

# Influenza A with hemorrhagic shock and encephalopathy syndrome in an adult

## A case report

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### Abstract

**Introduction:** Hemorrhagic shock and encephalopathy syndrome (HSES) is a type of acute encephalopathy mainly seen in infants. It is a syndrome encompassing an onset of high fever, disturbance of consciousness, convulsion, and shock that rapidly progresses to watery diarrhea and liver and renal dysfunctions. It is extremely rare in adults, and the number of reports is limited worldwide. We report the case of an adult patient with HSES, which occurred after influenza A infection.

**Patient concerns:** A 52-year-old man visited his family doctor 2 days after he noticed fever and was diagnosed with influenza A using an influenza rapid diagnosis kit; he underwent treatment on an outpatient basis. He was immediately hospitalized after developing fever, abdominal pain, malaise, and shock 16 hours after the commencement of the treatment. Abrupt acute brain swelling was noted 24 hours after hospitalization.

**Diagnoses:** The antibody titer to influenza A (H3N2) was 1:40. Computed tomography obtained 24 hours after treatment initiation confirmed acute cerebral edema and cerebral herniation. Electroencephalogram at that time showed a flat line.

**Interventions:** For the treatment of influenza A, laninamivir 150 mg was started immediately after the diagnosis by the family doctor, and 600 mg dose was given daily after hospitalization (or since 24 hours after the treatment initiation). For the management of shock, dobutamine 3 µg/kg/min and noradrenaline up to 0.2 µg/kg/min were used together with bolus infusion.

**Outcomes:** The patient was declared brain dead on his 6th hospital day and he died on his 27th hospital day.

**Conclusion:** Drastic courses such as that in our case with HSES can follow influenza infections even in adults.

**Abbreviations:** CT = computed tomography, DIC = disseminated intravascular coagulation, HSES = hemorrhagic shock and encephalopathy syndrome, JCS = Japan Coma Scale, LDH = lactate dehydrogenase, VAHS = virus-associated hemophagocytic syndrome.

**Keywords:** hemorrhagic shock and encephalopathy syndrome, influenza A, laninamivir

## 1. Introduction

Severe central nervous system dysfunction associated with influenza can lead to neurological sequelae and occasionally death. Influenza-associated encephalopathy is rapidly progressive and has an early onset in the course of influenza. Most cases in Japan occur in children younger than 5 years.<sup>[1]</sup> Onset of influenza-associated encephalopathy is associated with death,<sup>[2]</sup> but the syndrome is extremely rare in adults, and adult cases have

been barely reported worldwide.<sup>[3]</sup> Hemorrhagic shock and encephalopathy syndrome (HSES) proposed by Levin et al<sup>[4]</sup> is a type of acute encephalopathy with poor prognosis wherein healthy subjects develop sudden convulsion, disturbance of consciousness, and blood pressure drop following a fever, accompanied by metabolic acidosis, renal failure, and liver damage. Its early-stage mortality accounts for 35% to 82%.<sup>[5]</sup> Herein, we report on an adult case wherein the patient developed HSES following influenza A infection. Patient consent was obtained from family members for this study.

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## 2. Case presentation

### 2.1. Clinical course and diagnosis

A 52-year-old man presented with chief complaints of fever and disturbance of consciousness. His medical history included oral treatment with 20 mg olmesartan, 250 mg metformin, 20 mg duloxetine, 2 mg flunitrazepam, 200 mg valproate, 30 mg mianserin, and 0.4 mg alprazolam for hypertension, diabetes, anxiety neurosis, and adjustment disorder.

Fever over 39°C was confirmed 3 days before hospital admission. After an examination by the family doctor, the patient received oral treatment with 500 mg levofloxacin; consequently, fever dropped to approximately 36°C in 1 day after medication, but it relapsed to a temperature between 39°C and 40°C a day before hospital transfer. Then, the patient was

examined at the same hospital again. A rapid diagnostic kit showed nasal discharge tested positive for influenza antigen, and treatment with 150 mg laninamivir was initiated. Eight hours before admission to our hospital, the patient complained of fever, stomachache, and fatigue and was transferred to another hospital in an ambulance. Fever and disturbance of consciousness of 10 on the Japan Coma Scale (JCS) were confirmed, and convulsion gradually developed in the upper limbs. Accordingly, 500 mg acetaminophen intravenous drip was administered for fever. His blood pressure gradually dropped, and it did not increase despite of tracheal intubation and administrations of large-volume infusions (1500 mL lactated Ringer solution, 500 mL acetated Ringer solution, and 750 mL of 5% albumin transfusion administered over 8 hours) and of 5  $\mu$ g/kg/min dopamine. Thus, the patient was transferred to the Advanced Emergency Medical Service Center, Kurume University Hospital. His consciousness level during the transfer to our hospital was JCS 200 while using 70 mg/h propofol prescribed by the previous physician. With 8  $\mu$ g/kg/min dopamine, his blood pressure was 78/53 mm Hg, and his resting heart rate was 110 bpm with regular pulse. The bag valve mask ventilation respiratory rate was 16 breaths/min, and his body temperature was 36.7°C. Pupil sizes were 2 mm on both eyes (no difference) presenting normal pupillary light reflexes and mild nuchal rigidity was present. We found crackles in the right dorsal field by thoracic auscultation. In addition, peristaltic sounds were weak in the abdomen. We observed petechiae and purpura from suction caps of the electrocardiography performed by the previous physician in the thorax.

Patient consent was obtained from family members for this study as informed written consent was obtained from the family members for publication of this case report and accompanying images.

## 2.2. Laboratory tests

Blood test findings during admission are summarized in Table 1. Although blood cell counts showed hematocytopenia in 2 lineages, that is, white blood cell (2200/ $\mu$ L) and platelets (6.3/ $\mu$ L), anemia was absent. General biochemical tests showed elevated levels of aspartate aminotransferase (727 IU/L), alanine aminotransferase (338 IU/L), lactate dehydrogenase (LDH; 418 IU/L), and creatine kinase (557 IU/L). In addition, creatinine (2.02 mg/dL) and blood urea nitrogen (18 mg/dL) levels were elevated, indicating renal dysfunction. We found no evidence of hypoglycemia or hyperammonemia, but the C-reactive protein level was at 5.78 mg/dL, confirming an increased inflammatory reaction, and the interleukin-6 (IL-6) level was at 188,390 pg/mL (normal level <35 pg/mL). Based on the slightly long prothrombin time-international normalized ratio at 1.41 and increased fibrin/fibrinogen degradation level at 82.3  $\mu$ g/mL combined with the reduction in platelet counts, we diagnosed the patient as presenting disseminated intravascular coagulation (DIC). Similar to the results of his previous test performed by the previous physician, the influenza rapid diagnostic kit revealed positive results for influenza A antigen, and we eventually discovered that the influenza A (H3N2) antibody titer was at 1:40. Considering his age, head computed tomography (CT) presented mild frontal lobe atrophy. However, we found no abnormal findings that could account for the disturbance of consciousness.

## 2.3. Postadmission course

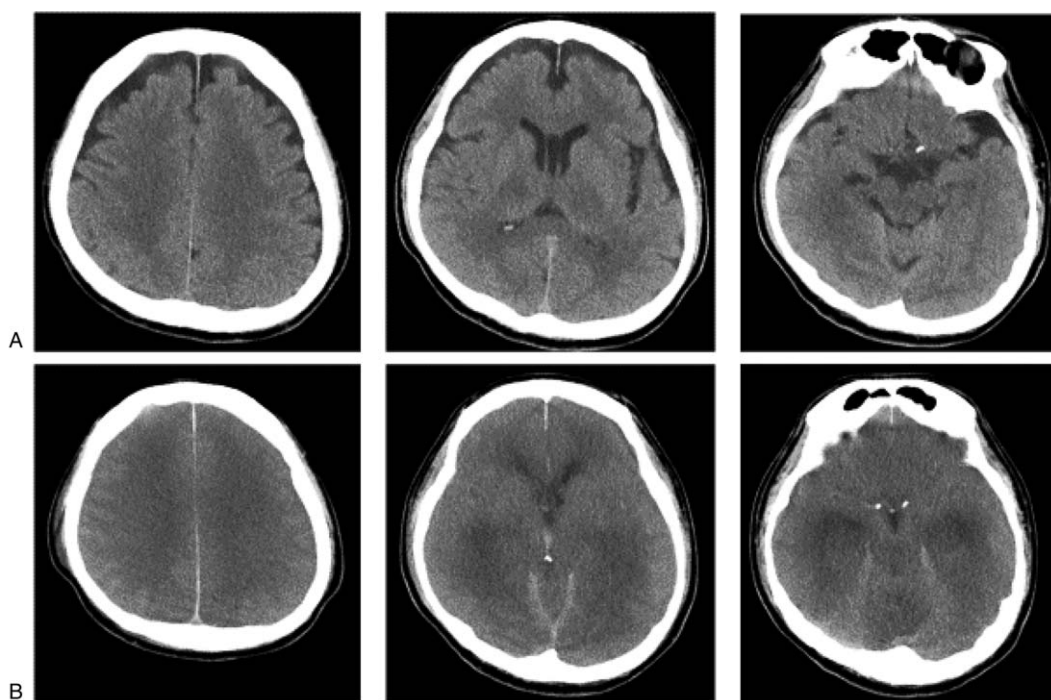
Based on the course until admission to our hospital and physical and laboratory findings, the patient was diagnosed as having influenza A infection. Regarding the cause of disturbance to

**Table 1**

### Laboratory data on admission.

		Biochemical analysis			
Blood cell count		Reference range		Reference range	
WBC	2200/ $\mu$ L	3300–8600/ $\mu$ L	Na	143 mEq/L	138–145 mEq/L
RBC	472/ $\mu$ L	435–555/ $\mu$ L	K	4.6 mEq/L	3.6–4.8 mEq/L
Hb	14.7 g/dL	13.7–16.8 g/dL	Cl	107 mEq/L	101–108 mEq/L
Ht	41.8%	40.7%–50.1%	Ca	9.38 mg/dL	8.8–10.1 mg/dL
Plt	6.3/ $\mu$ L	15.8–34.8/ $\mu$ L	Mg	2.3 mg/dL	1.80–2.40 mg/dL
Blood gas analysis			TP	7.52 g/dL	6.6–8.1 g/dL
pH	7.403	7.380–7.460	Alb	4.38 g/dL	4.1–5.1 g/dL
PaCO <sub>2</sub>	32.4 mm Hg	32.0–46.0 mm Hg	AST	727 IU/L	13–30 IU/L
PaO <sub>2</sub>	116.5 mm Hg	74.0–109.0 mm Hg	ALT	338 IU/L	10–30 IU/L
HCO <sub>3</sub> <sup>-</sup>	19.8 mmol/L	21.0–29.0 mmol/L	LDH	939 IU/L	124–222 IU/L
BE	-3.5 mmol/L	-2.0–2.0 mmol/L	T.bil	0.41 mg/dL	0.4–1.2 mg/dL
Hemostasis			BUN	18 mg/dL	8–20 mg/dL
PT-INR	1.41	0.85–1.15	Cre	2.02 mg/dL	0.65–1.07 mg/dL
APTT	41.9 s	24.0–39.0 s	CRP	5.78 mg/dL	≤0.14 mg/dL
Fib	331 mg/dL	200–400 mg/dL	CK	557 IU/L	59–248 IU/L
FDP	82.3 $\mu$ g/mL	<5.0 ng/mL	Ferritin	3333 ng/mL	13–277 ng/mL
D-dimer	37.7 ng/mL	≤1.0 ng/mL	IgG	446 mg/dL	861–1747 mg/dL
Antithrombin	70%	80%–130%	IgA	79 mg/dL	93–393 mg/dL
			IgM	16 mg/dL	33–183 mg/dL
			IL-6	188,390 pg/mL	<35 pg/mL
			Ammonia	49 $\mu$ g/dL	30–86 $\mu$ g/dL
			Glucose	128 mg/dL	73–109 mg/dL

Alb = albumin, ALT = alanine aminotransferase, APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BE = base excess, BUN = blood urea nitrogen, Ca = calcium, CK = creatine kinase, Cl = chloride, Cre = creatinine, CRP = C-reactive protein, FDP = fibrin/fibrinogen degradation products, Fib = fibrinogen, Hb = hemoglobin, HCO<sub>3</sub> = hydrogen carbonate, Ht = hematocrit, IgA = immunoglobulin A, IgG = immunoglobulin G, IgM = immunoglobulin M, IL-6 = interleukin 6, K = potassium, LDH = lactate dehydrogenase, Mg = magnesium, Na = sodium, PaCO<sub>2</sub> = partial pressure of arterial carbon dioxide, PaO<sub>2</sub> = partial pressure of arterial oxygen, pH = power of hydrogen, Plt = platelet, PT-INR = prothrombin time-international normalized ratio, RBC = red blood cell, T.bil = total bilirubin, TP = total protein, WBC = white blood cell.



**Figure 1.** Noncontrast cranial computed tomography of a 52-year-old man with influenza. A, On admission, no abnormalities and (B) on 24 hours after admission, diffuse cerebral edema observed.

consciousness, although the previous physician had used 70 mg/h propofol, we considered critical illness encephalopathy for differential diagnosis. Echocardiography after the transfer confirmed low circumferential left ventricular systolic function with ejection fraction of 38%. Thus, we initiated dobutamine, and assuming septic shock, we initiated noradrenaline treatment with large-volume infusion. Because circulatory dynamics remained unstable under the large-volume infusion and high-dose catecholamine administration, we did not perform magnetic resonance imaging. Potential bleeding accompanying DIC precluded cerebrospinal fluid examination. Regarding influenza treatment, we continued laninamivir at an increased dose of 600 mg daily, but because involvement of bacterial meningitis could not be eliminated, meropenem, and vancomycin were also administered. Furthermore, the patient's left pupil dilated 24 hours after the transfer and anisocoria was noted; therefore, we performed CT again that confirmed acute cerebral edema and cerebral herniation (Fig. 1). Accordingly, we initiated intravenous injection of mannitol to control intracranial pressure and initiated body temperature management therapy with a target temperature of 35°C to 36°C. We considered external decompression surgery, but we deemed it too risky because the platelet count had decreased to 1.0/ $\mu$ L. Brain wave measurement on that day revealed a flat line. Considering a markedly elevated serum ferritin level as per blood test during the transfer (3333 ng/mL on the day of hospitalization; 17,177 ng/mL on next day after hospitalization; 8380 ng/mL on hospitalization day 2; 1877 ng/mL on hospitalization day 3), we suspected virus-associated hemophagocytic syndrome (VAHS) and continued monitoring changes in monocyte count and LDH and ferritin levels. On day 2 after his admission to our hospital, ferritin level increased to 17,177 ng/mL, and it gradually improved thereafter (8380 ng/mL on day 3 and 1877 ng/mL on day 4). On his 6th hospital day, we discontinued all sedatives and re-evaluated the patient. The brain

wave remained flat, and auditory brainstem response showed loss of waveform beyond wave I. Then, we diagnosed the patient as being brain-dead based on the confirmed loss of brainstem response. His blood pressure gradually decreased, and the patient died on his 27th hospital day.

### 3. Discussion

With the progress of research on influenza-associated encephalopathy, it has become clear that cases are diverse and range from mild to severe cases that lead to early-stage death.<sup>[6]</sup> Among the syndromes that are virologically positive for influenza and accompany the chief complaints of disturbance of consciousness and acute onset, influenza-associated encephalopathy is diagnosed after eliminating demyelinating, autoimmune, and metabolic diseases. As a subtype, HSES has been reported,<sup>[4]</sup> which is an acute encephalopathy mainly observed in infants, with high fever, disturbance of consciousness, convulsions, and shock. HSES rapidly progresses with findings such as watery diarrhea, liver and renal dysfunctions, decreases in serum hemoglobin levels and platelet counts, and DIC. Existing diseases, metabolic disease, and Reye syndrome should be eliminated. In the present case, urinary organic acid analysis and tandem mass spectrometry did not confirm metabolic abnormalities in organic or fatty acids. Furthermore, acetylsalicylic acid was not used to control fever and only acetaminophen had been used. Because there was no hyperammonemia, the patient was diagnosed as having HSES. Our patient was an adult and did not have diarrhea. Otherwise, his symptoms were consistent with those reported for HSES.<sup>[4]</sup> Rapid progression to whole-brain edema observed using CT was also consistent with the finding obtained in a previous HSES report.<sup>[7]</sup> Our patient presented convulsions and disturbance of consciousness on the same day as the onset of influenza virus A (H3N2) infection. Shock, organ failure, DIC, and acute cerebral

edema rapidly progressed over the course of 24 hours, leading to brain death. In cases of adult influenza-associated encephalopathy, majority of cases present influenza A. Approximately within a day from the onset of fever, disturbance of consciousness, and/or convulsion are presented. In some cases, complications include organ failure and DIC, often leading to death or neurological sequelae.<sup>[8]</sup> The clinical picture in our patient is consistent with those previously reported. Because influenza A is seasonal, the onset on February was consistent with reports that most HSES occur in winter.<sup>[9]</sup>

Currently, the precise cause of HSES is unclear, but cytokine storm may reportedly lead to HSES acute encephalopathy.<sup>[10]</sup> Systemic vascular hyperpermeability accompanying cytokine storm induced by influenza viral infection and apoptosis are assumed to be the primary mechanisms of influenza-associated encephalopathy. Inflammatory cytokines such as IL-6, IL-1 $\beta$ , and tumor necrosis factor- $\alpha$  in serum or spinal fluid are high, particularly serum IL-6 (associated with severity and prognosis).<sup>[11]</sup> In our patient, serum IL-6 was notably elevated, and this result was consistent with reports stating that cytokines are high in HSES cases. As the cause of disturbance of consciousness in our patient, although blood culture tests were negative, his high procalcitonin level cannot exclude the complication of bacterial infection. However, we were unable to identify the cause of encephalopathy through a cerebrospinal fluid examination.

As a treatment for influenza-associated encephalopathy, methylprednisolone pulse therapy might have been effective in suppressing high cytokines in the central nervous system and hypercytokinemia. However, the therapy needs to be initiated at early stages.<sup>[12]</sup> In Japanese retrospective studies, steroids administered in cases without brain stem lesions within 24 hours improved prognosis.<sup>[13]</sup> In the present case, by the time the onset of encephalopathy was diagnosed, >24 hours had passed, and the brain stem was already damaged; therefore, we did not administer any steroid. If we could have suspected HSES and treated the patient with methylprednisolone pulse therapy at an early stage, the prognosis could have been better. However, it is possibly difficult to save patient's life or reduce neurological sequelae solely by methylprednisolone pulse therapy in cases such as this wherein encephalopathy and cerebral swelling rapidly progress. Number of adult cases with HSES is extremely small, and a standard treatment method has not been established to date. However, in HSES, because cytokine storm due to influenza virus may be the cause (increased IL-6 and VAHS), continuous hemodiafiltration<sup>[14]</sup> using a polymethyl methacrylate film that efficiently removes inflammatory cytokines via adsorption at an early-stage might have been effective. In addition, with cerebral hypothermia and systemic management (such as controlling intracranial pressure), special therapies such as high-dose intravenous  $\gamma$ -globulin, high-dose antithrombin III, therapeutic plasma exchange, and cyclosporine therapy may improve prognosis.

#### 4. Conclusions

We reported on an adult case of influenza A wherein the patient developed HSES. Although it is extremely rare in adults and

treatment cannot be immediately initiated, influenza-associated encephalopathy should be considered in differential diagnosis while diagnosing disturbance of consciousness accompanied by fever during the influenza season. Moreover, treating physicians should consider the possibility of a drastic course such as one with HSES. Pathogenetic mechanisms of this disease are unclear; therefore, accumulation and analysis of more cases are needed in the future.

#### Author contributions

**Conceptualization:** Masafumi Fukuda.

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**Visualization:** Masafumi Fukuda.

**Writing – original draft:** Masafumi Fukuda.

**Writing – review and editing:** Takasu Osamu.

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