

[CASE REPORT]

Successful Outcome in an Adult Patient with Influenza-associated Hemorrhagic Shock and Encephalopathy Syndrome

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Abstract:

A 50-year-old woman presented with coma and hemorrhagic shock. A rapid influenza antigen test revealed influenza A infection; other laboratory examinations ruled out any other suspected infections. She was diagnosed with hemorrhagic shock and encephalopathy syndrome (HSES) induced by influenza A. She was administered methylprednisolone pulse therapy and peramivir. Subsequently, she was discharged without any sequelae. Only a few cases of influenza-induced HSES have been reported, and the clinical outcomes were very poor. We herein report a successfully treated adult case of influenza-induced HSES and review this rare syndrome.

Key words: hemorrhagic shock and encephalopathy syndrome, influenza, HSES, influenza-associated encephalopathy, IAE

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Introduction

The main presentations of an influenza virus infection are a high fever and respiratory symptoms; however, influenza virus occasionally induces acute encephalopathy, which is known as influenza-associated encephalopathy (IAE). In 1983, hemorrhagic shock and encephalopathy syndrome (HSES) was proposed by Levin et al. as a severe subtype of infection-associated acute encephalopathy, where patients present with neurological disorder accompanied by gastrointestinal bleeding (1). In most cases, HSES occurs in children; the mortality rate has been reported to be approximately 60%, and most of the surviving patients suffered from sequelae (2). Few patients have experienced HSES triggered by influenza infection, and an adult onset of HSES is especially rare. Of the influenza-associated neurological complications classified by Goenka et al., HSES was one of the most aggressive (3).

We herein report a middle-aged woman with influenza A-

induced HSES who had a successful clinical course.

Case Report

A 50-year-old woman with no remarkable medical history was admitted to our hospital in February (an influenza season) with hematochezia and lethargy that had developed 2 hours before arrival at the hospital. She had no history of travel abroad. She had not been in contact with anyone who had presented with a high fever. Her family reported that she had had no complaints until she became drowsy. She had not taken any prescribed medications.

On arrival, a physical examination revealed epigastric tenderness and massive hematochezia. She was able to follow commands; however, she had a reduced level of consciousness. Her vital signs showed severe hypotension with a normal temperature (blood pressure of 50/30 mmHg and body temperature of 36.8°C). Laboratory tests revealed slightly elevated levels of liver enzymes, renal dysfunction, and systemic inflammation (Table 1). Based on the coagulation

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Table 1. Laboratory Findings on Admission.

Complete Blood Test		Biochemical Test			
WBC	3,600 / μ L	AST	130 U/L	Lactic acid	20 mg/dL
Neutrophils	67 %	ALT	43 U/L	Pyruvate	1.55 mg/dL
Lymphocytes	25 %	LDH	293 U/L	Vitamin B ₁₂	298 pg/mL
Monocytes	8 %	T-Bil	1.32 mg/dL	Folate	2.9 ng/mL
RBC	3.45 $\times 10^6$ / μ L	TP	5.7 g/dL	ANA	<40
Hb	9.4 g/dL	Alb	3.4 g/dL	PR3-ANCA	<1.0 IU/mL
MCV	83.5	BUN	35 mg/dL	MPO-ANCA	<1.0 IU/mL
MCH	29.3	Cre	3.72 mg/dL	IgG	841 mg/dL
Plt	73,000 / μ L	Glu	68 mg/dL	IgA	99 mg/dL
		CK	3,950 U/L	IgM	46 mg/dL
		Ca	8.5 mg/dL		
		Na	136 mmol/L	Arterial Gas Test	
Hemostasis Test		K	3.6 mmol/L	pH	7.2
PT	15.0 sec	Cl	103 mmol/L	pO ₂	215 mmHg
PT-INR	1.55	CRP	18.7 mg/dL	pCO ₂	33 mmHg
APTT	54.2 sec	Ammonia	60 μ g/dL	HCO ₃ ⁻	12.7 mmol/L
Fib	232 mg/dL	Ferritin	293 ng/mL	Base excess	-12 mmol/L
FDP	30.5 μ g/mL				

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, Plt: platelet, PT: prothrombin time, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, Fib: fibrinogen, FDP: fibrinogen degradation products, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, T-Bil: total bilirubin, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cre: creatinine, Glu: glucose, CK: creatine kinase, Ca: calcium, Na: sodium, K: potassium, Cl: chloride, CRP: C-reactive protein, ANA: anti-nuclear antibody, PR3-ANCA: proteinase-3-anti-neutrophil cytoplasmic antibodies, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibodies, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, pH: power of hydrogen, pO₂: partial pressure of oxygen, pCO₂: partial pressure of carbon dioxide, HCO₃⁻: bicarbonate

tests, we regarded the patient as presenting with disseminated intravascular coagulation (DIC).

Contrast-enhanced computed tomography (CT) did not demonstrate any abnormalities, including contrast media extravasation, except for small bowel edema. We performed exploratory laparotomy to exclude non-occlusive mesenteric ischemia; however, no evidence of ischemic bowel or ascites was observed. Laboratory tests and radiological findings did not indicate any specific diseases. Although this patient presented with few clinical characteristics associated with influenza infection, we performed a rapid influenza antigen test using a nasopharyngeal swab sample, as she had been admitted during influenza season. The test result was positive for influenza A infection.

Her blood pressure remained unchanged despite the administration of crystalloids and blood transfusion. Her level of consciousness decreased, and she eventually became completely unresponsive, requiring her to undergo endotracheal intubation. Repeat CT of the brain showed diffuse hypodense subcortical regions, corresponding to brain edema (Fig. 1A). We analyzed her cerebrospinal fluid (CSF), which demonstrated an increased intracranial pressure of 23 cmH₂O without pleocytosis. Viral-specific antibody tests for herpes simplex virus (HSV), mumps virus, measles virus, rubella virus, varicella-zoster virus, cytomegalovirus, and Epstein-Barr virus indicated past infections, and an HSV-DNA test performed using CSF yielded a negative result (Table 2). Subsequently, both blood and CSF cultures were

negative.

Based on the clinical characteristics and laboratory findings as well as the lack of any other clear etiology, a definite diagnosis of HSES induced by influenza A was established using the criteria proposed by Bacon et al. (4).

With supportive therapy, including catecholamine administration, fluid resuscitation, and mannitol administration, we administered peramivir, 300 mg for 5 days and methylprednisolone pulse therapy 1,000 mg for 3 days followed by 500 mg for 2 days. Hemodynamic stability was achieved within 2 days. On day 5, her consciousness gradually improved enough to follow our commands, and the radiological findings on repeat CT suggested recovery from the brain edema (Fig. 1B). On day 6, she was extubated without any supportive therapies. Massive gastrointestinal hemorrhage occurred only on admission, followed by diarrhea for 7 days. Her clinical course is shown in Fig. 2. Finally, she was discharged on day 29 without any neurological sequelae.

Discussion

Influenza infection may be complicated with neurological disorders, especially in children (3). IAE, a major neurological complication, has a significantly higher incidence in children than in adults. Okuno et al. reported through a search of a Japanese national database that the incidence of IAE was 2.83 cases for children and 0.19 cases for adults per 1,000,000 population (5).

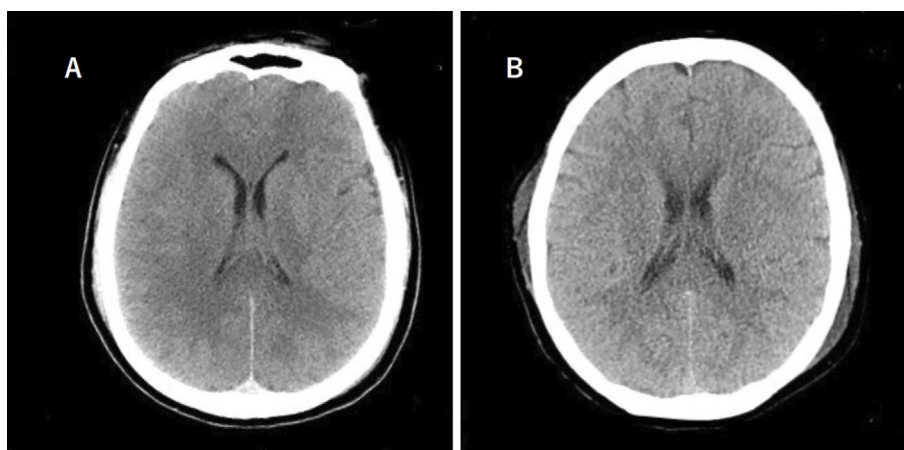


Figure 1. Brain CT findings in pre- and post- treatment. Loss of contrast between gray and white matter and hypodensity demonstrated at acute phase improved on day 5 (A; acute phase, B; recovery phase).

Table 2. Viral Specific Analysis.

Pathogens	Blood		Cerebrospinal fluid
	IgM (EIA)	IgG (EIA)	DNA (PCR)
Herpes simplex virus	0.21	38.2	negative
Mumps virus	0.14	3.8	-
Measles virus	0.12	21.2	-
Rubella virus	0.10	56.3	-
Varicella-zoster virus	0.12	13	-
Cytomegalovirus	0.23	28.4	-
Epstein-Barr virus (VCA)	0.10	6.2	-

EIA: enzyme immunoassay, PCR: polymerase chain reaction, IgM: immunoglobulin M, IgG immunoglobulin G, DNA: deoxyribonucleic acid, VCA: viral capsid antigen

No specific criteria for an IAE diagnosis have yet been established, so the diagnosis is based on eliminating other possible diseases. Laboratory data and the acute onset of the presentation in our patient did not suggest autoimmune or metabolic diseases. Reye's syndrome, a neurological disorder associated with influenza, was also ruled out because she was not taking any medication, including aspirin. Radiological examinations and serum and urine tests did not indicate any specific infections. Blood culture was eventually negative. A CSF test showed increased intracranial pressure without pleocytosis, and CSF culture also yielded a negative result.

The pathogenesis of IAE has not been elucidated. However, it is speculated that systemic inflammation induced by influenza infection, not direct viral invasion, likely triggers neurologic complications. In most cases, the CSF test shows the absence of pleocytosis, and a lack of viral RNA (6), although there have been a few autopsied cases in which viral RNA was detected by reverse transcription polymerase chain reaction in brain tissue (7). In addition, high levels of interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)- α have been detected in CSF and plasma (8).

Why IAE is more likely to occur in children than in adults is unclear; however, animal experiments have shown

that blood-brain barrier (BBB) efflux transporters had age-related differences in inflammatory responses (9). With activation of the brain immune response, a tendency to decrease BBB efflux transporters was shown in juvenile brains compared to adult brains, which may explain the high incidence of IAE in children (9). Adult patients with IAE, like our own, might have malfunctioning or a decreased number of BBB efflux transporters.

Our case was notable in that the characteristics of IAE were accompanied by hemorrhagic shock on admission. We did not perform upper or lower gastrointestinal endoscopy tests, as the patient presented with overt gastrointestinal bleeding only at admission; however, massive fluid resuscitation had no effect on her blood pressure. This phenomenon, a neurological disorder complicated with hemorrhagic shock, was first reported by Levin et al. in 1983 and was termed HSES, which is now regarded as a subtype of infection-associated acute encephalopathy, including IAE (1). Bacon et al. proposed the following criteria for the diagnosis of this syndrome: (1) encephalopathy, (2) shock, (3) disseminated intravascular coagulation, (4) diarrhea (may be bloody), (5) decreased hemoglobin concentration and platelet counts, (6) acidosis, (7) raised hepatocellular enzymes, (8) renal function impairment, and (9) negative

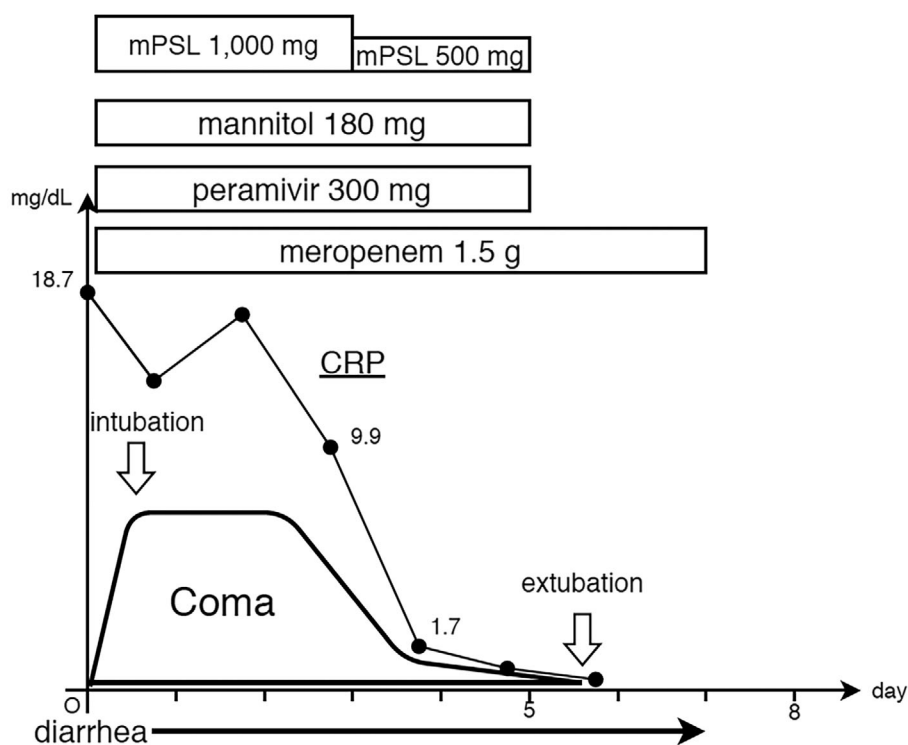


Figure 2. Clinical course of our patient. The vertical axis shows the level of CRP and horizontal axis shows days after admission. Rectangles above this chart demonstrate medications administered in the patient, and those durations and daily dosages. Several hours after admission, she developed coma, which required endotracheal intubation. On day 4, she opened her eyes in response to our voices. She could obey our commands on day 5 and was extubated on day 6. Massive gastrointestinal hemorrhage occurred only on admission and diarrhea ensued for 7 days.

Table 3. Characteristics and Clinical Courses of Patients with Influenza Induced Hemorrhagic Shock and Encephalopathy Syndrome.

Case	Age	Sex	Influenza subtype	Clinical course	Treatment regimens	References
1	2y	F	A(H3N2)	Dead	Antibiotics, Dex, Immunoglobulin, Mannitol	11
2	3y	F	A(H1N1)	Dead	Oseltamivir, Mannitol	3
3	3y	M	A(H1N1)	Dead	Oseltamivir	12
4	9y	F	A(H3N2)	Dead	Antibiotics, Dex, DrotAA	13
5	17y	M	A(H3N2)	Dead	Antibiotics, Dex, DrotAA	13
6	52y	M	A(H3N2)	Dead	Laninamivir, Antibiotics, Mannitol	14
7	50y	F	A	Alive	Peramivir, Antibiotics, Mannitol, mPSL	our case

F: female, M: male, DrotAA: Drotecogin-alfa, Dex: Dexamethasone, mPSL: methylprednisolone

blood and CSF cultures (4). Our case was diagnosed as HSES because it met all nine criteria. Since the first report in 1983, approximately 250 cases of HSES have been diagnosed according to these criteria (10).

The trigger of HSES was not detected in most cases. Six cases of HSES induced by the influenza virus were identified using PubMed (Table 3) (3, 11-14). Other pathogens, including rotavirus, norovirus, and adenovirus, have also been linked to this syndrome (15). Most patients with HSES have a very poor clinical course. Up to 60% of patients with HSES reportedly have died, and 30% of survivors had neu-

rological sequelae (2).

The pathogenesis of HSES is unclear. Systemic inflammation may be associated with this syndrome as well as IAE (15, 16). In the literature, most patients with HSES were children, although an adult Japanese patient with HSES was recently reported (14). The abovementioned mechanism of a BBB transporter disorder may be involved in the pathogenesis. Hyperpyrexia has often been also suspected as an important factor that induces HSES; however, some reports have contradicted this hypothesis because, in some cases, there was no high fever upon admission (2). In-

deed, the patient in our case did not present with a high fever on admission. Some reports have attributed the cause and severity of HSES to the individual's susceptibility, not the thermal environment. Heat-shock proteins, which protect organisms from a variety of stresses, including hyperthermia, may be constitutionally or transitionally defective in patients with HSES (2).

HSES has only a few characteristic symptoms. CT and magnetic resonance imaging (MRI) usually illustrate no specific radiological findings (15). Laboratory tests reveal elevated liver enzyme and creatine kinase levels upon admission and persistence of acidosis despite fluid resuscitation (15). These early signs have been reported to indicate HSES (15). As the mechanism of HSES is assumed to be based on systemic inflammation, cytokine marker levels are supposed to be elevated. Serum levels of IL-6 and soluble IL-2 receptors were elevated in one report; however, the degree of elevation varied (17). Thus far, no specific cytokine marker for the diagnosis of HSES has been identified.

Although the mortality rate of HSES is very high, a few patients, in addition to ours, have completely recovered without any sequelae (17), facilitating an investigation of the prognostic factors for HSES. According to the literature, epilepticus status and a coma of long duration appear to be associated with poor outcomes (2). A biphasic course (e.g. an initial recovery of 12-24 hours and secondary worsening in the neurological status) also may be a marker of a poor prognostic presentation (2).

The standard treatment regimen for HSES has not yet been established, and the therapeutic strategy should be focused on supportive therapy, such as large amounts of fluids and/or catecholamine infusion. In addition, controlling brain edema using intracranial pressure depressants may be a promising therapy. Considering the pathophysiology of HSES, corticosteroid therapy appears to be beneficial. Okumura et al. noted that early corticosteroid therapy (within 24 hours) contributed to improved outcomes in patients with acute necrotizing encephalopathy (ANE), which is also a subtype of influenza-associated neurological disorders (17). In a few reports, high-dose oseltamivir and methylprednisolone led to the successful treatment of patients with IAE and influenza-associated ANE (18, 19). ANE and HSES share many clinical and pathological features (16). From the clinical perspective, the onset of each disease occurs during the early febrile period of a viral infection, and it runs a fulminant course with the rapid development of a coma. Severe cases often show signs of systemic inflammatory response syndrome, such as shock, multiple organ failure, and DIC. From the pathological perspective, severe brain edema and perivascular plasma exudation have been found in each disease. These similar features suggest that high-dose oseltamivir may provide clinical benefit for HSES as well as ANE.

We cannot clearly explain the reason for the complete recovery of our patient without any sequelae, which is in contrast to previously reported cases. One reason may be that

we administered corticosteroid therapy within 12 hours from the onset of this syndrome concurrent with antiviral medication, while in a previous case with an adult onset of HSES induced by influenza, which was very similar to our own case, corticosteroid was not administered (14).

In conclusion, we report a successful clinical course in an adult patient with influenza-induced HSES. Only a few cases of influenza-induced HSES have been reported in the literature, especially in adults. As early initiation of treatment is essential to better clinical outcomes, we should consider HSES in patients with neurological disturbance along with gastrointestinal bleeding even when their body temperature is not extremely high. Further investigations must be performed to identify the pathogenesis and to establish a standard treatment for HSES.

The authors state that they have no Conflict of Interest (COI).

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