



Case Report

Fatal Influenza A-Associated Acute Hemorrhagic Leukoencephalitis with Features Overlapping Acute Necrotizing Encephalopathy in a Young Woman: A Case Report

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Abstract

Acute hemorrhagic leukoencephalitis (AHLE) is a rare, hyperacute inflammatory disorder of the central nervous system that is usually diagnosed on clinical and radiological grounds when tissue is unavailable. We report a previously healthy, unvaccinated 19-year-old woman with a 5-day febrile respiratory illness and a nasopharyngeal real-time reverse transcription polymerase chain reaction test positive for influenza A. Within approximately 12 h of admission, she progressed from full consciousness to coma with signs of brainstem dysfunction and developed shock requiring vasopressors. Brain magnetic resonance imaging showed bilateral confluent white-matter lesions with vasogenic edema, symmetric thalamic restricted diffusion, midbrain and pontine involvement, and petechial hemorrhages within the pons on susceptibility-weighted imaging. Cerebrospinal fluid showed elevated protein and mild lymphocytic pleocytosis. Despite intravenous methylprednisolone, intravenous immunoglobulin, oseltamivir, and intensive care, she died approximately 36 h after admission. The diagnosis of AHLE was clinicoradiological because neuropathological examination was not performed, and the symmetric thalamic and brainstem involvement overlapped with influenza-associated acute necrotizing encephalopathy (ANE). This case illustrates the fulminant course that influenza A-associated hemorrhagic encephalopathy can take in young adults, the value of early multisequence imaging, and the difficulty of distinguishing AHLE from ANE without neuropathological confirmation.

Keywords: acute hemorrhagic leukoencephalitis; Weston Hurst disease; influenza A; acute necrotizing encephalopathy; magnetic resonance imaging; susceptibility-weighted imaging; case report

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1. Introduction

Acute hemorrhagic leukoencephalitis (AHLE), first described by Weston Hurst in 1941, is a rare and rapidly progressive inflammatory disorder of the central nervous

system [1,2]. It is generally regarded as a hyperacute variant of acute disseminated encephalomyelitis (ADEM) [2,3], although this classification has been questioned [4]. Unlike ADEM, AHLE affects mainly adults; in a systematic review of 43 adult cases published since 2000, 67% of patients were men and overall mortality was 46.5%, lower than the figure of up to 70% cited in earlier case-based reports [2].

Histopathologically, AHLE is characterized by perivascular infiltration with neutrophils and macrophages, necrosis of small vessels, perivascular fibrin exudation, and ring-and-ball hemorrhages, whereas demyelination may be absent in patients who die within 1–2 days of onset [2]. Because no validated diagnostic criteria exist, the diagnosis rests on neuropathology or, when tissue is unavailable, on a fulminant clinical course combined with characteristic magnetic resonance imaging (MRI) findings: confluent white-matter lesions with edema, microhemorrhages, variable diffusion restriction, and variable enhancement, with brainstem and deep gray-matter involvement reported less often [2,3].

AHLE usually follows an infection, and a postinfectious immune-mediated mechanism is presumed; molecular mimicry and dysregulated innate immunity have been proposed, but the pathogenesis remains uncertain [2,4]. Influenza A has been reported only rarely in association with AHLE, mostly with the A(H1N1) subtype [5–8], and isolated cases have followed influenza vaccination [9,10]. Influenza is also among the infections most commonly associated with acute necrotizing encephalopathy (ANE), a parainfectious encephalopathy defined by symmetric thalamic lesions, which was first described in children [11] and also occurs in adults, although adult influenza-associated cases remain uncommon [12,13]. The clinical and radiological features of ANE and AHLE can overlap [14,15].

Here, we report a fatal, hyperacute encephalopathy associated with influenza A in a previously healthy, unvaccinated 19-year-old woman. The case is informative for three reasons. First, the course was exceptionally rapid, with death approximately 36 h after admission. Second, MRI combined confluent white-matter lesions with vasogenic edema, typical of AHLE, with symmetric thalamic restricted diffusion and hemorrhagic brainstem involvement, which are also features of ANE, illustrating how difficult these entities are to separate without neuropathology. Third, among the adults with influenza-associated AHLE summarized in Table 1, the only previously reported fatal case after natural infection occurred in a man [7], and our patient is the youngest of the tabulated patients.

2. Case Presentation

2.1. History and Examination

A previously healthy 19-year-old Saudi woman who had not received influenza vaccination presented to our hospital in December 2025, during an influenza season dominated by influenza A(H3N2) in Saudi Arabia [16], with a 5-day history of fever, cough, sore throat, rhinorrhea, and myalgia. She had been in contact with a sibling who had a respiratory illness. She had no chronic illness and no previous episode of encephalopathy. On admission, she was alert, with a Glasgow Coma Scale (GCS) score of 15. Her heart rate, blood pressure, respiratory rate, and oxygen saturation while breathing room air were within normal limits. The general and systemic examination, including the chest, heart, abdomen, and skin, was unremarkable, with no rash or petechiae, no neck stiffness, and no focal neurological signs.

2.2. Clinical Course

Shortly after admission, she developed confusion, severe hypotension, and respiratory failure, requiring vasopressor support, endotracheal intubation, mechanical ventilation, and transfer to the intensive care unit within the first 12 h after admission. Her GCS score fell to 9 at approximately 6 h after admission, before intubation (Figure 1A), and she

was intubated after this assessment. By approximately 12 h, she had developed decerebrate posturing and bilateral fixed and dilated pupils with absent light reflexes and absent plantar responses, and all motor responses were then lost (GCS 3T: eyes 1, verbal response not testable after intubation, motor 1), indicating severe brainstem dysfunction; the exact times of the individual signs are not available. The timing of key events, laboratory values, and treatments is shown in Figure 1.

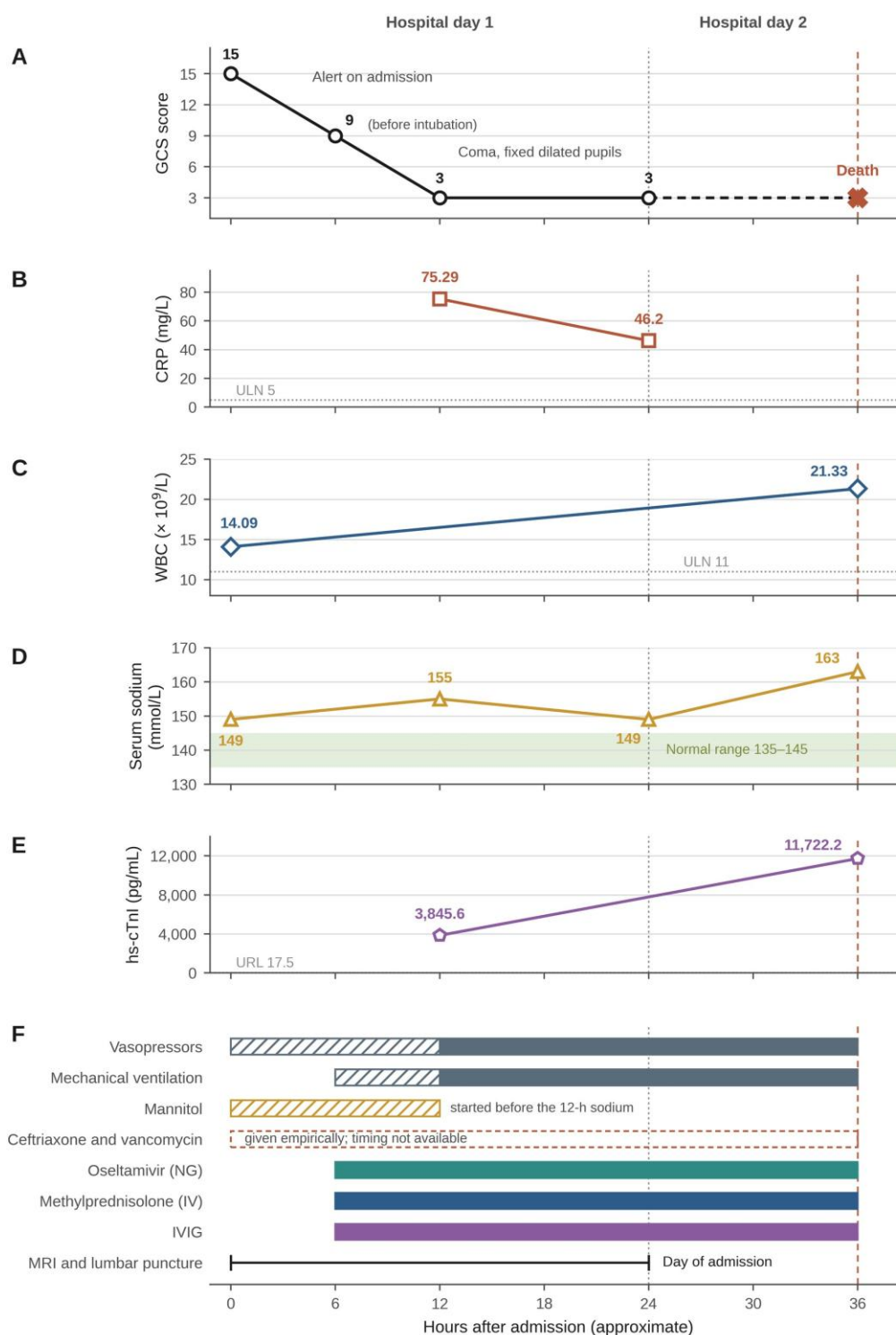


Figure 1. Clinical timeline over the approximately 36 h hospital course (hour 0, admission; hospital days are shown as consecutive 24 h periods from admission; death at approximately 36 h, on

hospital day 2). (A) Glasgow Coma Scale (GCS) score, declining from 15 on admission to 9 at approximately 6 h (before intubation) and 3 by approximately 12 h (after intubation, with the verbal response not testable); the dashed segment joins the last recorded score to the time of death. (B) C-reactive protein (CRP), 75.29 and 46.2 mg/L. (C) White blood cell (WBC) count, rising from 14.09 to $21.33 \times 10^9/\text{L}$. (D) Serum sodium, 149, 155, 149, and 163 mmol/L; the shaded band shows the normal range (135–145 mmol/L). (E) High-sensitivity cardiac troponin I (hs-cTnI), rising from 3845.6 to 11,722.2 pg/mL. (F) Treatments and investigations. Hatched segments show the interval within which a treatment was started when its exact start time is not available: vasopressors within the first 12 h, mechanical ventilation after the GCS assessment at approximately 6 h and before approximately 12 h, and mannitol before the sodium measurement at approximately 12 h (dose and duration not available). Ceftriaxone and vancomycin were given empirically; their timing is not available (outlined bar). Methylprednisolone and intravenous immunoglobulin (IVIG), both given intravenously (IV), and oseltamivir, given by nasogastric (NG) tube, were started at approximately 6 h. Brain magnetic resonance imaging (MRI) and lumbar puncture were performed on the day of admission (bracket spanning hospital day 1); their exact times and order are not available. In all panels, the dotted vertical line marks the start of hospital day 2, the dashed red vertical line marks death, and dotted horizontal lines mark the upper limit of normal (ULN) or the upper reference limit (URL); in panel E, the URL line lies close to the horizontal axis.

2.3. Neuroimaging

Brain MRI was performed on the day of admission (Figure 2). Diffusion-weighted imaging (DWI) showed bilateral symmetric hyperintensity in the thalami, with a corresponding low signal on the apparent diffusion coefficient (ADC) map, indicating restricted diffusion (Figure 2A,B), and fluid-attenuated inversion recovery (FLAIR) images showed bilateral thalamic swelling and hyperintensity, without clear involvement of the basal ganglia, together with periventricular white-matter hyperintensity (Figure 2C). The midbrain was swollen and hyperintense on FLAIR (Figure 2D). DWI showed hyperintensity involving most of the cross-section of the pons, including its central portion (Figure 2E); an ADC map was not available at this level. Susceptibility-weighted imaging (SWI) showed multiple punctate foci of signal loss within the pons, consistent with petechial hemorrhages (Figure 2F). At the level of the centrum semiovale, multifocal white-matter lesions were hyperintense on DWI (Figure 2G), showed increased diffusivity on the ADC map (Figure 2H), and formed bilateral confluent FLAIR-hyperintense areas with edema in the deep white matter, more extensive on the left (Figure 2I). The thalamic lesions therefore showed cytotoxic edema, whereas the hemispheric white-matter lesions showed predominantly vasogenic edema, with the DWI hyperintensity at that level most consistent with T2 shine-through; both patterns are described in AHLE and in ANE [3,12]. Venous imaging was not performed because of the rapid clinical course, and post-contrast images were not available.

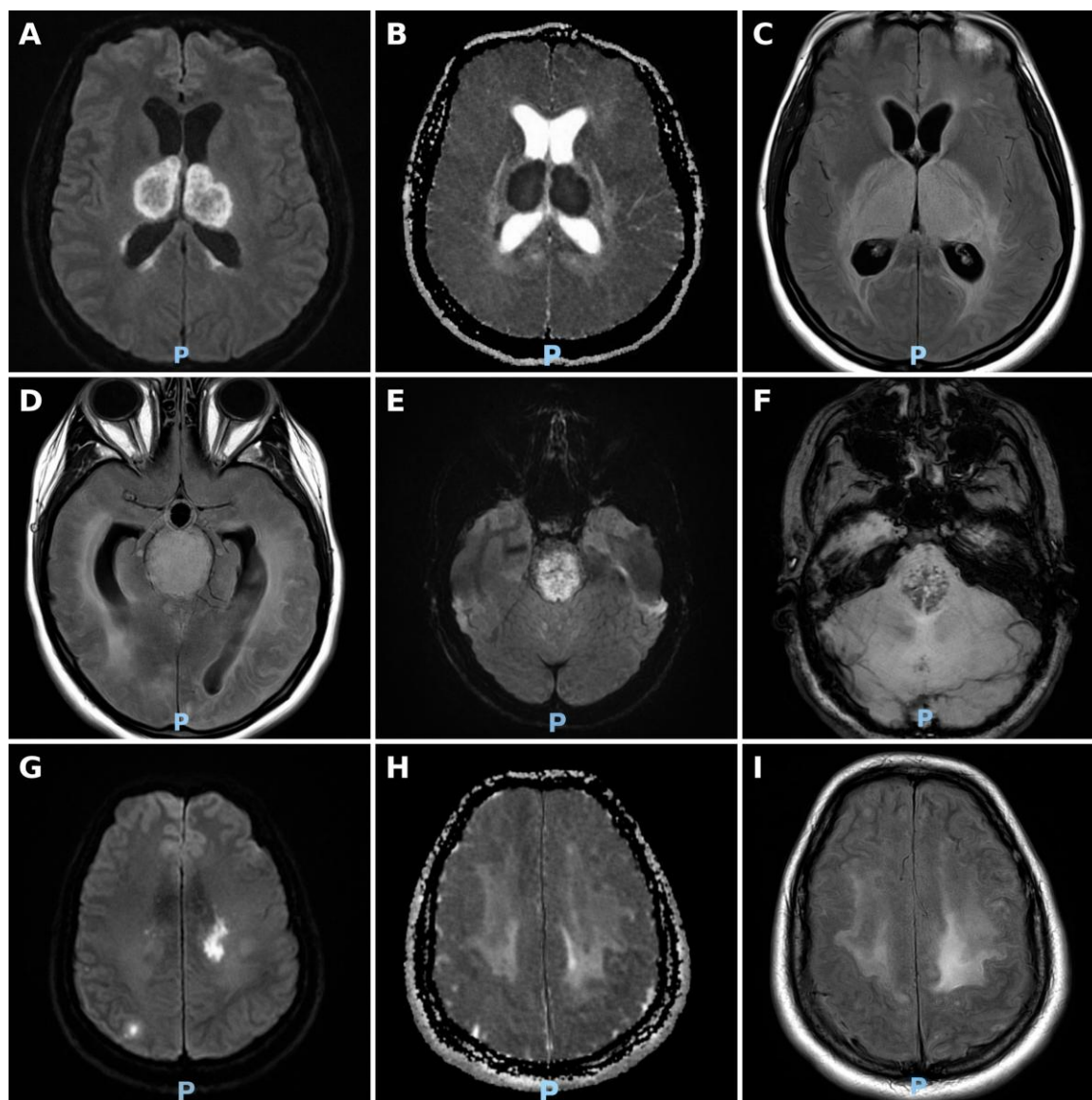


Figure 2. Brain magnetic resonance imaging obtained on the day of admission. Top row, level of the thalami: (A) axial diffusion-weighted imaging (DWI) shows bilateral symmetric thalamic hyperintensity; (B) the corresponding apparent diffusion coefficient (ADC) map shows low signal in the thalami, confirming restricted diffusion (cytotoxic edema); (C) axial fluid-attenuated inversion recovery (FLAIR) image shows bilateral thalamic swelling and hyperintensity with periventricular white-matter hyperintensity. Middle row, brainstem: (D) axial FLAIR image at the level of the mid-brain shows swelling and hyperintensity of the midbrain; (E) axial DWI at the level of the pons shows hyperintensity involving most of the pontine cross-section; (F) axial susceptibility-weighted image at the level of the pons shows multiple punctate foci of signal loss within the pons, consistent with petechial hemorrhages. Bottom row, level of the centrum semiovale: (G) axial DWI shows multifocal hyperintense white-matter lesions, most prominent on the left; (H) the ADC map shows increased diffusivity within the lesions, consistent with predominantly vasogenic edema; (I) axial FLAIR image shows bilateral confluent white-matter hyperintensities with edema, more extensive on the left. Images are displayed in radiological convention (the patient's left is on the image right); P, posterior.

2.4. Laboratory and Microbiological Investigations

The white blood cell count increased from 14.09 to $21.33 \times 10^9/L$, C-reactive protein decreased from 75.29 to 46.2 mg/L, and procalcitonin was 35.7 ng/mL. Serum sodium was 149 mmol/L on admission, 155 mmol/L at approximately 12 h, 149 mmol/L at

approximately 24 h, and 163 mmol/L at approximately 36 h (Figure 1D). High-sensitivity cardiac troponin I (hs-cTnI) increased from 3845.6 to 11,722.2 pg/mL (upper reference limit, 17.5 pg/mL). Aspartate aminotransferase (AST) was 389 U/L, alanine aminotransferase (ALT) was 183 U/L, and the platelet count decreased from 164 to 123×10^9 /L. Serum ammonia, lactate dehydrogenase, a peripheral blood smear, and urine osmolality were not available. Electrocardiography and echocardiography performed during the admission were reported as normal; their timing relative to the onset of shock, the start of vasopressors, and the two hs-cTnI measurements are not available.

A nasopharyngeal swab was tested with the Xpert Xpress Flu/RSV assay on the GeneXpert platform (Cepheid, Sunnyvale, CA, USA), a qualitative real-time reverse transcription polymerase chain reaction (RT-PCR) assay for influenza A, influenza B, and respiratory syncytial virus, and was positive for influenza A. The assay does not subtype influenza A, subtype-specific testing was not performed, and the residual specimen was not retained. Cerebrospinal fluid (CSF) obtained by lumbar puncture on the day of admission showed elevated protein (0.85 g/L), 15 white cells/ μ L (predominantly lymphocytes), and normal glucose; a red cell count was not reported, and the order of the lumbar puncture and the MRI on that day is not available. CSF polymerase chain reaction (PCR) testing for herpes simplex virus types 1 and 2 (HSV-1, HSV-2) and varicella-zoster virus (VZV) was negative. Serum antibodies against the N-methyl-D-aspartate receptor, leucine-rich glioma-inactivated 1, and contactin-associated protein-like 2 were negative. Blood cultures and other microbiological investigations were negative. Because of the rapid course, CSF testing for influenza RNA, myelin oligodendrocyte glycoprotein (MOG) and aquaporin-4 antibodies, complement studies (C3, C4, total hemolytic complement, factor H, and factor I), cytokine measurements, and genetic testing were not performed.

2.5. Treatment and Outcome

Intravenous methylprednisolone (1 g/day) and intravenous immunoglobulin (IVIG; 0.4 g/kg/day) were started approximately 6 h after admission, together with oseltamivir 75 mg twice daily via nasogastric tube. Empirical antimicrobial therapy with ceftriaxone and vancomycin was given pending culture results. Cerebral edema was treated with mannitol, which was started before the sodium measurement at approximately 12 h; its dose and exact start time are not available. Plasma exchange and decompressive craniectomy were not undertaken, because neither was available at our hospital at the time. Despite these measures, her neurological and hemodynamic status continued to deteriorate, and she died approximately 36 h after admission, on hospital day 2. A postmortem examination was not performed, because autopsy is not routine practice at our institution.

3. Discussion

3.1. Diagnostic Certainty and the Association with Influenza A

We describe a hyperacute, fatal encephalopathy that developed during a febrile respiratory illness associated with influenza A in a previously healthy young woman. The association is supported by the positive nasopharyngeal RT-PCR result and by the onset of neurological deterioration after 5 days of fever and respiratory symptoms, but a causal relationship cannot be established, because influenza RNA was not sought in CSF and neuropathology was not available. A negative CSF result would not have excluded the association, because influenza RNA was detected in CSF in only five of 32 adults with influenza-associated encephalopathy in one review [17], and viral PCR in CSF is typically negative in infection-triggered encephalopathy syndromes [12].

The diagnosis of AHLE relies mainly on neuroimaging, CSF analysis, and histopathology, and histopathological examination was performed in only 58% of the adult

cases in the systematic review by Grzonka et al. [2]. In our patient the diagnosis was clinico-radiological, so hemorrhagic necrosis and vasculitis are inferred from imaging rather than verified in tissue. The absence of neuropathological confirmation is the principal limitation of this report, and early multisequence MRI, including DWI and SWI, was the only means of characterizing the lesions.

3.2. Comparison with Previously Reported Cases

Table 1 summarizes previously reported adults with AHLE associated with laboratory-confirmed influenza infection or influenza vaccination. It is a narrative, non-systematic summary based on the systematic review by Grzonka et al. [2] and a supplementary search; the sources, search terms, inclusion criteria, and evidence standard are given in the table footnote. Cases after natural infection and after vaccination are shown separately because they represent immunologically distinct settings. Reports described by their authors as hemorrhagic encephalitis rather than AHLE were not tabulated [18,19]. The case of Mora-Aznar is nevertheless discussed in Section 3.3, because it also involved the thalamus and brainstem. A case of hemorrhagic longitudinally extensive transverse myelitis after influenza vaccination with a normal brain MRI was also excluded [20], as was a vaccine-associated case with hemorrhagic pontine lesions and a favorable outcome after plasma exchange and corticosteroids, because the patient's age is not stated in the published abstract, the full text could not be obtained, and adult status could therefore not be verified [10].

All four previously reported infection-associated cases in Table 1 involved influenza A(H1N1) [5–8], although hemorrhagic encephalitis associated with influenza A(H3N2) has also been described in an adult [19]. Our patient's virus was not subtyped; she presented during a season dominated by influenza A(H3N2) [16], but her subtype cannot be inferred from surveillance data. Two of the four patients were men and two were women, aged 27 to 56 years, and one, a 27-year-old man with autopsy-confirmed AHLE, died [7]. The single tabulated vaccine-associated case was fatal [9]. Including the present case, three of the six tabulated patients (50%) died, and no sex predominance was evident (three men and three women), in contrast to the male predominance in the broader adult AHLE literature [2]. These numbers are too small to estimate mortality or risk factors reliably. Vaccine-associated AHLE is known only from isolated reports, and its inclusion in Table 1 should not be read as evidence against influenza vaccination; our patient was unvaccinated.

Table 1. Previously reported adults with AHLE associated with laboratory-confirmed influenza infection or influenza vaccination and the present case.

Reference	Age/Sex	Associated Exposure	CSF Findings	Key Imaging Findings	Treatment	Outcome
<i>A. Natural influenza infection</i>						
Fugate et al., 2010 [5]	40/M	Influenza A(H1N1); severe infection with prolonged hypoxia and critical illness	Protein 2.4 g/L; RBC 157/ μ L ^a	Multifocal T2-hyperintense lesions with edema and hemorrhages; restricted diffusion in the basal ganglia attributed to hypoxic injury	Plasma exchange; high-dose corticosteroids ^b	Survived, severely disabled

Cisse et al., 2011 [6] ^a	56/F	Influenza A(H1N1)	Protein 0.51 g/L; WBC 8/ μ L (mono-nuclear); RBC 90/ μ L	Bilateral cerebral hemispheres; right striatum	Methyl-prednisolone 500 mg/day	Survived, mild action tremor
Jeganathan et al., 2013 [7]	27/M	Influenza A(H1N1) pneumonia with ARDS	NR ^a	Imaging not performed ^a ; brain edema with herniation and AHLE at autopsy	NR ^a	Died (brain death)
Srinath et al., 2025 [8]	50/F	Influenza A(H1N1)	WBC 18/ μ L (93% lymphocytes); elevated protein ^c	Cortical and sub-cortical white-matter lesions (bilateral fronto-parieto-temporal, left centrum semi-ovale, left occipital) with blooming on GRE	IV methyl-prednisolone 1 g/day for 5 days; oseltamivir	Survived, mild residual weakness
Present case	19/F	Influenza A (subtype not determined)	Protein 0.85 g/L; WBC 15/ μ L (lymphocytic)	Bilateral confluent white-matter lesions with vasogenic edema; symmetric thalamic restricted diffusion; midbrain and pontine involvement; pontine petechial hemorrhages on SWI	IV methyl-prednisolone 1 g/day; IVIG 0.4 g/kg/day; oseltamivir via NG tube	Died (about 36 h after admission)
B. Influenza vaccination						
Sinzo-bahamvya et al., 2018 [9] ^a	70/M	Seasonal influenza re-vaccination 3 days before onset	WBC 199/ μ L (mainly polymorpho-nuclear); protein 1.74 g/L	Bilateral hemispheres; corpus callosum; posterior brainstem	Methyl-prednisolone 1 g/day; plasma exchange	Died

Table 1 is a narrative, non-systematic summary. Sources: systematic review by Grzonka et al. [2] (adult cases published after 1 January 2000; all five influenza-related cases in that review were assessed [5–7,9,20], and one was excluded [20]); a PubMed search (to September 2026) combining “acute hemorrhagic leukoencephalitis”, “acute hemorrhagic leukoencephalopathy”, “Weston Hurst”, or “hemorrhagic encephalitis” with “influenza”, “H1N1”, “H3N2”, or “influenza vaccine”; and a general web search and the reference lists of retrieved reports. Inclusion criteria: age $\geq$ 18 years; AHLE diagnosed by the reporting authors on clinicoradiological or histopathological grounds; brain involvement; and a temporal association with laboratory-confirmed influenza infection or influenza vaccination. Evidence standard: every inclusion criterion had to be verifiable from the full text, the published abstract, or the case tabulation of Grzonka et al. [2]; data not available from these sources are shown as NR. The criteria and evidence standard were defined after the initial literature search and then applied to all identified reports. Exclusions: pediatric cases; conference abstracts; reports in which AHLE was not diagnosed [18,19]; isolated spinal cord involvement with a normal brain MRI [20]; cases with a documented concurrent infection by another virus, such as SARS-CoV-2 co-infection [21]; and reports whose eligibility could not be verified under this standard: a vaccine-associated case whose age is not stated in the published abstract and whose full text could not be obtained [10] and an indexed correspondence item without an abstract, not included in the review of Grzonka et al., whose full text could not be obtained [22]. ^a Data as tabulated by Grzonka et al.

[2]; a marker after the reference indicates that the whole row is taken from that source; units were not stated in that source, and conventional units are assumed. ^b Treatment as stated in the original report [5]. ^c A CSF multiplex panel reported low-level detection of a bacterial target; the authors attributed the illness to influenza A(H1N1)-associated AHLE [8]. Abbreviations: AHLE, acute hemorrhagic leukoencephalitis; ARDS, acute respiratory distress syndrome; CSF, cerebrospinal fluid; F, female; GRE, gradient-recalled echo; IV, intravenous; IVIG, intravenous immunoglobulin; M, male; MRI, magnetic resonance imaging; NG, nasogastric; NR, not reported; RBC, red blood cells; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SWI, susceptibility-weighted imaging; WBC, white blood cells.

3.3. Differential Diagnosis: AHLE Versus ANE and Other Mimics

The main alternative diagnosis is influenza-associated ANE. In a review of 22 adults with influenza-associated ANE, thalamic lesions were present in 91%, CSF pleocytosis in 29% of those with CSF analysis, and mortality was 32% [13]. The original diagnostic criteria of Mizuguchi comprise (1) acute encephalopathy after a viral febrile illness, with rapid deterioration of consciousness and convulsions; (2) increased CSF protein without pleocytosis; (3) symmetric, multifocal brain lesions involving both thalami; (4) elevated serum aminotransferases without hyperammonemia; and (5) exclusion of resembling diseases, which include AHLE [23]. Our patient met criterion 1, although no seizures were reported, and criterion 3. Criterion 2 was only partly met, because the CSF showed mild pleocytosis (15 cells/ μ L) rather than none, and criterion 4 could be assessed only in part, because the aminotransferases were elevated but serum ammonia was not available. Criterion 5 could not be satisfied, because excluding AHLE requires neuropathology. The recent international consensus definition likewise requires a febrile illness, decreased or altered consciousness lasting more than 24 h, and symmetric thalamic lesions, with exclusion of mimics that include ADEM with deep gray-matter involvement and AHLE [12]. Table 2 compares our patient with these criteria and with the typical features of AHLE.

Features favoring ANE were the symmetric thalamic restricted diffusion; the brainstem involvement, because the brainstem tegmentum is a common extrathalamic site in ANE [12], although the pontine lesion in our patient involved most of the pontine cross-section rather than only the tegmentum; and the elevated aminotransferases, shock, and falling platelet count, which are recognized systemic features of ANE [12,13]. The CSF findings did not discriminate reliably between the two entities: elevated protein without pleocytosis is typical of ANE, although pleocytosis occurs in 29% of adult influenza-associated cases [12,13], and pleocytosis, mononuclear-predominant in half of cases, is common in AHLE (65% of cases with CSF analysis) [2]. Among the comparable influenza-associated cases, erythrocytes were reported in the CSF of the patients of Fugate et al. and Cisse et al. [2,5,6], whereas a CSF red cell count was not available for our patient, so this comparison cannot be made. Even if erythrocytes had been absent, this would not exclude parenchymal petechial hemorrhage, because CSF erythrocytes are reported in only 39% of adults with AHLE who have CSF analysis [2]. The presence of hemorrhage does not discriminate either, because hemorrhage within lesions also occurs in ANE [12,13], and in our patient the hemorrhages documented on SWI lay within the pontine lesion. Some of them could also have been secondary (Duret) hemorrhages, which complicate rapid transtentorial herniation and are typically midline and paramedian in the pons [24]; because the pupils became fixed and dilated as she progressed to coma and the timing of the MRI relative to this change is uncertain, this possibility cannot be excluded. The main feature favoring AHLE was the lesion pattern in the cerebral hemispheres: extensive, confluent, and asymmetric (left-predominant) white-matter lesions with vasogenic edema, which extended beyond the symmetric periventricular distribution typical of ANE (Figure 2G–I) [3,12]. This asymmetry is relative rather than absolute, and the white-matter

involvement includes a bilateral periventricular component compatible with ANE (Figure 2C); the hemispheric pattern therefore favors, but does not establish, AHLE.

Deep gray-matter involvement does not exclude AHLE. Although one review states that symmetric thalamic involvement is not seen in AHLE [3], thalamic or basal ganglia lesions were present in eight of the 43 adult cases reviewed by Grzonka et al., including one with lesions in both thalami and the influenza A(H1N1)-associated case of Cisse et al., which involved the right striatum [2,6]. Bilateral thalamic involvement was also documented in a recent biopsy-supported adult case [4], and unilateral (left) thalamic and basal ganglia involvement were documented in a child with complement factor I deficiency [25]. Mora-Aznar described an adult with influenza A(H1N1)-associated hemorrhagic encephalitis involving the basal ganglia, thalamus, and brainstem [18], and a recent series of adults with ANE, AHLE, and ADEM associated with coronavirus disease 2019 highlighted the overlap among these syndromes [15]; imaging overlap among postinfectious inflammatory encephalopathies has long been recognized [14]. The CSF profile of our patient, mild lymphocytic pleocytosis with elevated protein, was also similar to that of a recently reported adult with influenza A(H1N1)-associated AHLE [8].

On balance, we retain AHLE as the working diagnosis, mainly because of the hemispheric white-matter lesion pattern, but we recognize that the case lies in the overlap between AHLE and ANE. It meets the clinical and radiological core of the ANE definition, whereas both the exclusion of AHLE required by that definition and the confirmation of AHLE itself depend on neuropathology, which was not available. The combination of shock, encephalopathy, and raised aminotransferases also overlaps with acute shock with encephalopathy and multiorgan failure, although that syndrome is characterized by diffuse cerebral edema rather than multifocal lesions, and the consensus definition gives precedence to ANE when both sets of criteria are met [12]. AHLE and ANE are thought to share a parainfectious onset, a hyperinflammatory state, and blood–brain barrier breakdown, and both are treated empirically with early high-dose corticosteroids, with or without IVIG or plasma exchange [2,12,13]; anti-interleukin-6 therapy has also been proposed for ANE [12,13]. Genetic testing for RAN binding protein 2 (RANBP2) variants, which confer susceptibility to familial and recurrent ANE [26], was not performed because of the rapid course, and no stored DNA is available. Our patient had no previous episode of encephalopathy, which argues against recurrent ANE, but familial ANE cannot be excluded without genetic testing, and because familial ANE with a RANBP2 variant has recently been reported from Saudi Arabia [27], genetic counseling could be offered to her family.

Other diagnoses were considered. Classic ADEM was considered unlikely because of the hyperacute course and hemorrhagic lesions and because neurological deterioration began during the febrile illness, whereas ADEM usually follows a less fulminant course [2] and develops a mean of about 12.5 days after the infection [13]. HSV-1, HSV-2, and VZV encephalitis were made unlikely by negative CSF PCR, and the tested autoimmune encephalitis antibodies were negative, although the panel was limited. MOG antibody-associated disease (MOGAD) can present with ADEM-like features, but its diagnosis requires the detection of MOG antibodies [28]; because MOG antibodies could not be tested within the short course, MOGAD cannot be excluded, although death within 36 h with shock would be unusual. The markedly elevated procalcitonin (35.7 ng/mL) raised the possibility of bacterial sepsis. Toxic shock syndrome is among the conditions to be excluded under Mizuguchi's criteria [23], and the consensus definition requires the exclusion of infectious, autoimmune, and other inflammatory, including systemic causes [12]. Blood cultures and other microbiological investigations were negative, and empirical ceftriaxone and vancomycin were given, but bacterial co-infection cannot be excluded completely. Septic emboli were considered unlikely because blood cultures were negative, echocardiography was reported as normal, the thalamic lesions were symmetric, and the

white-matter lesions were confluent rather than scattered in arterial territories. Thrombotic microangiopathy was considered unlikely because the platelet count remained above $100 \times 10^9/L$, although a peripheral blood smear and lactate dehydrogenase were not available, and hypertensive encephalopathy was incompatible with persistent hypotension. Hypoxic–ischemic injury from shock and respiratory failure can cause bilateral deep gray-matter restricted diffusion, and it coexisted with AHLE in the influenza A(H1N1)-associated case of Fugate et al. [5]; because shock and respiratory failure developed within hours of admission and the MRI was obtained on the same day, a hypoxic–ischemic contribution to the thalamic lesions cannot be excluded. Deep cerebral venous thrombosis, which can also produce bilateral thalamic lesions [12], was not specifically excluded, because venous imaging could not be performed within the rapid course.

Table 2. Comparison of the present case with the diagnostic criteria for ANE and with the typical features of AHLE.

Feature	ANE [12,13,23]	AHLE [2,3]	Present Case
Onset	Febrile illness preceding or concurrent with neurological onset (essential)	Preceding infection or flu-like illness in more than half of cases; usually postinfectious	Neurological deterioration after 5 days of fever and respiratory symptoms with influenza A
Course	Decreased or altered consciousness lasting more than 24 h (essential), often with rapid (hours) onset, with or without seizures	Fulminant; frequently progresses to coma or death within days	Confusion shortly after admission; GCS 3 by about 12 h; death at about 36 h
Thalamic and deep gray matter	Symmetric thalamic lesions (essential)	Reported in a minority (thalamic or basal ganglia lesions in 8 of 43 adults)	Symmetric thalamic restricted diffusion (cytotoxic edema)
Other lesion sites	Symmetric lesions in the brainstem tegmentum, periventricular white matter, and cerebellar dentate nuclei	Confluent, often asymmetric hemispheric white-matter lesions with edema; brainstem or cerebellum less often	Midbrain swelling; pontine lesion involving most of the pontine cross-section; confluent, left-predominant white-matter lesions of the centrum semiovale with vasogenic edema
Hemorrhage	May occur within lesions (best seen on SWI)	Petechial hemorrhages characteristic	Petechial hemorrhages on SWI within the pontine lesion
CSF	Protein often raised; pleocytosis typically absent (present in 29% of adult influenza-associated cases with CSF analysis)	In cases with CSF analysis: protein raised in 87%; pleocytosis in 65% (mononuclear in half); RBC in 39%	Protein 0.85 g/L; WBC 15/ μ L (lymphocytic); RBC count not reported
Systemic features	Shock, raised aminotransferases and LDH, thrombocytopenia, coagulopathy; no hyperammonemia	Neutrophil-predominant blood leukocytosis	Shock; AST 389 U/L and ALT 183 U/L; platelets 164 to $123 \times 10^9/L$; WBC up to $21.33 \times 10^9/L$; ammonia not available

Exclusion or confirmation	Mimics, including AHLE, ADEM with deep gray-matter involvement, hypoxia, and venous infarction, must be excluded (essential)	No validated criteria; diagnosis relies on neuroimaging, CSF analysis, and histopathology	Neuropathology not available; AHLE and ANE cannot be separated with certainty; hypoxic contribution and bacterial co-infection not excluded
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The present case meets the essential clinical and radiological criteria for ANE (febrile onset, altered consciousness lasting more than 24 h, and symmetric thalamic lesions) but not the exclusion criterion; the hemispheric white-matter lesion pattern favors AHLE, whereas the CSF findings and the presence of hemorrhage do not discriminate reliably. Abbreviations: ADEM, acute disseminated encephalomyelitis; AHLE, acute hemorrhagic leukoencephalitis; ALT, alanine aminotransferase; ANE, acute necrotizing encephalopathy; AST, aspartate aminotransferase; CSF, cerebrospinal fluid; GCS, Glasgow Coma Scale; LDH, lactate dehydrogenase; RBC, red blood cells; SWI, susceptibility-weighted imaging; WBC, white blood cells.

3.4. Hypernatremia

Serum sodium was 149 mmol/L on admission, 155 mmol/L at approximately 12 h, 149 mmol/L at approximately 24 h, and 163 mmol/L shortly before death (Figure 1D). Its cause could not be established with certainty in this short course. The admission value, measured after 5 days of fever and before any osmotherapy, suggests a free-water deficit. After severe traumatic brain injury, hypernatremia commonly results from hyperosmolar therapy, limited free-water intake, or diabetes insipidus, and mannitol can cause free-water loss [29]. In our patient, mannitol was started before the sodium measurement at approximately 12 h, so mannitol-induced free-water loss may have contributed to the rise from 149 to 155 mmol/L; its dose and exact start time are not available. Urine output, the fluids given, and any use of desmopressin between approximately 12 and 24 h, when sodium returned to 149 mmol/L, are also not available, so that fall cannot be attributed to a specific intervention. The terminal rise to 163 mmol/L, which occurred after the pupils had become fixed and dilated, is compatible with central diabetes insipidus due to hypothalamic–pituitary failure, although this could not be confirmed by urine studies, and it is therefore better regarded as a consequence of the catastrophic brain injury than as a cause. Acute hypernatremia can itself depress consciousness and, rarely, cause osmotic demyelination, for which the central pons is the classic site, although extrapontine lesions, including thalamic lesions, also occur [30,31]. Because the pontine lesion in our patient involved the central pons, this possibility deserves consideration. We consider it unlikely, however, that hypernatremia caused or compounded the neurological deterioration, because coma developed within about 12 h, when the measured sodium was 149 to 155 mmol/L; coma with fixed dilated pupils persisted when sodium had returned to 149 mmol/L at about 24 h; osmotic demyelination typically becomes apparent as a second phase, 1 to 14 days after the precipitating event [31]; and the pontine lesion contained petechial hemorrhages and accompanied midbrain and hemispheric white-matter lesions. The MRI was obtained on the day of admission, when all measured sodium values were between 149 and 155 mmol/L; because sodium was measured intermittently and the exact time of the MRI is not available, higher transient values before the MRI cannot be excluded. The terminal hypernatremia may have added to systemic instability in the final hours, but we regard it as a marker of brainstem and hypothalamic failure rather than an independent cause of death; the fatal outcome is attributed mainly to the fulminant encephalopathy, with shock as a probable contributor.

3.5. Myocardial Injury

The marked rise in hs-cTnI indicates acute myocardial injury [32]. Electrocardiography and echocardiography were reported as normal, so there was no documented electrocardiographic or imaging evidence of myocardial ischemia, which is required for a diagnosis of myocardial infarction [32]. Because their timing relative to the onset of shock and to the hs-cTnI measurements is not available, however, these normal findings carry limited weight; in particular, they cannot exclude ischemia or ventricular dysfunction that developed after the studies were performed. Coronary imaging, cardiac MRI, and histopathology were not available, and the mechanism of the injury therefore cannot be determined. Several mechanisms, which are not mutually exclusive, are plausible: supply–demand imbalance due to shock and respiratory failure [32]; direct influenza myocarditis, one of the most frequently reported extrapulmonary complications of influenza [33]; catecholamine-mediated neurogenic myocardial injury secondary to catastrophic brain injury [34]; and systemic inflammation, including sepsis if bacterial co-infection was present. We therefore do not attribute the troponin rise to any single mechanism.

3.6. Complement Dysregulation as a Hypothesis

Complement dysregulation has recently been described in AHLE: complete complement factor I deficiency in a 9-year-old boy who recovered completely after plasma exchange and early decompressive craniectomy [25] and partial factor I deficiency in a young adult man with relapsing AHLE and longitudinally extensive transverse myelitis whose attacks were suppressed by interleukin-1 receptor blockade with anakinra [4]. Complement studies and genetic testing were not performed in our patient because of the rapid course, and no stored DNA is available, so no conclusion can be drawn about a role for complement in her illness. Whether complement testing should form part of the evaluation of unexplained fulminant AHLE and whether complement-directed or cytokine-directed treatments have a role remain hypotheses for future research.

3.7. Treatment Considerations

Oseltamivir was given by nasogastric tube. Enteral oseltamivir is well absorbed in critically ill, ventilated adults, including those receiving vasopressors [35]; however, plasma concentrations in that study were measured after the fourth or later dose, whereas our patient received at most three doses before death, so adequate exposure during the first hours of shock cannot be confirmed. A higher dose would not be expected to improve outcomes, because double-dose oseltamivir did not improve virological or clinical outcomes in a randomized trial of children and adults hospitalized with severe influenza [36]. Plasma exchange, used in 26% of the adults with reported treatment in the systematic review by Grzonka et al. [2] and in two of the tabulated cases (Table 1), and decompressive craniectomy were not undertaken, because neither was available at our hospital at the time. Whether either would have altered the outcome is uncertain, because the patient had GCS 3 with fixed dilated pupils by approximately 12 h. Earlier recognition and early transfer to a center able to provide plasma exchange and neurosurgical care may create a window for escalating treatment in future cases.

3.8. Limitations

This report has several limitations. Neuropathological confirmation was not obtained, influenza A was not subtyped, and CSF was not tested for influenza RNA. MOG and aquaporin-4 antibodies, complement, cytokines, and RANBP2 were not studied, cardiac evaluation was limited to electrocardiography and echocardiography of unknown timing, and several laboratory results, including serum ammonia, were not available. The exact times of the MRI, the lumbar puncture, and the individual neurological signs, the dose of

mannitol, urine output, fluid balance, and any use of desmopressin are not available, which limits the interpretation of the sodium trajectory. Because the order of the lumbar puncture and the MRI is unknown, we cannot state whether imaging preceded the procedure; given the cerebral edema and brainstem involvement documented on MRI, the lumbar puncture may have carried a risk of herniation. The available images did not include post-contrast sequences, and SWI was available only at the level of the pons. In addition, a hypoxic–ischemic contribution to the deep gray-matter lesions, secondary brainstem hemorrhage, and bacterial co-infection could not be excluded, and deep cerebral venous thrombosis and thrombotic microangiopathy were not fully evaluated. These gaps reflect the hyperacute course, which allowed only about 36 h for investigation, and no residual respiratory specimen or stored DNA was available for later testing. In future cases, retaining respiratory samples for subtyping, testing CSF for influenza RNA, and seeking consent for postmortem examination would strengthen the diagnosis.

4. Conclusions

This case describes a fatal, hyperacute encephalopathy associated with influenza A in a previously healthy, unvaccinated young woman. The hemispheric white-matter lesion pattern favored AHLE, whereas the thalamic, brainstem, and systemic features overlapped with ANE, and the distinction could not be confirmed without neuropathology. Shock probably contributed to the fatal outcome, whereas the terminal hypernatremia more likely reflected than caused the catastrophic brain injury. Clinicians should consider both AHLE and ANE in patients with abrupt neurological deterioration during influenza and obtain early multisequence MRI, including DWI and SWI. The roles of complement dysregulation and cytokine-directed therapy in these disorders remain hypotheses for future research.

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Institutional Review Board Statement: Ethical review and approval were waived for this study by the Ethics Committee of King Khalid University because it is a retrospective description of a single patient. The report was prepared in accordance with the Declaration of Helsinki.

Informed Consent Statement: The patient was comatose within approximately 12 h of admission and died approximately 36 h after admission without regaining the capacity to consent. Written informed consent for publication of this report, including clinical data and images, was therefore obtained from her father as her next of kin, in accordance with institutional policy and applicable regulations in Saudi Arabia. The report contains no identifiable personal information.

Data Availability Statement: All data relevant to this case report are included in the article. Further inquiries can be directed to the corresponding author.

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