



Nationwide survey of influenza-associated acute encephalopathy in Japanese adults



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ABSTRACT

Background: Knowledge of adult patients with influenza-associated acute encephalopathy (IAE) is limited. We conducted a detailed survey to investigate the prevalence, clinical features, associated outcomes, and prognostic factors in adult IAE patients.

Method: A nationwide questionnaire on IAE patients was sent to the departments of Internal Medicine, Neurology, Neurosurgery, and Emergency and Critical Care at all hospitals with ≥ 200 beds in Japan.

Results: 118 patients were diagnosed with IAE during the 2013/14 to 2015/16 influenza seasons, and the estimated annual incidence of IAE in Japanese adults was 0.98/1000,000 population. 44 patients were subsequently enrolled in the detailed study. 93% of patients exhibited disturbance of consciousness. Convulsions and delirious behavior were present in 26% and 40% of patients, respectively. 65% of patients received pulse corticosteroid therapy with methylprednisolone and 21% of patients received intravenous gamma-globulin therapy. 63% of patients achieved a good recovery, but 7% died. Multiple logistic regression analysis revealed that plasma glucose level demonstrated a statistically significant association with poor outcome.

Conclusion: This nationwide survey provided data for the annual incidence and clinical features of IAE in Japanese adults. Hyperglycemia was indicated as an independent predictor of poor prognosis in IAE patients and reflected systemic hypercytokinemia in IAE pathogenesis.

1. Introduction

Influenza viruses cause seasonal infections and may result in worldwide epidemics with significant morbidity and mortality. The 2009 influenza A pandemic H1N1 caused the death of > 280,000 persons worldwide because of respiratory or cardiovascular complications [1]. Median annual influenza-associated respiratory death was estimated at about 410,000 cases globally using country-specific influenza-associated excess respiratory mortality estimates from 1999 to 2015 [2]. Severe influenza virus infection is associated with not only respiratory and cardiovascular complications but also neurological complications [3]. Though involvement of the central nervous system (CNS) in influenza virus infection is less frequent, serious manifestations, such as altered or loss of consciousness, convulsions, psychosis, and abnormal behavior, have been described in individual cases [4]. A large number of patients with influenza-associated acute encephalopathy

(IAE) have been reported since the late 1990s [4–8]. Influenza virus infection is the most commonly identified pathogen in pediatric patients with acute encephalopathy in Japan, the details of which have been well documented [9,10]. However, IAE has been considered to occur rarely in adults [11,12]. Although fatal prognosis was reported in some adult IAE patients [13,14] and the case-fatality proportion of IAE is higher in adults than children [8], knowledge of adult patients with IAE is limited. Therefore, we conducted a national survey to investigate the prevalence, clinical features, associated outcomes, and prognostic factors in adult patients with IAE.

2. Methods

2.1. Case definition

The diagnosis of encephalopathy was based on the definition

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provided in the Infectious Diseases Control Law in Japan. Acute encephalopathy is defined on the basis of all clinical signs. All patients had a fever and altered or loss of consciousness. Influenza infection was defined on the basis of either (1) a positive result from a viral antigen test, a viral culture, or viral RNA PCR or (2) by significant increases in hemagglutination inhibition test titers. Specimens from throat swabs were used for viral culture, viral antigen testing, and viral RNA PCR. Viral antigens were detected by enzyme-linked immunosorbent assay. Viral RNA was detected by reverse transcriptase PCR.

2.2. Data collection

In September 2016, the first questionnaire on the incidence of patients with IAE during September 2013 to August 2016 was sent for completion to the 5626 departments of Internal Medicine, Neurology, Neurosurgery, and Emergency and Critical Care at all hospitals with ≥ 200 beds in Japan. A total of 1797 departments responded to the first questionnaire. In Japan, nationwide sentinel surveillance of influenza-like illness (ILI) is conducted annually. Approximately 5000 influenza sentinels (3000 from pediatrics and 2000 from internal medicine) report the number of ILI cases diagnosed with influenza weekly to National Institute of Infectious Diseases (NIID)/Ministry Labor, Health and Welfare through local public health centers/local Government. Approximate 10 % of influenza sentinel designated as laboratory sentinel send specimen to the local public health laboratory for virological examination. This information is sent to NIID, and further laboratory examination in details are performed in NIID, if it is necessary. In the 2013/14 influenza season, 8197 ILI cases were reported from sentinel surveillance sites (influenza A H1N1pdm, 43%; influenza A H3 subtype, 21%; influenza B, 36%). In the 2014/15 season, 6164 ILI cases (influenza A H3 subtype, 85%; influenza B, 14%) and in the 2015/16 season, 7510 ILI cases (influenza A H1N1pdm, 48%; influenza A H3 subtype, 8%; influenza B, 43%) were reported [15].

Subsequently, a second questionnaire that requested data on matched cases and detailed clinical and laboratory data was sent to each department of the hospitals. Furthermore, the second questionnaire was also sent to local public health offices, which reported IAE cases as defined according to the Infectious Diseases Control Law. A total of 51 cases were reported and deemed appropriate for further study. One duplicate patient, three patients with doubtful cases, and three patients who declined to participate in the second questionnaire were excluded from further analysis. Overall, 44 patients with cases defined as IAE were enrolled in this study (Fig. 1).

2.3. Statistical analysis

The annual incidence per 1000,000 population was estimated on the basis of the number of registered patients and the total population of Japan in 2015 [16], and regional differences in incidence were analyzed using the binomial test [17,18].

Differences in patient age and duration of hospitalization between the three influenza seasons were assessed using the Kruskal-Wallis test. The Glasgow outcome scale (GOS) [19] at discharge was used to assess IAE outcomes. Studied patients were divided into two groups based on GOS results: good outcome group, GOS 5 (good recovery, resumption of normal life despite minor deficits) and poor outcome group, GOS 1 (dead) to 4 (moderately disability, able to work in a sheltered environment and travel by public transportation). We then assessed differences in sex, age at onset, duration of hospitalization, clinical symptoms, laboratory data, and treatment between the two outcome groups. The Glasgow coma scale (GCS) score [20] was treated as a continuous variable. Continuous variables were assessed using the Mann-Whitney *U* test. Categorical variables were assessed using Fisher's exact test. When statistical differences were revealed between these factors and two outcome groups, multiple logistic regression analyses were employed to assess confounding factors. A dichotomous

dependent variable of outcome was assigned a value of 0 when the GOS score was 5 and 1 when the score was ≤ 4 . The sex category was defined as follows: female = 0, male = 1. IBM SPSS Statistics version 25.0 (IBM Corp, Armonk, NY, USA) was used for statistical analyses. In this study, the level of statistical significance was set at $\alpha = 0.05$. This research protocol was approved by the research and ethical committees for the use of human subjects of the National Institute of Infectious Diseases.

3. Results

3.1. Estimated annual incidence and regional differences

The response rate for the first questionnaire sent to the hospitals was 32% (1797 of 5626 departments). This first questionnaire revealed that 118 patients were diagnosed with IAE during the 2013/14 to 2015/16 influenza seasons. The estimated annual incidence in Japan was 0.98/1000,000 population. The annual incidences in each region ranged from 0.72 to 1.49 per 1000,000 population and regional differences were found to be non-significant (Table 1).

3.2. Diagnosis of influenza virus infection

Among the 44 patients enrolled, detailed information including how the influenza virus type was determined was unavailable for one patient who died. All remaining 43 patients were diagnosed by a positive result from viral antigen detection using nasopharyngeal swab specimens; 35 patients were infected with influenza A virus and 8 patients were infected with influenza B virus. Influenza virus was isolated in one patient and influenza A virus (H3 subtype) was detected. Viral RNA was detected from nasopharyngeal swab specimens in two patients; influenza A virus (H3 subtype, $n = 1$) and influenza B virus (subtype unknown, $n = 1$) were detected. Sequential serological tests were conducted in four patients and influenza A viruses (H1N1pdm, $n = 2$; H3 subtype, $n = 2$) were detected. Influenza RNA viral detection in cerebrospinal fluid (CSF) was not reported in these IAE patients.

3.3. Clinical features

Table 2 shows the clinical features of the two outcome groups. Fifty percent of the 44 patients enrolled were male. Information about outcome was not available for three patients. Of the 41 patients for whom outcome was noted, 3 of 41 patients died and 12 patients experienced disability (7 patients had severe sequelae and 5 patients had moderate sequelae). Their ages ranged from 16 to 90 years. The duration of hospitalization ranged from 2 to 136 days. Half of the patients were discharged within 15 days. Patient age and duration of hospitalization were not significantly different between the three influenza seasons. However, duration of hospitalization was significantly longer in the poor outcome group ($p = .002$).

As initial symptoms, fever was observed in 50%, consciousness disturbance in 31.8%, convulsion in 11.4%, and headache in 6.8% of patients. Duration between the days that fever appeared and the day that encephalopathy appeared ranged from 0 to 10 days. Diarrhea was present in 13.5% of patients. Approximately 33% of patients received influenza vaccination before the influenza season. Additionally, 56.3% of patients received antipyretic drugs. No patient received diclofenac sodium or mefenamic acid. As for history, 20.9% had hypertension, 14.0% had diabetes, 4.7% had allergic disease, and 2.3% of patients had autoimmune disease. Additionally, 11.6% had neurological disorders and 9.3% of patients had mental disorders. Lastly, 2.3% had epilepsy and 7.0% of patients had a history of convulsion.

On admission, disturbance of consciousness was observed in 93% of patients; 30% had GCS scores ≥ 13 and 27.5% had GCS scores ≤ 8 . GCS score was significantly lower in the poor outcome group ($p = .038$, Table 3). Convulsion was observed in 25.6% of patients and 18.2% of

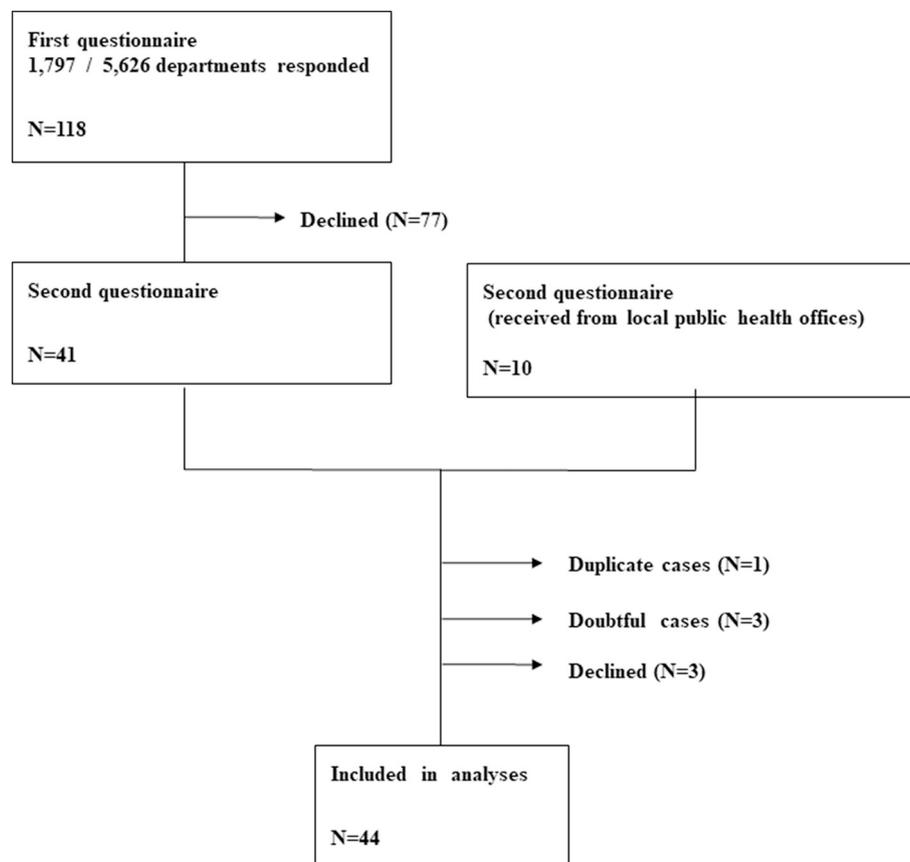


Fig. 1. Flowchart of study participant inclusion from first and second questionnaires.

Table 1

Regional differences in annual incidence of IAE among registered adult patients.

Region	Annual incidence (/1000,000 population)
Hokkaido-Tohoku	0.72
Kanto	0.99
Chubu-Hokuriku	0.91
Kinki	1.07
Chugoku-Shikoku	1.49
Kyushu-Okinawa	0.80

IAE = influenza-associated acute encephalopathy.

The estimated annual incidence of adult IAE in Japan was 0.98/1000,000 population. Regional differences were assessed using the binomial test and did not show statistical significance.

convulsive seizures continued for a prolonged period. Abnormal behavior was observed in 40% of patients. Frequencies of convulsion and abnormal behavior were not different between the two outcome groups.

Concerning the neurological examination, abnormalities were observed in 16 of 40 patients. Cranial nerve palsy was observed in 7.5%, pyramidal tract sign in 20%, parkinsonism in 2.5%, involuntary movement in 17.5%, and dysautonomia in 7.5% of patients. Meningeal signs were observed in 13.2% of patients. Frequencies of these neurological findings were not different between the two outcome groups.

3.4. Laboratory findings

Table 4 shows laboratory findings of the two outcome groups. On admission, the rates of patients with elevated serum aspartate aminotransferase (AST) level > 100 IU/l, elevated serum urea nitrogen (BUN) level > 30 mg/dl, and abnormal serum glucose level > 150 mg/dl were significantly more frequent in the poor outcome group

($p = .036$, $p = .007$, and $p = .004$, respectively). The levels of serum BUN and glucose were significantly higher in the poor outcome group ($p = .033$ and $p = .002$, respectively). During hospitalization, the rates of patients with elevated serum AST level > 100 IU/l were significantly more frequent in the poor outcome group ($p = .006$). Minimum platelet count in blood was significantly lower and maximum serum AST level was significantly higher in the poor outcome group ($p = .011$ and $p = .012$, respectively).

CSF analyses were performed in 72% of patients during hospitalization; 44% had a normal cell count ($< 5/\text{mm}^3$), 52% had a CSF protein level > 40 mg/dl, and 8.7% had a CSF/plasma glucose ratio < 0.4. Frequencies of normal cell count, elevated CSF protein level, and decreased CSF/plasma glucose ratio were not different between the two outcome groups.

Brain computed tomography (CT) was performed in 91% of patients and revealed abnormalities in 23.1%. Loss of gray and white matter differentiation ($n = 5$), effacement of cortical sulci ($n = 3$), brain edema ($n = 1$), and low density in localized area ($n = 1$) were noted. Brain magnetic resonance imaging (MRI) was performed in 72% of patients and revealed abnormalities in 45.2%. Lesions with T2-prolongation ($n = 13$), lesions with restricted diffusion ($n = 6$), and lesions with T1-prolongation ($n = 1$) were noted. Gadolinium contrast imaging was studied in six patients and revealed enhanced lesions in one patient. Frequencies of detection of abnormal lesions using CT and MRI were not different between the two outcome groups. Electroencephalogram (EEG) was performed in 53% of patients and revealed abnormalities in 86.4%. Abnormal background activity on EEG ($n = 17$), diffuse high amplitude slow wave ($n = 7$), paroxysmal activity ($n = 4$), and spike and wave complex ($n = 2$) were noted. No patient had periodic lateralized epileptiform discharges. Frequencies of detection of abnormality in EEG were not different between the two outcome groups.

Table 2
Characteristics of study patients.

	Good outcome group (GOS 5)	Poor outcome group (GOS 1–4)	p
	n = 26	n = 15	
Male	54%	44%	0.52
Age (years)	51 (16–90)	69 (17–87)	0.14
Duration of hospitalization (days)	11(2–95)	33 (2–136)	0.002*
Fever	58%	40%	0.34
Diarrhea	13%	9%	1.00
Use of anti-influenza antiviral drugs	43%	50%	0.75
Use of antipyretics	33%	42%	0.71
History			
Hypertension	15%	33%	0.25
Diabetes	4%	27%	0.051
Allergic diseases	8%	0%	0.52
Autoimmune diseases	4%	0%	1.00
Neurological disorders	12%	13%	1.00
Mental disorders	8%	13%	0.62
Epilepsy	4%	0%	1.00
Convulsion	12%	0%	0.29
Height (cm)	162 (140–176)	155 (147–170)	0.62
Weight (kg)	58.0 (33.5–110)	60.0 (33–73.8)	0.84
Body temperature (°C)	38.5 (35.2–41.6)	38.8 (34.7–39.7)	0.88
Systolic blood pressure (mmHg)	126 (71–203)	138 (89–208)	0.47
Diastolic blood pressure (mmHg)	70 (40–100)	75 (47–126)	0.64
Pulse rate (/min)	104 (64–148)	102 (58–190)	0.96
Respiratory rate (/min)	21 (15–44)	30 (18–35)	0.90

GOS = Glasgow outcome scale. The GOS reflects better outcome with a higher score (1–5): GOS 5, good recovery, resumption of normal life despite minor deficits; GOS 4, moderate disability, able to work in a sheltered environment and travel by public transportation; GOS 3, severe disability, dependent for daily support by reason of disability; GOS 2, persistent vegetative state; and GOS 1, death.

Continuous variables are expressed as median (minimum–maximum). Categorical variables are expressed as percentage. The p value of continuous variables was calculated using the Mann-Whitney U test. The p value of categorical variables was calculated using Fisher's exact test.

* p < .05.

3.5. Treatment

On admission, anti-influenza antiviral drugs were administered to 91% of patients. As for supporting therapeutics, corticosteroids were administered to 72% of patients; 90% received pulse corticosteroid therapy with methylprednisolone, 21% of patients received high-dose intravenous gamma-globulin, and 9.3% of patients received blood purification therapy. Seven percent of patients received therapeutic hypothermia, 2.3% of patients received high-dose antithrombin III, and 4.7% of patients received edaravone. No significant difference was revealed between these supporting therapeutics and the two outcome groups. Patients who received corticosteroids tapered after pulse corticosteroid therapy were significantly more frequent in the poor

Table 3
Relation between GCS score and outcome groups.

GCS		3	4	5	6	7	8	9	10	11	12	13	14	15	p
Good outcome group (GOS 5)	n = 23	2	0	0	1	1	2	1	1	2	2	2	6	3	0.038*
Poor outcome group (GOS 1–4)	n = 8	1	1	0	2	0	1	0	0	1	1	1	0	0	

GCS = Glasgow coma scale; GOS = Glasgow outcome scale. The GOS reflects better outcome with a higher score (1–5): GOS 5, good recovery, resumption of normal life despite minor deficits; GOS 4, moderate disability, able to work in a sheltered environment and travel by public transportation; GOS 3, severe disability, dependent for daily support by reason of disability; GOS 2, persistent vegetative state; and GOS 1, death.

The p value was calculated using the Mann-Whitney U test.

* p < .05.

outcome group than the good outcome group (44% vs 5%, p = .026, Table 5).

Approximately 21% of patients required mechanical ventilation, which was initiated within 1–2 days of hospitalization. The duration of mechanical ventilation ranged from 2 to 334 days. Requirement of mechanical ventilation was more frequent in the poor outcome group than the good outcome group (47% vs 8%, p = .006). The duration of mechanical ventilation was not significantly different between the two outcome groups. Additionally, 14% of patients required treatments for shock; however, no significant difference was observed between the two outcome groups.

During hospitalization, antipyretics were administered to 42% of patients. Approximately 94% of patients received acetaminophen. Anticonvulsants were administered to 46.5% of patients. Frequency of use of antipyretics and anticonvulsants was not significantly different between the two outcome groups. Antibiotics for accompanying pneumonia, bacteremia, suspicion of bacterial infection, or prevention of bacterial infection were administered to 53.5% of patients. Use of antibiotics was significantly more frequent in the poor outcome group than the good outcome group (79% vs 42%, p = .046).

3.6. Clinical course

Highest body temperature during hospitalization ranged from 36.7 °C to 41.6 °C and 2.4% of patients experienced a body temperature of > 41.0 °C. Symptoms suggestive of disseminated intravascular coagulation (DIC) were observed in 18.6% of patients. Frequency of DIC symptoms was not significantly different between the two outcome groups. Acme phase ranged from 1 to 43 hospital days and was significantly longer in the poor outcome group than the good outcome group [median 10.5 days (2–17 days) vs median 3 days (1–43 days), p = .0001]. At the time of hospital discharge, 69.8% of patients returned home.

3.7. Assessment of confounding factors that influenced the outcome of influenza-associated acute encephalopathy

Stepwise multiple logistic regression analysis using the method of maximum likelihood to assess the effect of confounding factors in the poor outcome group detected plasma glucose level and BUN level on admission as useful factors to make a good regression formula. Plasma glucose level was indicated as a significant predictor of poor outcome [odds ratio (OR) = 1.034 (95% confidence interval (CI): 1.006–1.062), p = .018]. BUN was not significant [OR = 1.144 (95% CI: 0.981–1.335)]. However, GCS scores on admission, duration of hospitalization, minimum platelet count, experienced serum AST level > 100 IU/l during hospitalization, requirement of mechanical ventilation, use of antibiotics, and duration of acme phase were not taken into account in this stepwise multiple logistic regression analysis. Multiple logistic regression analysis with corticosteroids tapered after pulse corticosteroid therapy, plasma glucose level, and BUN level as independent variables also indicated corticosteroids tapered after pulse

Table 4
Relation between Laboratory Findings and Outcome.

	Good outcome group (GOS 5)	Poor outcome group (GOS 1–4)	p
	n = 26	n = 15	
On admission			
Proteinuria (≥ 2+)	27%	38%	0.69
Hematuria (≥ 2+)	40%	38%	1.00
Hemoglobin (g/dl)	14.5 (10.6–18.5)	13.1 (9.5–18.8)	0.19
> 14	60%	23%	0.33
White blood cell count (1000/mm ³)	8.8 (2.4–31.5)	8.7 (1.1–13.2)	0.42
Platelet count (1000/mm ³)	193 (77–340)	153 (56–308)	0.086
< 100,000 (/mm ³)	4%	13%	0.55
C-reactive protein (mg/dl)	14.2 (0.1–18.6)	1.28 (0.2–28.4)	0.88
AST (IU/l)	47 (19–111)	58 (20–894)	0.33
≥ 100	8%	40%	0.036*
ALT (IU/l)	29 (7–175)	31 (7–131)	0.39
LDH (IU/l)	301 (148–551)	313 (195–1646)	0.29
ALP (IU/l)	245 (121–482)	298 (142–503)	0.46
gamma GTP (IU/l)	31 (5–395)	37 (6–113)	0.82
CPK (IU/l)	254 (22–2510)	165 (16–4565)	0.52
≥ 1000	26%	8%	0.38
TP (g/dl)	7.0 (5.3–8.9)	6.9 (5.2–8.4)	0.27
BUN (mg/dl)	12.6 (5.4–34.1)	19.1 (9.0–72.7)	0.033*
≥ 30	4%	40%	0.007*
Creatinine (mg/dl)	0.75 (0.5–3.1)	1.28 (0.3–7.7)	0.21
Ammonia (μg/dl)	52.5 (16–92)	68 (40–359)	0.10
Glucose (mg/dl)	105.5 (58–208)	181 (88–291)	0.002*
≥ 150	8%	54%	0.004*
Hemoglobin A1c (%)	5.5 (5.1–6.5)	6.35 (5.2–9.3)	0.06
Prothrombin activity (%)	90.5 (46.7–115.0)	73.0 (13.5–119.4)	0.32
D-dimer (μg/ml)	1.75 (0.20–7.40)	1.60 (0.50–5.00)	0.85
≥ 5.0	80%	80%	1.00
During hospitalization			
Minimum platelet (1000/mm ³)	190 (34–252)	100 (26–225)	0.011*
< 100,000	42%	70%	0.15
Maximum serum AST (IU/l)	52 (19–2224)	251 (23–12,644)	0.012*
≥ 100	22%	69%	0.006*
Maximum serum CPK (IU/l)	546.5 (27–7432)	1019 (120–30,537)	0.29
≥ 1000	39%	46%	0.74
CSF analysis			
Cell count (/mm ³)	9 (1–533)	4 (1–103)	0.90
Polymorphonuclear cell count (/mm ³)	0 (0–122)	1 (0–52)	0.87
Protein (mg/dl)	39 (15–120)	53.5 (31–98)	0.19
Glucose (mg/dl)	69 (31–152)	84.5 (62–174)	0.10
Serum:CSF glucose ratio	0.61 (0.38–0.83)	0.52 (0.44–0.93)	0.69

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; CSF = cerebrospinal fluid; gamma GTP = gamma glutamyl transpeptidase; GOS = Glasgow outcome scale. The GOS reflects better outcome with a higher score (1–5): GOS 5, good recovery, resumption of normal life despite minor deficits; GOS 4, moderate disability, able to work in a sheltered environment and travel by public transportation; GOS 3, severe disability, dependent for daily support by reason of disability; GOS 2, persistent vegetative state; and GOS 1, death.

Continuous variables are expressed as median (minimum–maximum). Categorical variables are expressed as percentage. The p value of continuous variables was calculated using the Mann-Whitney U test. The p value of categorical variables was calculated using Fisher's exact test.

* p < .05.

corticosteroid therapy as an independent risk factor that influenced IAE outcome [OR = 31.5 (95% CI: 1.143–865.7), p = .041, Table 6].

4. Discussion

IAE is characterized by sudden onset of coma and seizure a few days after development of high-grade fever. Morishima et al. conducted the first national survey of IAE in Japan and described that 148 IAE patients were reported during the 1998/99 influenza season and about 6% of patients were aged older than 16 years [4]. Okuno et al. studied the IAE

Table 5
Relation between supporting therapeutics and outcome.

	Good outcome group (GOS 5)	Poor outcome group (GOS 1–4)	p
	n = 26	n = 15	
Corticosteroids	21 (81%)	10 (67%)	0.45
Pulse corticosteroid therapy with methylprednisolone	19 (90%)	9 (90%)	1.00
Corticosteroids tapered after pulse corticosteroid therapy	1 (5%)	4 (44%)	0.026*
High-dose intravenous gamma-globulin therapy	5 (19%)	4 (27%)	0.70
Blood purification therapy	2 (8%)	2 (13%)	0.62
Hypothermia	3 (12%)	0 (0%)	0.29
High-dose antithrombin III	1 (4%)	0 (0%)	1.00
Edaravone	1 (4%)	1 (7%)	1.00

GOS = Glasgow outcome scale. The GOS reflects better outcome with a higher score (1–5): GOS 5, good recovery, resumption of normal life despite minor deficits; GOS 4, moderate disability, able to work in a sheltered environment and travel by public transportation; GOS 3, severe disability, dependent for daily support by reason of disability; GOS 2, persistent vegetative state; and GOS 1, death.

Categorical variables are expressed as number (percentage). The p value was calculated using Fisher's exact test.

* p < .05.

reports collected by the National Epidemiological Surveillance of Infectious Disease (NESID) database in Japan from 2010 through 2015 influenza seasons and estimated mean annual incidences of IAE among children and adults were 2.83 and 0.19/1000,000 population, respectively [8]. In this study, estimated annual incidence of IAE among adults in Japan was 0.98/1000,000 population. Our first questionnaire on the incidence of IAE patients was sent to all hospitals with ≥ 200 beds in Japan. One potential explanation for the difference between the two estimated IAE incidences among Japanese adults is the surveillance design. NESID received reports of all cases of acute encephalitis or encephalopathy, including IAE, diagnosed by clinicians, whereas we utilized a questionnaire sent to all hospitals with ≥ 200 beds in Japan. To our knowledge, this is the first national survey to investigate the prevalence, clinical features of disease, associated outcomes, and prognostic factors in adult patients with IAE.

In pediatric patients with IAE, consciousness disturbance, convulsion, abnormal behavior, upper respiratory symptoms, vomiting, diarrhea, headache, and fatigue were described as major clinical signs. Low platelet counts, liver dysfunction with elevation of serum transaminase levels and prolonged coagulation time, elevated creatine phosphokinase level, and abnormal brain CT and EEG findings were frequently observed [4]. These characteristics of pediatric IAE are commonly observed in adult IAE.

Though the pathogenesis of IAE remains unclear, a hyperactive cytokine response is thought to be responsible [4,21]. Serum and CSF levels of interleukin (IL)-6, tumor necrosis factor (TNF)-α, and soluble TNF receptor 1 were elevated in IAE patients [21,22]. The following pathophysiology of IAE was speculated: (1) direct virus-glia cell interaction or viral stimulation of glial cells induces the production and accumulation of pro-inflammatory cytokines, especially TNF-α, in the CNS. (2) The cytokine storm results in neural cell damage as well as the apoptosis of astrocytes because of TNF-α-induced mitochondrial respiratory failure. (3) The disruption of the blood-brain barrier progresses to the systemic cytokine storm, resulting in DIC and multiple organ failure (MOF) [23]. Peak body temperature > 41 °C, thrombocytopenia, severely elevated levels of transaminase and creatine phosphokinase, hypoglycemia or hyperglycemia, and hematuria or proteinuria were documented as poor prognostic factors in pediatric IAE [24]. In our study, elevated serum AST and BUN levels and hyperglycemia

Table 6
Effects of confounders on outcomes of adult IAE by multiple logistic regression analysis.

	β	SE	χ^2	p	OR	95% CI
Corticosteroids tapered after pulse corticosteroid therapy (received = 1, not received = 0)	3.449	1.691	4.158	0.041*	31.5	1.143–865.7
Plasma glucose level (mg/dl)	0.038	0.020	3.732	0.053	1.04	0.999–1.079
Serum BUN level (mg/dl)	0.127	0.070	3.338	0.068	1.136	0.991–1.301

β = regression coefficient; BUN = blood urea nitrogen; CI = confidence interval; IAE = influenza-associated encephalopathy; OR = odds ratio; SE = standard error. The dichotomous dependent variable was defined as follows: good outcome group [Glasgow outcome scale (GOS) score of 5] = 0, poor outcome group (GOS score of ≤ 4) = 1. The GOS reflects better outcome with a higher score (1–5): GOS 5, good recovery; GOS 4, moderate disability; GOS 3, severe disability; GOS 2, persistent vegetative state; and GOS 1, death.

* $p < .05$.

were detected as poor prognostic factors in adult IAE. These prognostic factors were associated with DIC, MOF, and hemophagocytosis resulting from hypercytokinemia induced by IAE. In our study, plasma glucose level was detected as an independent predictor of poor outcome. IL-6 also leads to increased cortisol levels, followed by a pronounced dose-dependent increase in plasma glucose [25,26]. Thus, systemic hypercytokinemia in IAE causes hyperglycemia and the plasma glucose level could reflect the degree of pathogenicity [24].

The management of IAE is mainly supportive and no randomized trial of specific therapies has been performed. In this study, 91% of IAE patients received anti-influenza antiviral drugs on admission. Anti-influenza antiviral drugs reduce expansion of influenza virus infection of the respiratory tract and have been used in IAE patients, although it remains unclear whether anti-influenza antiviral drugs contribute to the recovery of the patients [27]. Most physicians consider early steroid treatment to be beneficial because reduction of systemic hyperactive cytokine responses could improve the pathophysiology of IAE. Approximately 72% of our IAE patients received corticosteroids and 90% of them received pulse corticosteroid therapy with methylprednisolone. Surprisingly, our investigation implied corticosteroids tapered after pulse corticosteroid therapy might influence the prognosis of IAE patients. This result implied that the use of short-term, high-dose corticosteroid, including pulse corticosteroid therapy with methylprednisolone, at an early stage of IAE may be beneficial.

There are limitations associated with the present study. Especially, this survey could not assess fetal IAE cases. In addition, information about deceased patients could not be assessed because of refusal of the next of kin to participate. Moreover, patients who declined to complete the survey may have had severe symptoms or disease complications.

In conclusion, our nationwide survey provided data for the annual incidence and clinical features of IAE in Japanese adults. Hyperglycemia was detected as an independent predictor of poor prognosis and thought to be related to systemic hypercytokinemia in IAE.

Most patients received anti-influenza antiviral drugs and therapeutics against hypercytokinemia, and > 60% of adult IAE patients in Japan had good outcomes with GOS 5. Further investigation is needed to better understand the pathophysiology and development of effective management for IAE, especially in adults.

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Potential conflicts of interest

All authors report no potential conflicts.

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