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Case report

CASE REPORT: Fulminant acute hemorrhagic Leukoencephalitis (AHLE): A rare and ruinous outcome with cerebral herniation (COVID-19)

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ABSTRACT

Background: Acute hemorrhagic leukoencephalitis (AHLE) is a very rare demyelinating disease with rapid fulminant inflammation of the white matter. Although the exact etiology is unknown, AHLE usually manifests post a viral or bacterial infection and less often seen post vaccination for measles or rabies. AHLE has a very poor prognosis and a high mortality rate. Owing to the rarity of this entity there is not clear consensus on the proper line of management. In this report, we present a case of AHLE as a para-infectious sequel to COVID-19 in a young patient.

Clinical presentation: We report a 30-year-old turkish patient with an initial presentation of upper respiratory tract infection due to COVID-19. Initially, she was admitted to the hospital with generalized tonic-clonic seizure (GTCS) and deterioration in her level of consciousness lapsing into a coma. An initial CT scan showed diffuse brain edema and an MRI head confirmed the suspicion of Acute hemorrhagic leukoencephalitis (AHLE). Despite prompt and diligent osmotic therapy and pulsed intravenous (IV) methylprednisolone, her condition rapidly depreciated and progressed into cerebral edema with gravid sequela of brainstem herniation.

Conclusions: AHLE is a very rare entity and perhaps its fulminant debilitating course and high mortality should warrant further studies on disease pathophysiology and its optimal treatment parameters. Life-saving decompressive hemicraniectomy should be considered in the multidisciplinary approach of the management with tailored osmotic and immunotherapy.

1. Introduction

In 1941, Edward Weston Hurst described the first case of acute hemorrhagic leukoencephalitis (AHLE) which delineates a rare and fulminant form of demyelinating disease that is also known as Hurst disease [1]. In the literature, AHLE is classified as a fulminant subtype of acute demyelinating encephalomyelitis (ADEM) or a rare subtype of tumefactive multiple sclerosis (MS) [2]. The hallmark features encompass a rapidly progressive course with a clinical presentation variable on a spectrum from fever, altered mentation, headache, seizures, coma, and inevitably death [3]. Histopathological, it resembles ADEM with progressive multifocal white matter inflammation, necrosis, and hemorrhage [2,3]. While the incidence of ADEM is estimated to be 0.3–0.6 per 100,000 per year, the incidence of AHLE remains unknown due to the rarity of this entity [4]. Hurst disease tends to have a predilection toward younger adults compared to ADEM which is commonly seen in children, however, cases of AHLE in the elderly have been reported [2,4].

AHLE gravid and fulminant course with lesions of space-occupying effect holds a morality as high as 70% with a percentage of complete

Abbreviations: AHLE, Acute hemorrhagic leukoencephalitis; ADEM, Acute demyelinating encephalomyelitis; AHEM, Acute hemorrhagic encephalomyelitis; ADLs, activities of daily living; CSF, cerebrospinal fluid; HIV, Human immunodeficiency virus; IV, Intravenous; ED, emergency department; MRI, magnetic resonance imaging; DTR, deep tendon reflexes; LP, lumbar puncture; FLAIR, fluid attenuated inversion recovery; ANA, autoimmune screen (anti-nuclear antibody); ANCA, antineutrophil cytoplasmic antibody.

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remission estimated to be as low as 14% despite immunotherapy and raised intracranial pressure measures [4]. We herein report a rare case of fulminant AHLE-COVID-19 with rapidly progressive global brain edema and brain herniation.

2. Case presentation

A 30-year-old right-handed Turkish woman, with an unremarkable past medical history, was brought to the emergency department (ED) with multiple episodes of generalized tonic-clonic seizures (GTCS), preceded by a three-day history of fever, headache, and myalgia.

Upon arrival to the ED, she had another episode of GTCS that aborted spontaneously in three minutes. The patient did not regain consciousness warranting endotracheal intubation and was admitted to the medical intensive care unit (MICU). She was managed with Status epilepticus protocol, with Lorazepam 4 mg IV once followed by a loading dose of Levetiracetam 4.5 g intravenous (IV) and started on a maintenance dose of Levetiracetam 1.5 g twice daily. An urgent EEG [electroencephalogram] obtained showed continuous low to medium voltage generalized irregular delta activity intermixed with runs of low voltage irregular theta activity with occasional sharply contoured transients in the right frontocentral region with no definite epileptiform discharges were recorded or features of non-convulsive status epilepticus (NCSE). Further collateral history revealed no preceding abnormal behavior. No recent history of travel, or trauma. A review of systems was unremarkable for joint pains, rashes, or constitutional symptoms, and no history of recreational drug use.

Her vital signs upon arrival to Hamad General Hospital ED were within normal limits with a temperature of 36.4 °C, respiratory rate of 17 breaths per minute, blood pressure of 129/62 mmHg, and oxygen saturation of 98% on Mechanical ventilation. On examination in an emergency, the patient was sedated on a mechanical ventilator, with symmetrical reactive 3 mm pupils. The neck was supple with generalized pyramidal signs of spasticity, hyperreflexia (DTR +3) in all the limbs, and bilateral upgoing plantar reflexes.

Her initial blood workup included blood cell counts, biochemistry, thyroid function tests, and vitamins B12 and B1 levels, which were all within normal limits, with normal inflammatory markers (CRP 6 mg/L). The autoimmune screen revealed negative ANA (Anti-nuclear antibody) and other autoimmune workup, and negative HIV (human

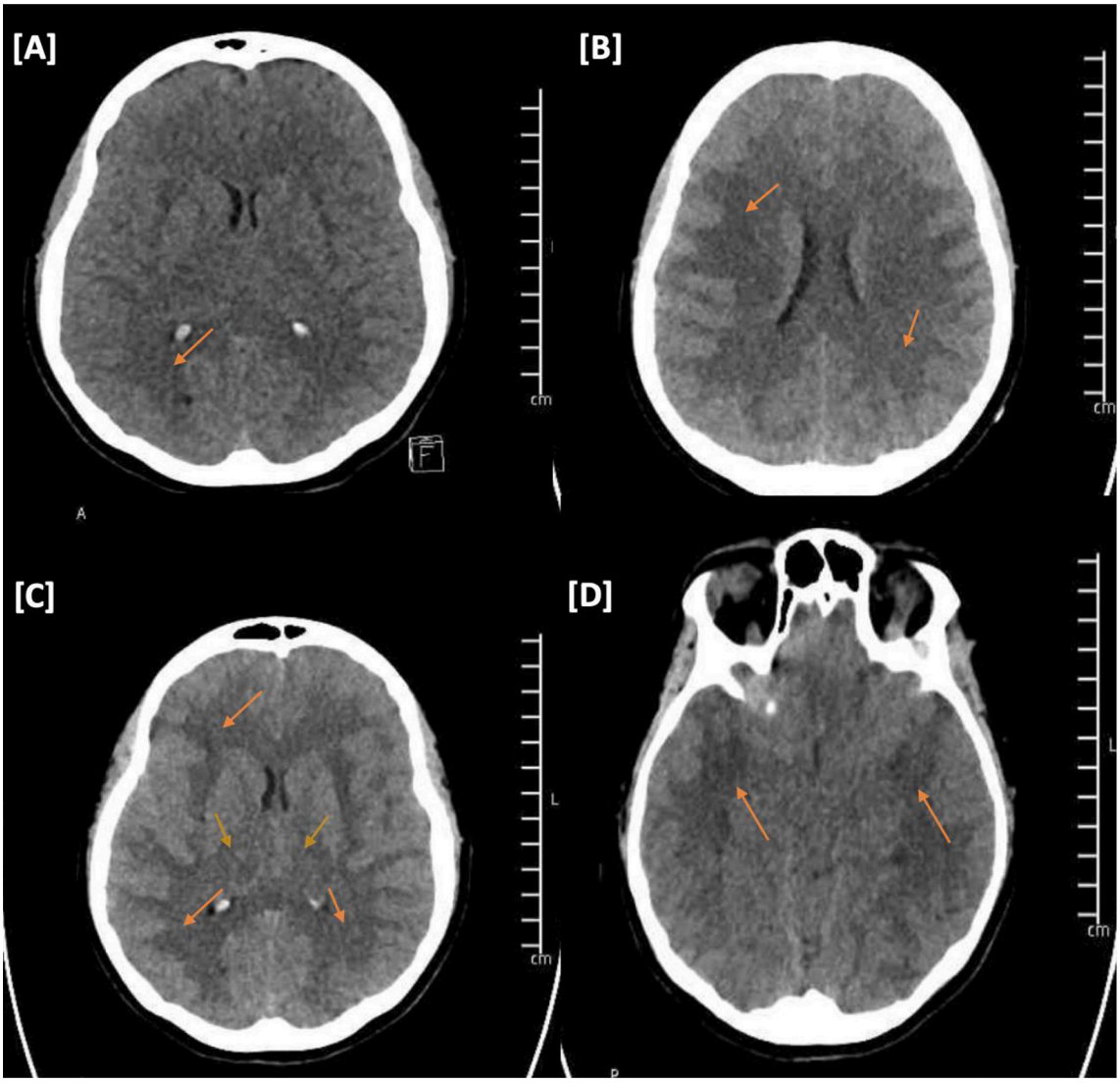

Fig. 1. CT head none contrast enhanced.
[A] initial CT head: Presence of generalized cerebral oedema and diffuse white matter hypodensity (orange arrows).
[B—D] 12-h follow CT head: Significant progression of generalized cerebral oedema (orange arrows). Diffuse white matter hypodensity involving cerebrum and cerebellum. Bilateral thalamic hypodensities (yellow arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

immunodeficiency virus) serology. Computed tomography (CT) of the head on the day of admission showed mild vasogenic brain edema with effacement of sulci (Fig. 1A). A lumbar puncture (LP) was performed, and the patient was empirically started on Acyclovir 800 mg and Ceftriaxone 1 g. Cerebrospinal fluid (CSF) analysis revealed a normal white cell count of 1 cell per mm3, elevated Protein of 0.5g/L, and elevated glucose levels of 4.2 mmol/l. CSF viral panel, smear, and polymerase chain reaction (PCR) for tuberculosis, and cryptococcus were negative with negative CSF cultures and cytology. Hence Antivirals and antibiotics were stopped. CSF oligoclonal bands were not detected and the CSF IgG Index was 0.5 (normal). OCB are usually not present in ADEM/AHLE or may be present.

transiently.

In less than 24 h from hospital admission, the patient was found to have anisocoria with a left pupil 5-mm non-reactive to light. Urgent CT head was ordered and Neurology on call was consulted. Upon reassessment, examination revealed a Glasgow coma scale (GCS) of 4 E (Eye) 1 V (Verbal) T M (Motor) 2, with a decerebrating posture to pain. Brainstem reflexes examination showed anisocoria (right 3 mm, left 5 mm nonreactive to light), conjugate gaze with intact horizontal and vertical vestibulocochlear reflex (VOR) intact symmetrical corneal reflex, cough reflex, and no pathological respiratory pattern was observed. Pyramidal signs were present with generalized hypertonia and bilateral Babinski's sign.

Urgent repeat CT head (Fig. 1B-D) showed newly developed diffuse white matter hypodensity involving cerebrum, cerebellum, and bilateral thalamic with significant generalized cerebral edema, with obliteration of suprasellar cistern suggestive of bilateral uncal herniation. A preliminary diagnosis of Fulminant ADEM (Acute demyelinating encephalomyelitis) was suspected. A neurosurgical consult was obtained with the suggestion of no surgical intervention. Patient management encompassed a multidisciplinary approach and structured Tiers of Supportive Medical Care and Standard Intracranial Pressure–Directed Measures were followed. Owing to a preliminary diagnosis of fulminant ADEM, she was started on IV pulsed methylprednisolone of 1 g daily and 3% Hypertonic saline for five days with parameters of Tier 1 and 2 of raised intracranial pressure.

Contrast-enhanced Magnetic Resonance Imaging (MRI) of the brain revealed diffuse brain swelling, radiologic evidence of increased intracranial pressure, scattered bilateral white matter, thalamus, and brainstem diffusion restriction along with bilateral microhemorrhages. Bilateral leptomeningeal enhancement was noted on postcontrast FLAIR images.

(Fig. 2). Such findings confirmed a working diagnosis of fulminant acute hemorrhagic leukoencephalitis/encephalomyelitis (AHLE/AHEM). Endotracheal SARS-CoV-2 RNA was positive, with normal Chest X-ray and CT thorax, raising the possibility of para-infectious COVID-19 associated Fulminant AHLE. The infectious disease team started the patient on a course of IV remdesivir 200 mg loading dose on the first day, followed by 100 mg from the second day to the fifth day for COVID-19 infection.

Patient management was meticulous with scheduled follow-up CT scans of the head (Day 2) revealed no discernable interval change with persistent generalized cerebral edema and bilateral diffuse white matter hypodensity. Patient level of consciousness was not improving with high mortality of AHLE, Tier 2 and 3 of raised ICP was instigated. She was started on mannitol boluses every 4–6 h 35–70 g with frequent monitoring of urine and serum osmolality along with sedation with propofol and midazolam.

On the third day of admission, the patient displayed features of stage

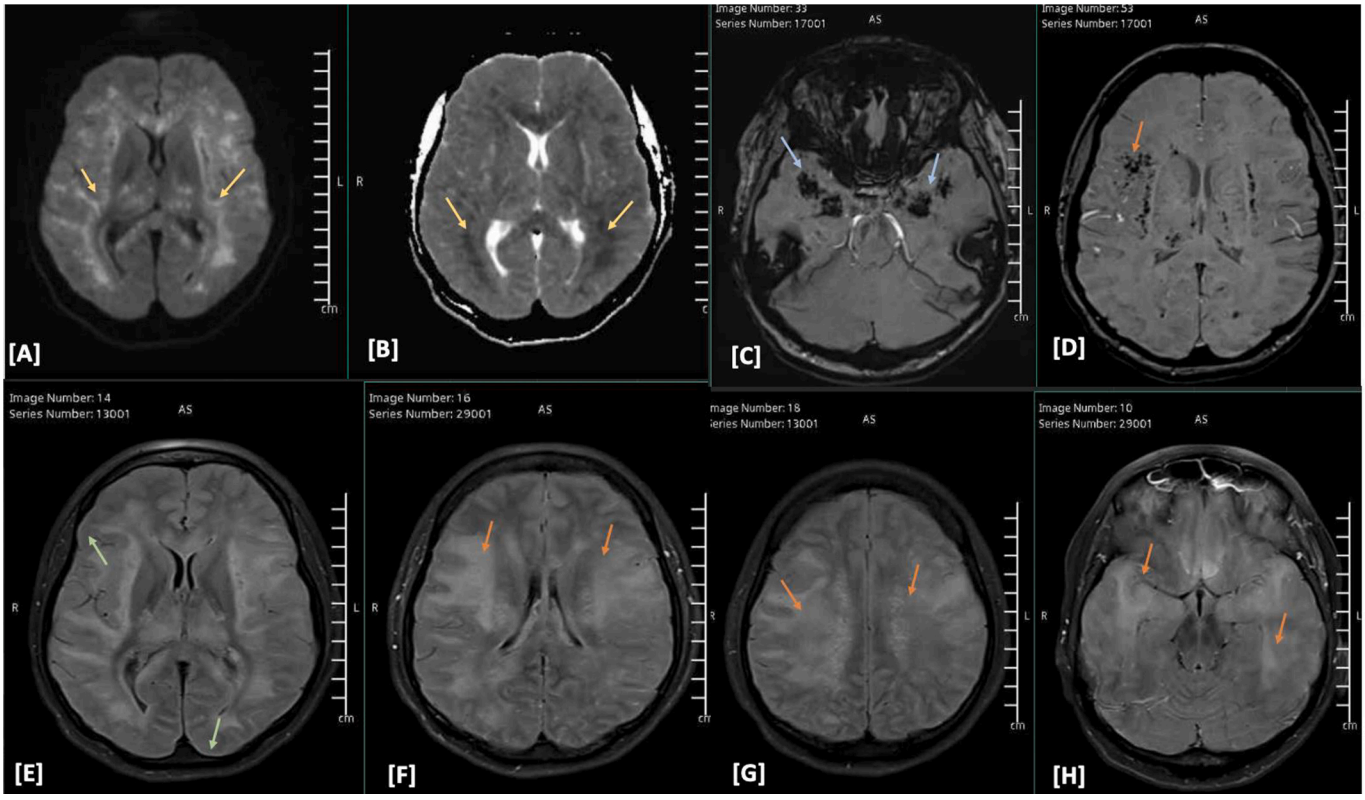

Fig. 2. MRI head contrast enhanced.
[A-D] DWI/ADC sequences shows radiologic evidence of increased intracranial pressure, scattered bilateral white matter, thalamus and brainstem diffusion restriction (yellow arrows) along with bilateral microhemorrhages (blue arrows).
[*E*-H] FLAIR images showed evidence of bilateral leptomeningeal enhancement noted on postcontrast images (green arrows) and diffused cerebral edema (orange arrows). Intracranial angiography is unremarkable (not shown). Overall impression in favor of acute disseminated hemorrhagic encephalitis (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

three Cushing reflex with Bradycardia at 34 beats per minute and a high BP of 170/93, urgent CT head showed no worsening in edema or any remarkable interval change.

On the fourth day of admission, despite being managed with five days of IV pulsed steroids, tightly regulated osmotic therapy, and sedation, progression of cerebral edema was inevitable with a follow-up CT head (Fig. 3) which showed a significant interval increase of the diffuse cerebral brain edema which extended to involve the brainstem, interval increase in the mass effect with more effacement of the ventricular system and tonsillar herniation.

On the fifth day of admission, the patient had fixed dilated pupils, with absent brainstem reflexes. Brainstem death pre-requisites were achieved with suspension of sedation and anti-seizure medication, brainstem death was confirmed by apnea test and absent cerebral flow on CT intracranial angiogram (Fig. 4). The patient's parents and her fiancé were onboard from admission, owing to such ruinous diagnosis and high mortality despite management; withdrawal of care was agreed upon and the patient passed away gracefully in MICU.

3. Discussion

Acute hemorrhagic leukoencephalitis pathogenesis to date remains a bewildering dilemma, with up to 50% of cases have a preceding infectious (viral and bacterial) illness [5]. As observed with our patient, with progressive refractory cerebral edema post COVID-19 infection; Its speculative pathogenesis remains elusive and unraveled despite proposed underlying immune etiology similar to what is observed in ADEM, yet up to 50% of AHLE patients exhibit no preceding illnesses [5,6].

3.1. Pathophysiology and immunogoloical triggers

The proposed pathogenesis delineates a cross-reactivity mechanism in AHLE between viral or bacterial antigens and human myelin antigens that fuels a severe immunological response that triggers demyelinating [6]. In literature, preceding upper respiratory tract infection in AHLE is reported in up to 35% of patients that encompass a spectrum of viruses and bacteria including *Staphylococcus epidermidis*, *Epstein Barr Virus* (*EBV*), *Influenza H1N1*, *Coxsackie* B6 *Cytomegalovirus* (*CMV*), *Human Herpes virus 6* (*HHV-6*), *Herpes simplex* (*HSV*), (*Varicella zoster* (*VZV*), *Mumps* virus, *Mycoplasma pneumoniae*, *Plasmodium vivax*, and *Mycobacterium tuberculosis* and coronavirus disease 2019 (COVID-19) as observed with our patient [4,7,9]. In addition, there were two cases of AHLE post-influenza vaccination [4]. Pirko et al. in a recent study support the notion of possible underlying a cross-reactivity mechanism

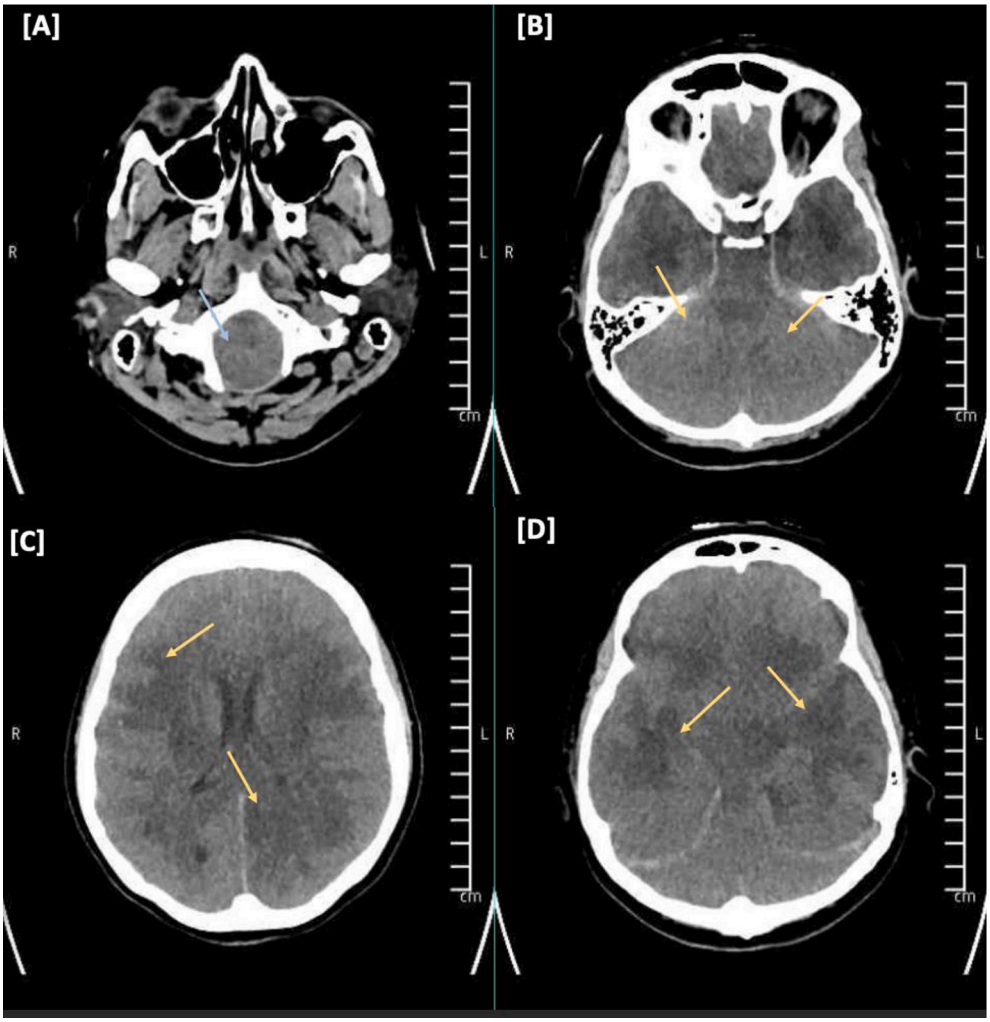

Fig. 3. CT head none contrast enhanced.
[A-D] Significant interval increase of the diffuse cerebral brain oedema which extended to involve the brainstem, cervico-medullary junction and extending to the visualized part of the cervical spinal cord. The ventricular system,the basal cisterns are completely effaced with diffuse blurring of the gray-white matter junction with loss of differentiation. (yellow arrows).
Crowding with almost complete obliteration of the foramen magnum signifying tonsillar herniation (blue arrows) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

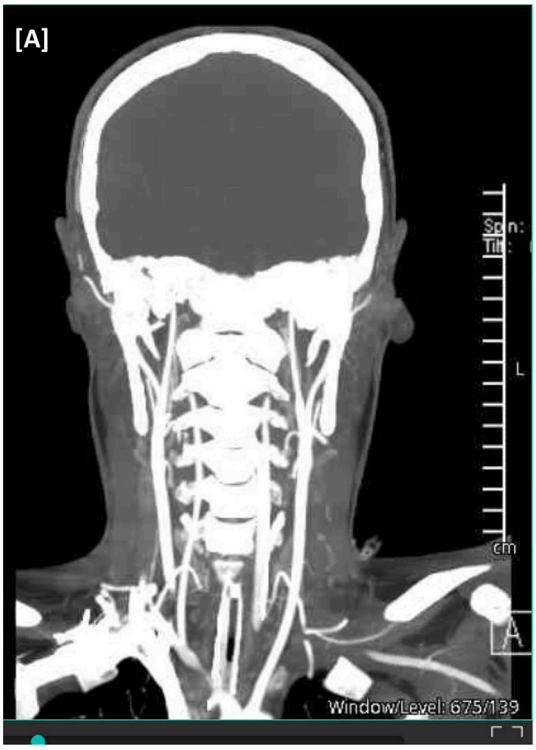

Fig. 4. CTA Intracrnaial angiography.
[A] Faint flow of bilateral intracranial ICAs and MCAs with paucity of the distal branches. Absent flow of the vestibulobasilar system and bilateral ACAs. Cervical arteries opacified normally with contrast with no evidence of stenosis or occlusion.

between viral or bacterial antigens and human myelin antigens that fuels a severe immunological response that triggers demyelinating [7]. He proposed the first murine model of AHLE by injecting VP2121–130 viral capsid of the Theiler's murine encephalomyelitis virus that provoked a robust in vivo activation of CD8+ T cells in C57BL/6 mice leading to the development of hyperacute hemorrhagic demyelination as early as within 24-h [7].

3.2. Prognosis and mortality

As observed with our pateint and previously reported cases; clinical course in AHLE is fulminant with hyper-acute focal neurological symptoms, seizures and coma [5]. It often manifests with bi-thalamic lesions of space-occupying effects that exhibit signs of rapid elevated intracranial pressure and possible herniation syndrome [4]. Mortality is estimated to be as high as 80% and patients deteriorate within 2–4 days to frequently evolve to coma and death [4,10,11]. Despite our patient and most reported cases with AHLE had a gravid prognosis and fulimannt course with diffuse disease [11,12]. Two reported cases had favorable outcome of 10-year old with 2 years follow up post AHLE with subtle decline in cognitive skills and Solis et al., reported a 30 years old in 2017 of focal right hemispehric lesion suggestive of AHLE with favorable outcome which dictates the hetergeniesty of this condition [8].

3.3. Vaccination and AHEM

A pathophysiologic link between vaccination and AHEM may be explained by molecular mimicry (shared pathogenic epitopes between infectious agent/vaccine and molecular central nervous structures) or via blood-brain-barrier increase permeability and breakdown of immune tolerance by a preceding CNS infection [15]. ChAdOx vaccines have been proven to elicit particularly strong T cell responses, biased toward IFNγ secretion and a Th1-phenotype [15]. Even though both the mRNA and vector-based vaccines encode the production of the spike (S) protein of SARS-CoV-2, they differ concerning the adjuvant required to stimulate the innate immune system: for mRNA vaccines, the mRNA itself acts as both immunogen and adjuvant, due to its recognition by endosomal and cytosolic innate sensors (i.e., TLR3, TLR7), whereas in the case of vector-based vaccines it is elements of the virus particle that are recognized by pattern recognition receptors (i.e., TLR9) [14].

There was a case series which described three patients who developed acute demyelinating and hemorrhagic lesions of the central nervous system consistent with AHEM within 9 days of the first dose of the ChAdOx1 nCoV-19 vaccine during 7 weeks between May and June 2021 [14]. In this context, however, given the high numbers of people already vaccinated against COVID-19, a fortuitous link between the inoculation event and a neurological disorder occurring by chance in the post-vaccination window is also probable [14]. The short period from inoculation to the onset of neurological symptoms is common for vaccine-associated ADEM/AHEM, which may occur between 1 and 30 days after inoculation with non-neurotropic vaccines [14,15].

3.4. Differntial diagnosis

AHLE is considered a monophasic condition with other possible differential diagnosis include tumifactive multiple sclerosis [13]. Although there is no absolute criteria, it is important to differentiate ADEM from MS as multiple sclerosis lesions are periventricular in location, solitary, perpendicular to the corpus callosum, shows open ring post contrast enhancement, and 'black hole appearance' on T1 sequences gray [13]. Other differential diagnosis to consider are MOG antibody-associated disease, neuromyelitis optica spectrum disorder, Progressive multifocal leukoencephalopathy–John Cunningham virus, and sarcoidosis [15]. Acute necrotizing encephalopathy (ANE) might be another differential diagnosis in this case. It is a new disease entity proposed by Mizuguchi et al. in 1997 and is characterized by symmetrical, multifocal lesions, usually associated with edematous necrosis and hemorrhage, without inflammatory cells. ANE always affects the thalami and, thus, causes a rapid disturbance of consciousness [15]. The etiology remains unknown, but a triggering viral infection is expected. Point mutations in the RAN binding protein 2 and ephrin type-B receptor 2 as a novel autoantigen are reported to be involved in disease mechanisms [15].

The clinical differentiation between AHLE and ANE is a challenge because both diseases present similar findings on MRI and CSF [15]. In this regard, the diagnostic criteria of ANE, proposed by Neilson et al. in 2010, might help to discern the appropriate diagnosis. The crucial difference between ANE and AHLE is the invasion of inflammatory cells. In ANE, the pathologic hallmark is the absence of inflammatory cells, while in AHLE, neutrophilic infiltrates are detected almost regularly. [16]

3.5. Manegement and treaments

To date, there have been no randomized controlled trials and treatment of ADEM is not standardized. High-dose steroids are the first line of treatment, followed by intravenous Ig (IVIG) and plasmapheresis in non-responders [12]. High-dose steroids consist of intravenous methylprednisolone administered at 30 mg/kg/d (maximum 1 g/day for 5 days), followed by an oral taper for 4–6 weeks that has shown to be effective in 60%–80% of the cases [12].

In a study, eight patients received combination therapy with IV methylprednisolone as well as IVIg. There was no mortality in any of these patients, and all of them showed partial recovery. Four patients received only IVIg, while the other four patients received only IV methylprednisolone and two patients received convalescent plasma [13]. Acyclovir was given in two, remdesivir in one, hydroxychloroquine in two, and antibiotics in four patients. The treatment

details of one patient were unavailable [13].

3.6. Surgical approach and decompressive hemicraniectomy

Surgical decompression for elevated ICP is a well-established neurosurgical intervention in other conditions like malignant transformation in acute/subacute infarction, infection, and trauma. In severe ADEM, such intervention was only reported as a successful therapy in very few cases worldwide, and so the long-term outcome and quality of life of these patients remain a concern, especially if this intervention was performed in the dominant hemisphere of the brain [14]. This report emphasizes that aggressive intervention such as decompressive hemicraniectomy should be highly considered as lifesaving measure in patients with severe ADEM/AHLE who deteriorate despite standard immunosuppressive and osmotic therapy [16].

4. Conclusion and limitations

Acute hemorrhagic leukoencephalitis pathogenesis to date remains a dilemma in understanding its pathogenesis and progression in certain patients with tailoring the optimal management plan. Most reported cases of AHLE progress to refractory cerebral edema and death in 2–4 days, leaving neurologists and critical care physicians handcuffed and helpless.

Perhaps a limitation in our case and other reported cases is the lack of instigating continuous ICP measurement (via EVD or intraparenchymal sensors) to monitor Lundberg intracranial pressure waves which can guide the possibility of lifesaving decompressive hemicortectomy as a pivotal approach in manegement.

Ethics approval and consent to participate

This case report was approved by the Hamad Medical Corporation's Medical Research Center.

Consent for publication

Written informed consent was obtained from the patient's family for publication of this case report, any accompanying images and photography. A copy of the written consent is available for review from the Editor of this journal.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

CRediT authorship contribution statement

Abeer Sabry Safan: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Zeba Noorain:** Writing – original draft. **Mohamed A. Atta:** Writing – original draft. **Razna Thekkoth:** Writing – original draft. **Aasir M. Suliman:** Conceptualization. **Abdalrazig Fadlelmula:** Conceptualization. **Mohammed Abdelatey:** Supervision.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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