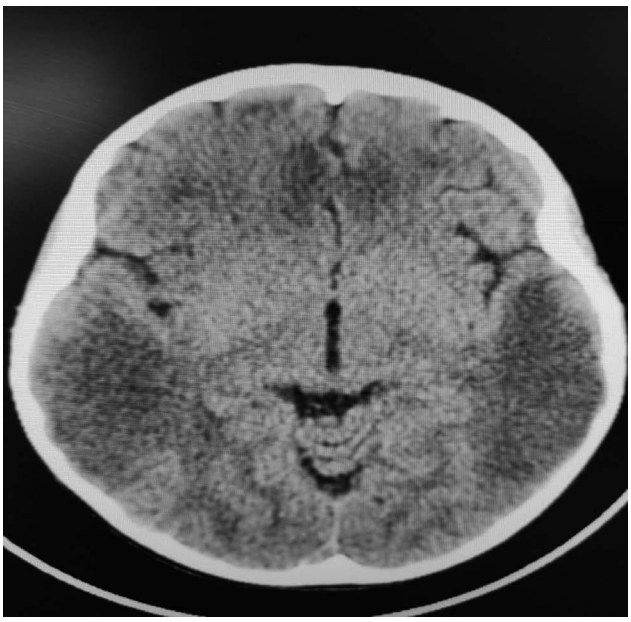

Figure 1. Single axial noncontrast computed tomography image demonstrates low density in the bilateral frontal, temporal, and inferior occipital lobes.

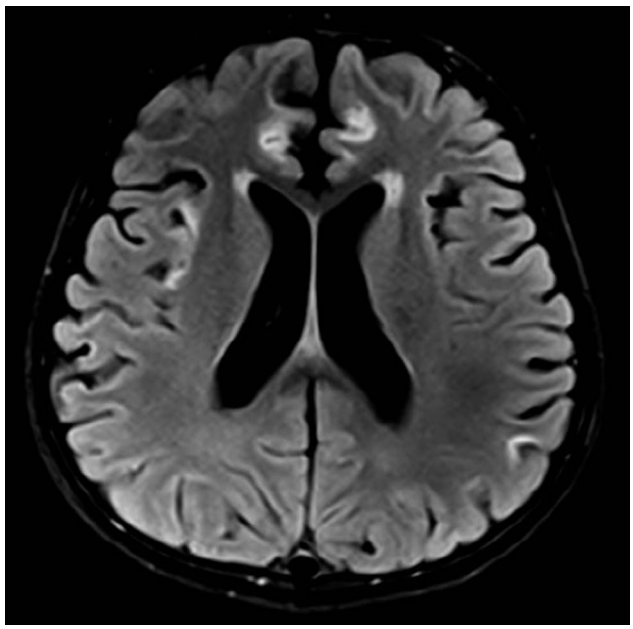

Figure 3. Axial flair MRI showing bilateral hyperintense subcortical frontal lobes, peri frontal horns, and mini subcortical lesions in temporal lobes with mild-moderate enlarged lateral ventricles.

Since the histologic testing cannot be done, all nonfatal cases were diagnosed on clinical and radiographic grounds alone[12].

Several findings, including an acute fulminant course of the disease, a history of upper respiratory infections, increased intracranial pressure, normal CSF analysis, and high ESR, along with the clinical course of the disease and MRI results, strongly supported the diagnosis of AHLE.

The most frequently discussed path mechanistic hypothesis is an autoimmune process promoted by cross-reactivity (i.e. molecular mimicry) between human myelin and viral or bacterial antigens, but the exact mechanisms remain to be elucidated[15].

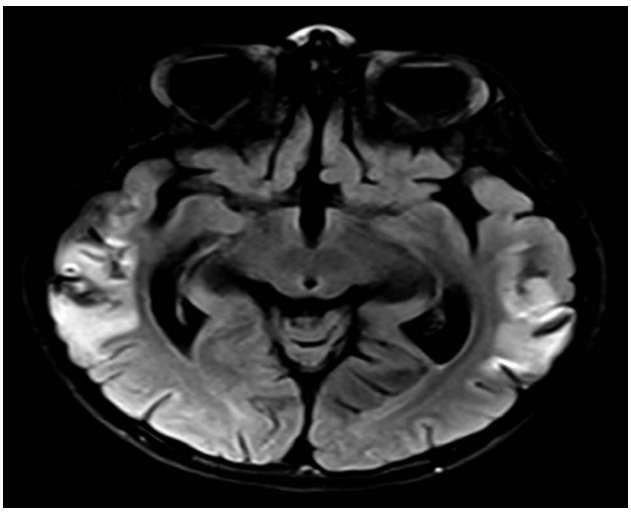

Figure 2. Axial flair MRI showing hyperintense lesions bilateral temporal lobes as well as signs of microhemorrhage.

Previous studies have shown that treatment with IV methylprednisolone, IVIG, acyclovir, and plasmapheresis are helpful and can be life-saving[16]. It is biologically plausible that corticosteroids attenuate the autoreactive lymphocyte responses that play a key pathologic role in CNS demyelinating conditions. 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. Evidence from multiple series and case reports suggests that plasmapheresis should be used when steroid and IVIG fail[17]. Following the same protocol, our patient treated with steroid and IVIG, recovered and was extubated and discharged with dysarthria, bradykinesia, with 15/15 GCS, which was considered to be a good prognosis compared to the high rates of mortality and morbidity of the disease.

Limitations: we may have missed the hemorrhage in the images of the patient because of the outdated CT scanning devices, however, it was overcame by relying on the clinical scenario, and going for the next step in the management protocol for AHLE.

Conclusion

Our study showcased how manipulative this disease might be, and discussed the outcomes in comparison to what the medical literature states.

This study may be the nidus to future studies, especially after the COVID pandemic, as viral infection may be a leading thread to the disease's bead. We recommend doing cross-sectionals for the prevalence of the disease to shed more light onto it. Furthermore, retrospective cohort studies will be of good use to understand how the disease manifests in different environments, and maybe unravel the undiagnosed cases.

Ethical approval

Ethical approval for this study (The Ethical Committee of Faculty of Medicine No: JD 023) was provided by the Ethical Committee of Damascus University, Damascus, Syria on 9th September, 2023.

Consent

Written informed consent was obtained from the patient's legal guardian for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

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The authors declare no conflict of interest.

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Data is available.

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This paper is published solely and not invited.

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