

# Acute hemorrhagic leukoencephalitis in a young female with excellent response to corticosteroids

Fathima N Nasim<sup>1</sup>, Mohamed Z F Fasrina<sup>2</sup>, Sunil B Bowattage<sup>3</sup>, Wickramasooriyage K Kularatne<sup>3</sup>, Vipuli J Kobbegala<sup>2</sup>

(Key words: acute hemorrhagic leukoencephalitis, acute disseminated encephalomyelitis, methyl prednisolone, magnetic resonance imaging)

## Abstract

**Background:** Acute hemorrhagic leukoencephalitis (AHLE) is a rare fulminant entity of acute disseminated leukoencephalitis (ADEM) that has a rapidly progressive polysymptomatology corresponding to areas of brain affected. It's characterized by rapid cognitive decline, coma or even rapid death. It is postulated to be a post infective immune mediated monophasic demyelinating disease. Diagnosis is clinical supported by CSF and MRI findings. It is challenging to differentiate the disease from MDEM (multiphasic demyelinating encephalomyelitis) and multiple sclerosis during the initial presentation.

**Case presentation:** Here we report a case of a 36-year-old Sri Lankan Sinhalese lady who presented with seizure following febrile illness followed by gross right sided hemiparesis later progressing to mutism and cognitive decline. Her CSF showed pleocytosis 12/cumm with 5% polymorphs, red cells, mildly high proteins with normal glucose and positive oligoclonal bands. MRI showed evidence of multiple focal supra and infratentorial signal abnormalities and gyral thickening with hemorrhages, largest lesions being in left frontal region with mass effect but no herniation. She was diagnosed with AHLE and treated with high dose IV methyl prednisolone later converting to oral prednisolone tapering regime. She was continued on intravenous cefotaxime and acyclovir as per meningoencephalitis. Improvement with steroids was dramatic with complete neurological recovery, minimal sequel and no recurrences at 6 months follow up.

**Conclusion:** The case is a representation of a very rare entity of an infrequently reported disease which needs

high degree of clinical suspicion with early imaging for aggressive and early immunosuppressive treatment that may hinder progression to commonly described sequel including coma, death or residual neurology. The predictions on future MDEM or MS on first presentation and overlap are areas that need further exploration.

## Background

Acute hemorrhagic leukoencephalitis (AHLE) is rare fulminant form of acute disseminated encephalomyelitis (ADEM) [1,2]. While ADEM is commonly reported in children AHLE is more frequent in adults [3]. Dating back to 1941 when Weston Hurst first described the disease as a monophasic demyelinating disease with variable presentations typically involving the cerebrum [2,4]. However, diverse regional involvement including cerebellar, brain stem and even spinal cord is described [1,3,4]. Triggered by post-infective and autoimmune processes occurring 1-3 weeks following viral infections or vaccinations, the disease is characterized by focal neurology, encephalopathy and rapid, devastating neurological deterioration [3-5]. The diagnosis relies on a combination of clinical features, MRI findings, and CSF analysis although brain biopsy may also be helpful [4]. Treatment is with immunosuppressive therapy but the response is variable and typically less favorable compared to ADEM [3]. Prognostic markers have not been identified and mortality can be as high as 70% [2,3].

Within this context we present a case of a young lady coming with rapidly deteriorating focal neurology and encephalopathy illustrating her journey from an acute

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<sup>1</sup>Registrar in Medicine, <sup>2</sup>Senior Registrar in Medicine, <sup>3</sup>Consultant General Physician, National Hospital, Kandy, Sri Lanka.

Correspondence: FNN, e-mail: <nujnasim@yahoo.com>. Received 22 December 2022 and revised version 26 February 2023 accepted 06 March 2023



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febrile illness to the application of immunosuppressive therapy that ultimately facilitated her full neurological recovery.

### Case presentation

A 36-year-old previously well Sri Lankan Sinhalese lady was transferred to our tertiary care center at National Hospital, Kandy following development of seizures, right sided weakness and progressive aphasia with confusion.

What began as a six-day bout of high-grade fever, generalized arthralgia, myalgia, and headache with photophobia and phonophobia quickly escalated into generalized tonic-clonic convulsions on her second day of admission to a Base hospital in the suburbs of Kandy. By this time, she was fever free for two days and didn't complain of cough, or shortness of breath, dysuria, rashes, and didn't give a contact history of fever, leptospirosis or dengue. Subsequently she was noted to have right sided upper and lower limb weakness with aphasia and progressive confusion. Notably, her medical history was unremarkable for joint pain, stiffness, autoimmune conditions, or prior history of seizure.

Upon transfer the right sided weakness progressed to gross hemiparesis over one day with restricted mobility.

On examination she was overweight with a BMI of 28.3kg/cm<sup>3</sup>. She had no peripheral stigmata of infective endocarditis. No carotid bruit or murmurs were noted. Although neck stiffness was present kernig sign was negative. She was afebrile with stable hemodynamics (Blood pressure 120/70mmHg equal bilaterally) and regular pulses of 80bpm. Neurological examination revealed fluctuating GCS of 9/15 (E3,V1,M5) to 11/15 (E4 V1 M6) due to aphasia, gross right sided hypotonia with hemiparesis (MRC-0/5) and exaggerated reflexes on right upper and lower limbs with up going planters on the same side and preserved sensations. Profound cognitive impairment was evident by an impaired orientation to time and place, rendering the patient unable to comprehend and follow simple commands. Given the global aphasia and paresis of the dominant hand, an objective cognitive assessment was unfeasible.

Her full blood count revealed low WBC counts ( $2.7 \times 10^9$  / liter ref-  $4-10 \times 10^9$ /L), hemoglobin of 12g/dL (ref 11-16 g/dL) with platelets of 327,000 (ref 150-450 $\times 10^9$ /L). C reactive protein was 1.1mg/L, ESR was elevated at 93mm/1<sup>st</sup> hour. Renal functions and serum electrolytes including calcium, phosphate and magnesium were normal. Liver functions revealed elevated ALT 368U/L (ref $\leq$ 35U/L), AST 219U/L (ref $\leq$ 45U/L), GGT was 173U/L (ref-11-61U/L) with normal ALP. Total protein was 9.7 g/dL (ref-6.6-8.3g/dL) with albumin of 4.4 g/dL (3.5-5.3g/dL) and globulin of 5.3g/dL. Her urine was negative for dysmorphic red cells and proteins. She was started on IV cefotaxime meningitic dose and IV acyclovir and IV phenytoin on admission.

Her Non contrast brain showed hyper-dense area (<1cm) in left frontal lobe with peripheral vasogenic edema/hypo-density causing mass effect with compressed left lateral ventricles and midline shift to right side (Figure 1-a).

CECT brain (Figure 1) showed an ill-defined non contrast-enhancing hypodensity involving left sided fronto-parietal and left medial temporal regions, causing mild effacement of left lateral ventricle (Figure 2-a,b). Cerebellar hypodensities were subtle (Figure 2-c). Features suggested early cerebritis involving left fronto-parietal and medial temporal lobes with mass effect. Intravenous dexamethasone was commenced due to concerns with cerebral edema.

While awaiting MRI, lumbar puncture was carried out after extensive discussion regarding safety with neurology and radiology teams on day three of admission. CSF revealed pleocytosis (12/cumm) with lymphocytic predominance, RBC 55/cumm, Glucose 7.76mmol/L (blood glucose 8mmol/L) and protein level of 56.53 mg/dL with positive oligoclonal bands (Figure 4). CSF cytology, cultures and PCR for HSV were negative.

MRI brain showed multiple focal areas of gyral thickening and hemorrhage in the supra and infra-tentorial brain (Figure 3 a-e). Specifically, left superior and inferior frontal, right superior frontal and right cingulate gyri and supplementary motor areas, left hippocampal medial temporal lobe and right peri-insular region (Figure 3- a, b, d, e). Similar changes were seen in the dentate nucleus of the cerebellum (Figure 3-c). Largest lesions were in left inferior and middle frontal gyri extending to the adjacent striatum, body and tail of caudate nucleus and putamen (Figure 3- a, b). The Findings suggested encephalitis with hemorrhage. There was mass effect with no evidence of herniation. Magnetic resonance angiography (MRA) showed irregular luminal narrowing in the distal MCA branches, superior cerebellar and posterior cerebral arteries that could not exclude small vessel vasculitis. MR venography was not suggestive of CVT (cerebral venous sinus thrombosis).

EEG showed continuous generalized theta slow activity with occasional scattered alpha activity. No epileptiform discharges were seen. EEG was consistent with mild generalized cerebral dysfunction (encephalitis/encephalopathy).

Blood cultures and urine culture showed no growth. Rheumatoid factor was 185 IU/ml (<16 IU/ml). Echocardiography did not show evidence of infective endocarditis. Complement C3 and C4 and antinuclear factor were in normal ranges. Blood picture showed left shift of neutrophils with some toxic changes, but was otherwise normal. CMV, EBV serology COVID rapid antigen and Dengue NS1, IgM, IgG came negative.

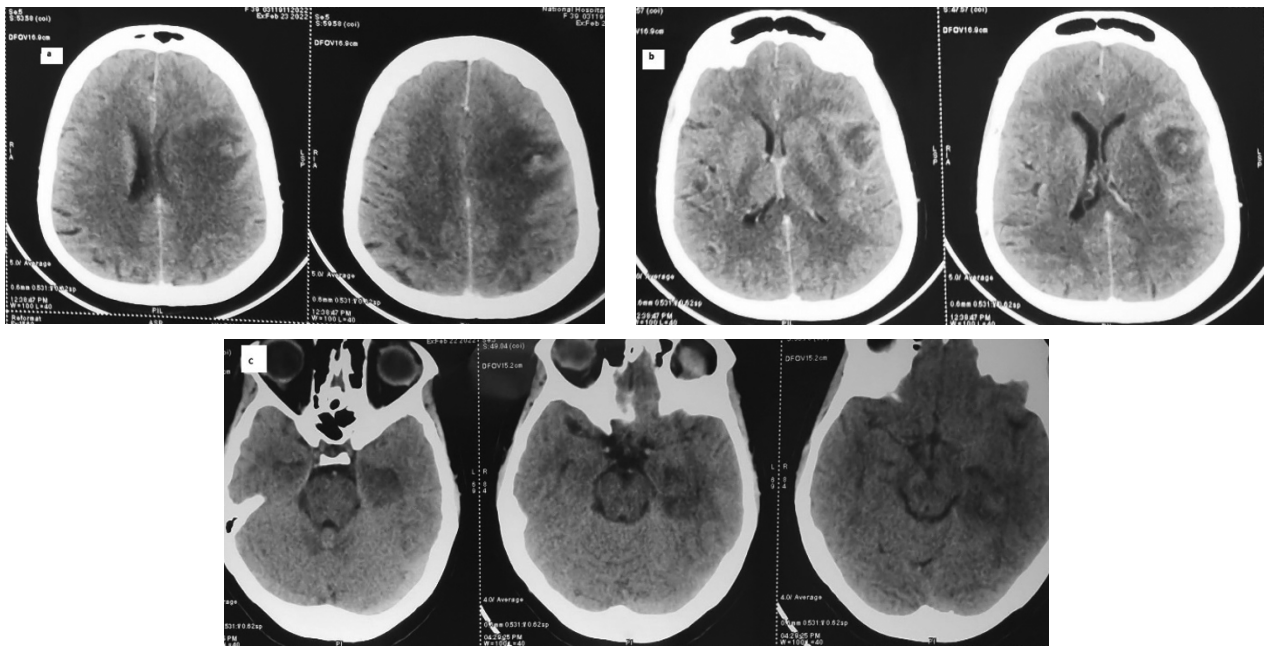


Figure 1. a,b – Initial non contrast CT scan of brain showing hyperdensity in left frontal lobe with vasogenic edema and hypodensity in left fronto-parietal area. c – Multiple hypodense areas noted in left medial temporal and cerebella hemispheres.

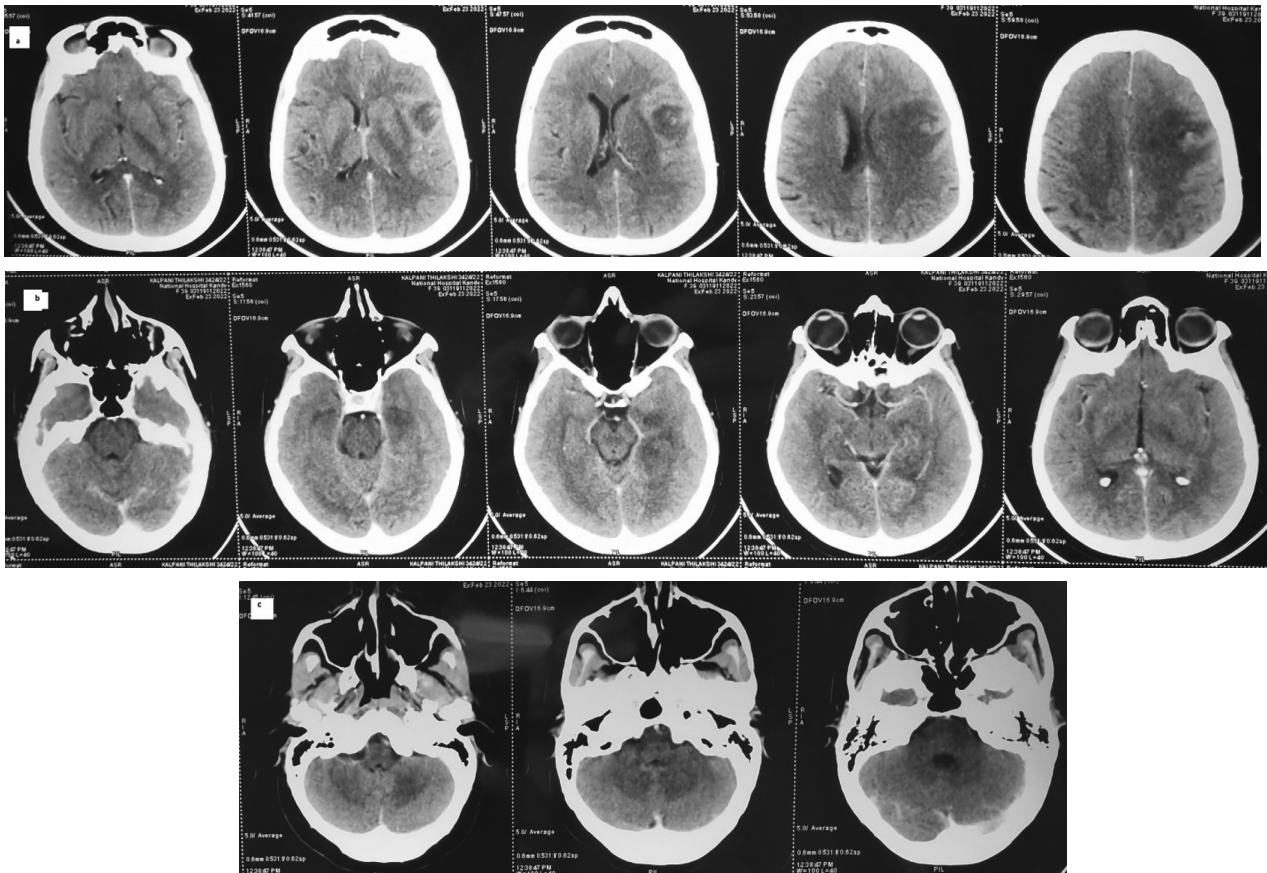


Figure 2. a,b – CECT brain showing ill-defined hypo densities in left fronto-parietal and medial temporal region, causing mild effacement of left lateral ventricle. c – Cerebellar involvement noted as bilateral cerebellar hypodensities.

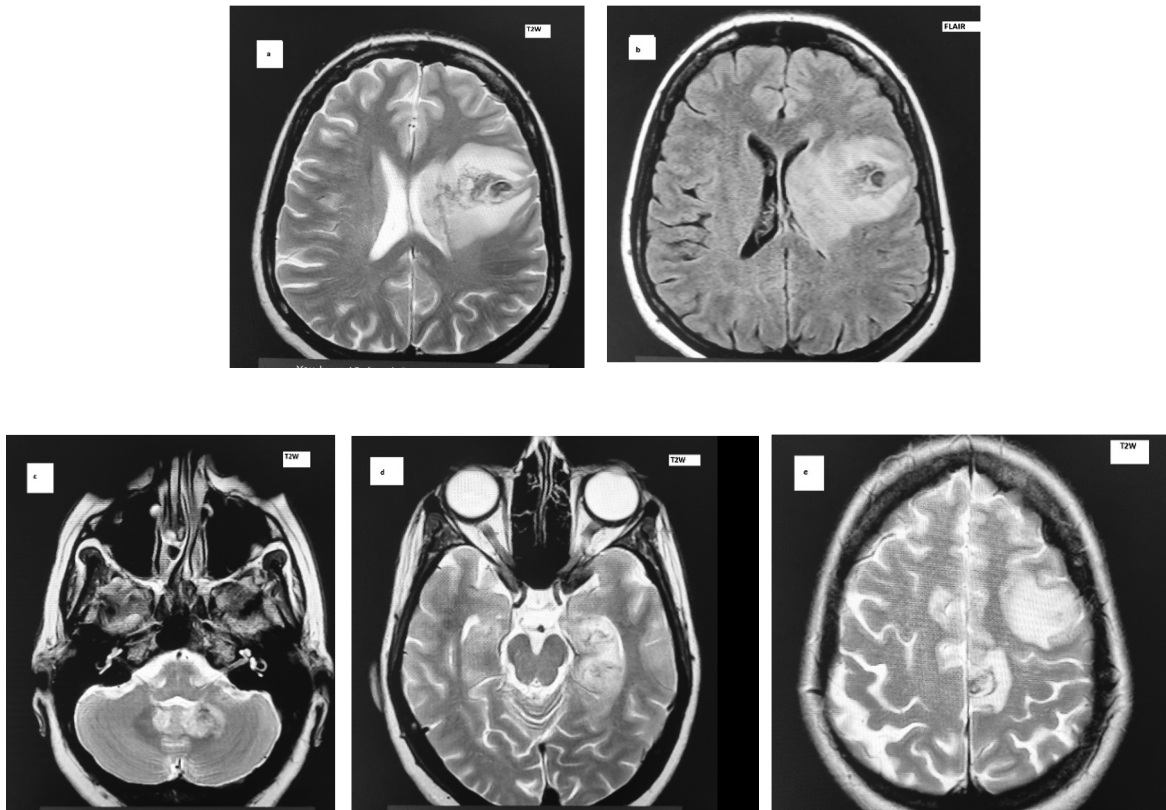


Figure 3. MRI brain showing diffusion restriction with hyperintensity in T2W (a,c,d,e) and FLAIR (b) sequences in the areas noted in CT. a,b Note the gyral thickening in multiple areas including left frontal region. c High signal intensity also seen in cerebellar dentate nuclear area.

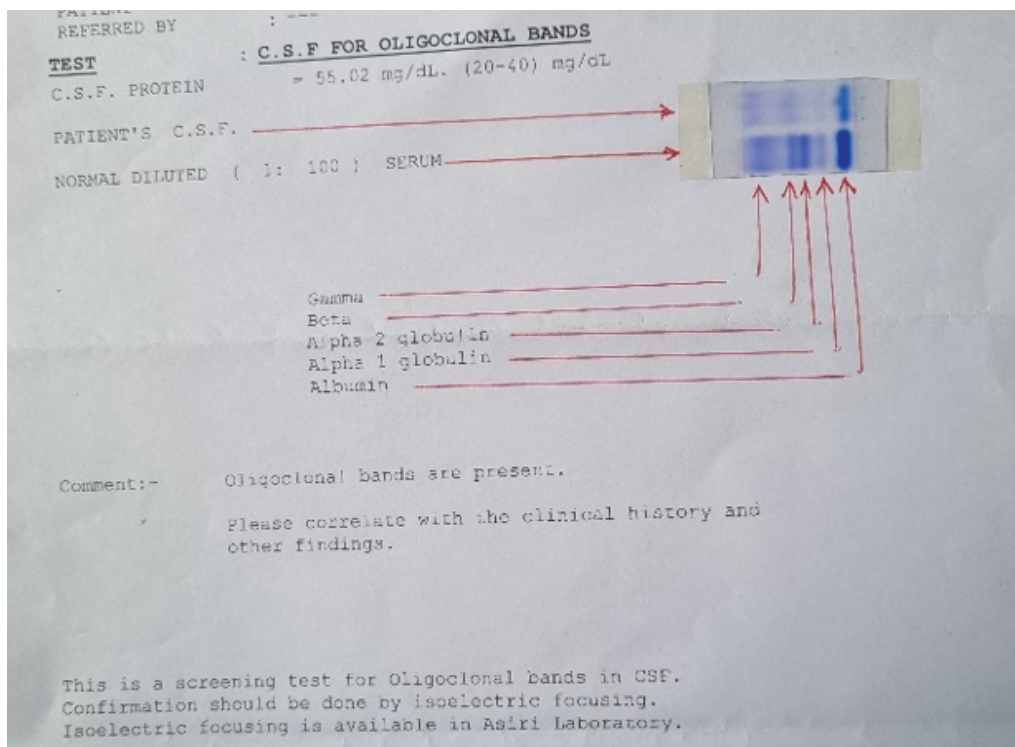


Figure 4. CSF oligoclonal bands.

Following a presumed diagnosis of AHLE the patient was started on intravenous methyl prednisolone 1g/daily for five days followed by oral prednisolone 60mg/day. Response to steroids were marked with gradual improvement in sensorium. Her speech improved by the fourth day of treatment. Gradual recovery of limb weakness was noted with a power of MRC 4/5 by day 10 of treatment regaining ability to mobilize independently at the time of discharge.

Intravenous antibiotics and acyclovir were continued for 14 days. At the time of discharge her GCS was 15/15 (E4V5M6) and mini mental state examination was 27/30. ESR had normalized.

During the follow up visit, her neurology and cognition had completely normalized following which steroids were eventually tailed off.

## Discussion and conclusions

ADEM a rare disease affecting mostly children of the ages 5-8 years, has an incidence of 0.6 /100,000/y [5]. Although considered a monophasic disease, recurrence may be seen in 15% of adults (multiphasic disseminated encephalomyelitis). Majority don't progress beyond three months following initial episode [5]. Reported cases of AHLE are sparse in literature, resulting in limited insight into pathogenesis, diagnosis, prognosis, and treatment. Diagnosis is challenging due to absence of diagnostic tests or criteria, but is largely clinical with supportive CSF and MRI [3,6]. High degree of clinical suspicion is vital in resource-constrained settings in the background of acute cerebral inflammation of unknown origin, to prompt early MRI [3].

While our patient exhibited several common clinical features of AHLE, similar presentations can also be observed in conditions like MS, viral encephalitides, posterior reversible encephalopathy syndrome (PRES), progressive multifocal encephalopathy (PML), adult onset leukodystrophies, and toxic encephalopathies [5].

Despite initial indication of infection with symptoms of headache and fever our patient's limited response to antibiotics and antivirals contrasted with the notable response to steroids. Such remarkable and complete neurological recovery, uncommon in AHLE is more typical of ADEM [2,7].

ADEM/AHLE being post infective immune mediated diseases, the pathology is presumed to be related to molecular mimicry in genetically susceptible population. Increased CNS vascular permeability, demyelination and gliosis following an inflammatory cascade are also implicated [5,6]. The term para-infectious is preferred over post-infectious as evidence of infection can be present in brain parenchyma at the time of diagnosis [3,6].

Infective agents include viral (HSV, varicella zoster, corona virus, CMV, coxackie, measles, rubella) and bacterial

(mycoplasma pneumoniae, leptospira, borrelia burgdoferi, rickettsia) types [5]. Although Patient's CSF viral serology came negative, IV cefotaxime and IV acyclovir were administered for 14 days due to delayed CSF sampling. CSF, HSV PCR is 98% sensitive, however negativity is known to occur with time [8]. As such acyclovir was continued despite negative PCR based on positive outcomes reported in treated cases [9].

Our patient displayed leukopenia, unlike the peripheral leukocytosis often reported [3]. Pinto P *et al*, 2011 reports a similar case of AHLE confirmed on autopsy in a patient with an initial diagnosis of ADEM [10]. Thus, even the most severe forms of AHLE can have absence of leukocytosis and should not preclude a diagnosis of AHLE.

CSF studies in ADEM patients reported mild lymphocytic pleocytosis, with mildly increased proteins while AHLE displayed distinct polymorphonuclear cells with higher protein content [6]. A systemic review by Grzonka P *et al*, 2020 found that 65% cases had elevated WBC counts out of which 50% were mononuclear and 40% polymorphonuclear suggesting neutrophil predominance in AHLE is not universal [2,3]. CSF red cells were used to differentiate ADEM from AHLE in many cases [9,10]. Our patient had 5% neutrophils with mildly high proteins and few red cells. This picture, although not archetypal of AHLE or ADEM was more supportive of the former. CSF lymphocytosis, linked to milder inflammation and early steroid treatment, aligns with our case where early dexamethasone was administered for cerebral edema [2]. CSF oligoclonal band an immunological response to infection is not a reliable discriminator of ADEM vs acute fulminant multiple sclerosis [11]. The frequency of positivity is high in multiple sclerosis (64-95%) compared to 29% in ADEM while being undefined in AHLE [6,10]. Oligoclonal bands were found to be negative in convalescence in ADEM where as it may remain positive in MS [12].

ADEM/AHLE, multiphasic disseminated encephalomyelitis (MDEM), MS and NMO (neuromyelitisoptica) are immune mediated demyelinating disease entities that may be diagnostically challenging at first presentation. ADEM a typically monophasic disease with diverse symptoms has a 45% recurrence (MDEM) and 20% risk of developing MS [10]. MS presents usually with monosymptomatology such as optic neuritis, transverse myelitis or brainstem syndromes [12]. MRI lesions of ADEM are usually indistinct, subcortical with periventricular sparing and confined to perivenous areas with minimal hemorrhage. MS lesions being fairly distinct can be seen in subcortical and periventricular areas. However, 22% of ADEM patients will have periventricular lesions that aren't distinguishable from MS [13]. MRI shows large, confluent FLAIR lesions in varying locations with edema, space occupancy in AHLE. T2-weighted images may display petechial hemorrhages, sparing of subcortical U fibers [10]. Key distinction is the presence of hemorrhage [6,12]. Our



patient's MRI aligned with AHLE, with multifocal hemorrhagic lesions and mass effect (Figure 3). Cerebellar and brainstem involvement is linked with poor outcome in AHLE, although standardized prognostic markers are lacking [2,7]. Solis *et al.*, (2017) reports a histology proven AHLE with favorable outcome, suggesting potential markers of better prognosis such as unifocal disease and lack of CSF pleocytosis. Predominant lymphocytosis in CSF and lack of peripheral leukocytosis, might be a predictor of indolent disease course in our case despite the presence of multifocal large and cerebellar lesions.

Most cases of AHLE/ADEM report unremarkable MR angiograms and venograms [7,14]. While irregular luminal narrowing in MRA could suggest potential small vessel vasculitis there was lack of supportive evidence. However, histology in AHLE is associated with necrotizing angitis of small vessels and perivascular inflammation [2,3]. Although the role of MRA in AHLE has not been explored before, MRA findings in the index case may represent AHLE related angitis.

Treatment of ADEM/AHLE is mostly directed via clinical data, and case report evidence. While the available therapeutics include steroids, immunoglobulins, plasmapheresis, cyclophosphamide and rituximab. Spontaneous resolution of ADEM has also been reported [8]. High dose methyl prednisolone or dexamethasone later converting to oral prednisolone tapering regime over 4-6 weeks is commonly suggested [6]. Most improvement in AHLE has been noted with plasmapheresis, if an infectious agent found targeted treatment is recommended [9].

Our patient had headache, fever focal neurology with rapid deterioration to encephalopathy, CSF leukocytosis with some neutrophils and red cells, typical imaging of multifocal large confluent lesions with micro-hemorrhages and mass effect with MRA showing evidence of angitis, favoring a diagnosis of AHLE over ADEM.

Our case dramatically improved with steroids, not needing further immunosuppression. 4-week review revealed minimal neurological sequel. A similar success rate is uncommon, however best outcomes were reported with early aggressive therapy [15], as in our case. The absence of peripheral leukocytosis and presence of lymphocyte predominance in CSF and excellent response to steroids may indicate a milder form of AHLE [2].

## Conclusion

AHLE, a fulminant variety of ADEM is a clinical diagnosis supported by rapidly deteriorating neurology that can mimic many CNS disorders. CSF analysis and typical MRI findings accompanied by multiple hemorrhages with evidence of mass effect will be supportive of the diagnosis. Although CSF oligoclonal bands are in favor of MS, they might be positive in ADEM and AHLE representing the immunogenic nature of the disease. Rapid diagnosis and treatment may reduce morbidity and mortality and long-term neurological sequel.

Predictors of better outcome in AHLE need further exploration.

## List of abbreviations

1. AHLE: Acute hemorrhagic leucoencephalitis
2. ADEM: Acute disseminated encephalomyelitis
3. MS: Multiple sclerosis
4. MDEM: Multiphasic demyelinating encephalomyelitis
5. CSF: Cerebrospinal fluid
6. MRI: Magnetic resonance imaging
7. CNS: Central nervous system
8. NCCT: Non contrast computed tomography
9. CECT: Contrast enhanced CT
10. GCS: Glasgow coma scale
11. ESR: Erythrocyte sedimentation rate
12. CRP: C-reactive protein
13. AST: Aspartate transaminase
14. ALT: Alanine transaminase
15. GGT: Gamma-glutamyl transferase
16. MCA: Middle cerebral artery
17. MRV and MRA: Magnetic resonance venography and magnetic resonance angiography
18. CVT; Cerebral venous sinus thrombosis
19. CMV, EBV, HSV: Cytomegalovirus, Epsteinbar virus, Herpes simplex virus
20. PRES: Posterior reversible encephalopathy syndrome
21. PML: Progressive multifocal encephalopathy
22. PCR: Polymerase chain reaction
23. EEG: Electroencephalogram

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## Declarations

### Statement of ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was taken from the patient for publication of this case report and any accompanying images. The study is exempt from ethics committee approval because complete patient anonymity was guaranteed.

### Conflict of interest statement

The authors declare that they have no conflicts of interests.

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This study was self-funded by the investigators, no external organization or institution was involved in the study

## Data availability

Data generated during this study are included in this published article. All the data are available in the repository of National Hospital, Kandy,

## Authors' contributions

All authors read and approved the final manuscript. FN conceptualized the article collected information, and drafted the manuscript. MFZ and VJ helped in collecting data and diagnostics. SB and WSKS supervised with diagnostics and manuscript writing.

## References

1. Khademi GR, Hasan Aelami M, Aelami MH. Acute Hemorrhagic Leukoencephalitis in Children: A Case Report. *Iran J Med Sci* 2016; **41**(3): 245.
2. Solis WG, Waller SE, Harris AK, Sugo E, Hansen MA, Lechner-Scott J. Favourable Outcome in a 33-Year-Old Female with Acute Haemorrhagic Leukoencephalitis. *Case Rep Neurol*. 2017; **9**(1): 106-13.
3. Grzonka P, Scholz MC, De Marchis GM, Tisljar K, Ruegg S, Marsch S, *et al.* Acute Hemorrhagic Leukoencephalitis: A Case and Systematic Review of the Literature. *Front Neurol*. 2020; **11**: 1-11.
4. Alsaïd HM, Atawneh MAA, Abukhalaf S, Daoud A, Hamadah A, Gharaibeh K. Acute Hemorrhagic Leukoencephalitis – A Rare but Fatal Form of Acute Disseminated Encephalomyelitis – Complicated by Brain Herniation: A Case Report and Literature Review. *American Journal of Case Reports* 2022; **23**(1): 1-7.
5. Almaghrabi N, Saab A. Adult onset acute disseminated encephalomyelitis: A case report. *Radiol Case Rep* [Internet]. 2021; **16**: 2469-73. Available from: [www.sciencedirect.com/journal/homepage/www.elsevier.com/locate/radcr](http://www.sciencedirect.com/journal/homepage/www.elsevier.com/locate/radcr)
6. Steiner I, Kennedy PGE. Acute disseminated encephalomyelitis: current knowledge and open questions. *J Neurovirol*. 2015; **21**(5): 473-9.
7. Varadan B, Shankar A, Rajakumar A, Subramanian S, Sathya AC, Hakeem AR, *et al.* Acute hemorrhagic leukoencephalitis in a COVID-19 patient – a case report with literature review. *Neuroradiology*. 2021; **63**(5): 653-61.
8. Milhomem Martins H, Teixeira AL, Lana-Peixoto MA. Acute hemorrhagic leukoencephalitis mimicking herpes simplex encephalitis: Case report. *Arq Neuropsiquiatr*. 2004; **62**(1): 139-43.
9. Kabakus N, Gurgoze MK, Yildirim H, Godekmerdan A, Aydin M. Acute hemorrhagic leukoencephalitis manifesting as intracerebral hemorrhage associated with herpes simplex virus type I. *J Trop Pediatr*. 2005; **51**(4): 245-9.
10. Pinto PS, Taipa R, Moreira B, Correia C, Melo-Pires M. Acute hemorrhagic leukoencephalitis with severe brainstem and spinal cord involvement: MRI features with neuropathological confirmation. *Journal of Magnetic Resonance Imaging*. 2011; **33**(4): 957-61.
11. Haqiqi A, Samuels TL, Lamb FJ, Moharrum T, Myers AE. Acute haemorrhagic leukoencephalitis (Hurst disease) in severe COVID-19 infection. *Brain Behav Immun Health*. 2021; **12**(January):100208.
12. Dale RC, De Sousa C, Chong WK, Cox TCS, Harding B, Neville BGR. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. *Brain*. 2000; **123**(12): 2407-22.
13. Repic-Bulicic A, Filipovic-Grcic P, Jadrijevic E, Jurinovic P, Titlic M. Successful treatment of acute disseminated encephalomyelitis (Adem) by prompt usage of immunoglobulins – case report and review of the literature. *Acta Clin Croat*. 2019; **58**(1): 173-9.
14. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: Imaging features. *Radiology*. 2020; **296**(2): E119-20.
15. Borlot F, Da Paz JA, Casella EB, Marques-Dias MJ. Acute hemorrhagic encephalomyelitis in childhood: Case report and literature review. *J Pediatr Neurosci*. 2011; **6**(1): 48.