MAJOR ARTICLE

Encephalitis and Encephalopathy Associated with an Influenza Epidemic in Japan

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During the winter of 1998–1999, there was an outbreak of encephalitis/encephalopathy in Japan that appeared to be associated with influenza. We conducted a national survey of the prevalence and clinical features of disease and the associated outcomes and prognostic factors related to this outbreak. A total of 202 cases were analyzed, of which 148 were diagnosed as influenza-associated encephalitis/encephalopathy on the basis of virologic analysis. Of the 148 cases studied, 130 (87.8%) were type A influenza and 17 were type B. Encephalitis/encephalopathy developed mainly in children age <5 years, either on the day that influenza signs appeared or on the next day. The major signs included altered consciousness or loss of consciousness, convulsions, cough, and vomiting. In many patients, multiple-organ failure developed, and rates of mortality (31.8%) and disability (27.7%) were high. Thrombocytopenia and severely elevated transaminase levels were factors associated with a poor prognosis. Thus, influenza-associated encephalitis/encephalopathy progressed rapidly and was associated with poor outcomes.

Encephalitis lethargica is a lethal, epidemic brain infection that was first described by Flexner [1]. An epidemic of CNS infections raged between 1918 and 1930, coinciding with the influenza pandemic, the so-called "Spanish flu" [2, 3]. Despite intensive investigation, the relationship between influenza and epidemic encephalitis remains unclear [1–5]. Some CNS diseases have been reported to accompany influenza infection, including Reye syndrome, influenza-associated encephalitis/encephalopathy, myelitis, and acute necrotizing encephalitis. Reye syndrome, which involves acute encephalopathy and fatty degeneration in the liver, often follows viral infection and salicylate therapy [6–8]. In addition to cases of Reye syndrome, many investigators have described cases of influenza-associated encephalitis/encephalopathy [9–12]. However, the clinical features of this disease have not yet been clarified.

Recently, the number of reports of encephalitis/encephalopathy associated with influenza has increased in Japan, especially reports of cases in children aged <5 years. During the winters of 1997–1998 and 1998–1999, when an epidemic of type A influenza (H3N2) occurred, many pediatricians reported cases of influenza-associated encephalitis/encephalopathy [13–17]. The abrupt onset of seizure and coma a few days after development of high-grade fever is a prominent indicator of CNS involvement during influenza infection. Therefore, we conducted a national survey to investigate the various parameters of the disease outbreak (prevalence and clinical features of disease and associated outcomes and prognostic factors) that occurred in Japan during the winter of 1998–1999.

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MATERIALS AND METHODS

Data collection. Questionnaires were developed by the Collaborative Study Group on Influenza-Associated Encephalopathy, which was organized by the Japanese Ministry of Health, Labor, and Welfare. The study was done as a cross-sectional survey of cases of influenza treated at all medical facilities. In July 1999, every local health care center in Japan received a questionnaire that asked for the number of cases of influenza-associated encephalitis/encephalopathy in all hospitals, clinics, and local pediatric practices within their jurisdiction. In addition to virus isolation, the sudden onset of high fever with respiratory signs, myalgia, and headache were used as diagnostic markers. A total of 217 cases were reported in returns of the primary questionnaires [16]. Subsequently, a second questionnaire that sought data on matched cases and detailed clinical and laboratory data was sent to each hospital. A total of 202 cases (corresponding to an effective answer rate of 93%) were reported and deemed appropriate for further study.

Case definition. The diagnosis of encephalitis/encephalopathy was made on the basis of all clinical signs. All patients had altered consciousness or loss of consciousness. Patients with meningitis, myelitis, and febrile convulsions without prolonged unconsciousness were excluded. Postictal unconsciousness with prompt recovery was classified as febrile convulsion.

Influenza infection was defined on the basis of either (1) a positive result of a viral culture, a viral antigen test, or viral RNA PCR or (2) by significant increases in hemagglutination inhibition–test titers (table 1). Specimens from throat swabs were used for viral culture, viral antigen testing, and viral RNA PCR. Viral antigens were detected by ELISA (Directigen fluA; Becton Dickinson). Viral RNA was detected by reverse-transcriptase (RT) PCR [18]. When virus was isolated, the subtype was determined by means of a hemagglutination inhibition test that used antisera to current antigens. For other patients, the virus subtype was determined by the detection of subtype-specific antibodies.

Patients with doubtful cases were excluded from further analysis (54 patients). Overall, 148 patients with cases defined as influenza-associated encephalitis/encephalopathy were enrolled in this study. The outcomes of influenza-associated encephalitis/encephalopathy were defined as the following: (1) normal resolution, (2) mild sequelae, (3) severe sequelae that require personal help for daily life activities, and (4) death.

Statistical analysis. Statistical analysis was done by use of Dr. SPSS, version 8.0J, for Windows (SPSS Japan).

RESULTS

Epidemiology. During the winter of 1998–1999, a large influenza epidemic occurred in Japan that was associated with many reports of acute encephalitis and encephalopathy. During this epidemic, millions of patients had "the flu," and the number of associated deaths was estimated to be 22.65 deaths per 100,000 persons [19]. The unforeseen CNS disease that occurred during the influenza epidemic attracted a great deal of attention.

Table 1. Methods used to confirm influenza infection and infecting influenza virus types in 148 patients with influenza-associated encephalitis/encephalopathy.

	No. of patients, by infecting influenza virus type		
Method	Type A	Type B	Unclassified
Viral culture	86	8	0
Antigen detection	7	0	0
RT-PCR	0	0	1
Serologic testing[a]	37	9	0
Total	130	17	1

NOTE. RT-PCR, reverse-transcriptase PCR.

[a] A serologic test result positive for influenza infection was defined as one for which hemagglutination inhibition–test titers were significantly elevated.

Influenza-associated encephalitis/encephalopathy was diagnosed in 148 patients (78 male and 70 female patients). Of these 148 patients, 121 (81.8%) were aged <5 years, with a peak incidence among those aged 1 year (figure 1). On the other hand, the disease was rare in patients aged >10 years. Of the 148 patients, 125 (84.5%) had no underlying disease, which indicates that most of the patients were otherwise healthy.

The influenza virus type was determined in 147 cases: 130 patients were infected with influenza A, and 17 patients were infected with influenza B (table 1). All cases of influenza A infection in which the subtype could be determined were due to type H3N2. The genetic analysis showed that most type A isolates were A/Sydney/5/97-like. The incidence of encephalitis/encephalopathy increased to a peak of type A (H3N2) infection approximately during the third week of 1999 and gradually decreased thereafter. Subsequently, another peak of type B infection occurred during the eighth week of 1999. According to the information from the National Institute of Infectious Diseases, Japan, the influenza subtypes recovered from patients aged <15 years during this second season were 2626 type A (H3N2) (from 42.8% of patients) and 3506 type B isolates (from 57.2% of patients). On the other hand, the influenza virus type recovered from most patients with encephalitis/encephalopathy was type A (87.8% of patients). Our data indicate that type A influenza (H3N2) was significantly associated with encephalitis/encephalopathy ($P < .0001$; χ^2 test). There were no regional differences in the incidence of disease. The main routes of virus transmission were between family members (43.9% of

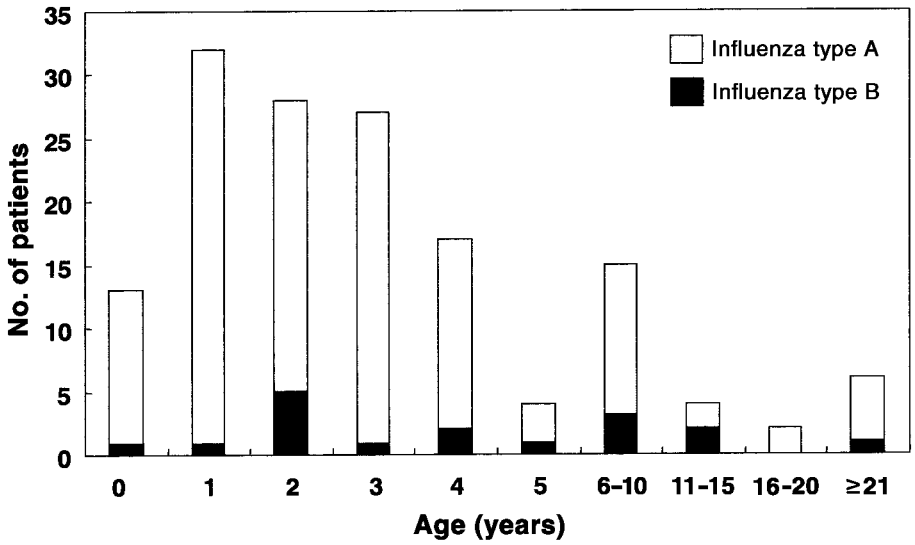

Figure 1. Age distribution of patients with influenza-associated encephalitis/encephalopathy associated with an influenza epidemic in Japan during the winter of 1998–1999.

cases) and within elementary schools and nursery schools (20.9% of cases).

Clinical features. The major clinical signs reported were loss of consciousness, convulsions, cough, and vomiting (table 2). Approximately one-third of the patients had convulsions or coma on the day of the onset of fever. Overall, 79.8% of patients developed CNS diseases either on the day that influenza signs appeared or on the next day. Of the 147 patients for whom outcomes were noted, 31.8% died and 27.7% experienced disability (8.8% had severe sequelae and 18.9% had mild sequelae). Approximately 40% of the fatalities were due to rapidly progressing multiple-organ failure that occurred ⩽2 days after the development of neurological signs. None of the patients showed any signs that suggested other microbial infections, such as measles, rubella, mumps, exanthem subitum, infectious mononucleosis, or enterovirus infection. Aspirin was administered to only 2 patients, 1 of whom had a history of Kawasaki disease. Ibuprofen was administered to 2 patients, diclofenac sodium to 18, mephenamate to 6, and acetaminophen to 58. None of the patients had received influenza vaccinations before the season.

Laboratory findings. We frequently observed decreased platelet counts, liver dysfunction with elevation of serum levels of transaminases and lactate dehydrogenase (LDH), and prolonged coagulation time. On the other hand, hypoglycemia (blood glucose level, <60 mg/dL) was observed in only 6 patients (4.0%). Hyperammonemia (ammonia level, >100 μg/dL) was observed in 15 patients (10.1%). CSF analyses showed that 134 of the patients had normal cell counts. We categorized influenza-associated CNS diseases into 3 types on the basis of laboratory findings (table 3): (1) encephalitis with increased CSF WBC counts (>8 cells/μL); (2) Reye syndrome–like condition, with normal cell counts, hypoglycemia (glucose level, <60 mg/dl), and increased serum transaminase levels; and (3) all other conditions. Patients with encephalitis were older, and had later onset of neurological signs than did the other patients, although these differences were not statistically significant ($P = .16$ and $P = .74$, respectively; Kruskal-Wallis test). Patients with a Reye syndrome–like condition showed a trend toward worse prognosis than patients in the other 2 categories ($P = .08$; Pearson's χ^2 test). The patients in the category "other" made up 86% of all patients and seemed to comprise those who had influenza-associated CNS diseases during the 1998–1999 season.

It is noteworthy that blood abnormalities correlated with disease outcome. The platelet count correlated with the out-

Table 2. Major clinical signs of influenza-associated encephalitis/encephalopathy in 148 patients.

Clinical sign(s)	No. (%) of patients
Altered or loss of consciousness	148 (100.0)
Convulsions	119 (80.4)
Cough	53 (35.8)
Vomiting	37 (25.0)
Diarrhea	19 (12.8)
Nasal discharge	27 (18.2)
Headache	13 (8.8)
Fatigue	9 (6.1)
Sore throat	9 (6.1)
Hallucinations or abnormal behavior	6 (4.0)
Motor paralysis or sensory loss	4 (2.7)

Table 3. Comparison of the characteristics of 148 patients with influenza-associated encephalitis/encephalopathy, according to 3 clinical categories of disease.

Clinical condition	No. of patients	Age, mean years	Neurological onset[a]	Influenza virus type, no. of patients		Outcome, no. (%) of patients			
				A	B	Normal resolution	Mild sequelae	Severe sequelae	Death
Encephalitis	14	12.6	5.6	12	2	3 (21.4)	5 (35.7)	1 (7.1)	5 (35.7)
Reye syndrome–like	6	2.8	1.5	6	0	1 (16.7)	0 (0.0)	1 (16.7)	4 (66.7)
Other	128	3.6	1.2	112	15	55 (43.0)	23 (18.0)	11 (8.6)	38 (29.7)

[a] Time of onset of neurological symptoms is mean no. of days after the onset of high-grade fever.

come of influenza-associated encephalitis/encephalopathy. Of the patients with thrombocytopenia (<50,000 platelets/μL), 82.8% died, whereas, of the patients with normal platelet counts ($\geqslant$150,000 platelets/μL), only 6.7% died (table 4).

Similarly, a severely elevated serum aspartate aminotransferase level (>1000 IU/L) was associated with poor outcome (mortality rate, 74.2%; table 5). Elevated serum levels of alanine aminotransferase, LDH, and creatine phosphokinase, as well as prolonged coagulation test times, were also linked to unfavorable outcomes (data not shown). These trends were also observed when the patients with encephalitis and Reye syndrome–like condition were excluded.

For 86% of patients, electroencephalogram findings were abnormal. Brain CT revealed abnormalities in 66% of patients. The most frequent findings, seen in 20% of patients, were brain edema and low densities in localized areas, such as in the thalamus, brain stem, and parenchyma. Acute necrotizing encephalopathy, which is characterized by multifocal, symmetric brain lesions that affect the thalami bilaterally, was recently proposed to be one of the features of influenza-associated encephalitis/encephalopathy [20, 21]. The characteristic radiological finding of acute necrotizing encephalopathy was noted for ~10% of the patients we studied.

Autopsies were performed in some cases, and 4 autopsy reports are currently available. Brain, lung, bronchus, spleen, liver, kidney, heart, bone marrow, and lymph nodes were examined. In these 4 patients, the main finding was massive brain edema without inflammatory cell infiltration. Immunostaining with use of a monoclonal antibody against the influenza nucleoprotein was performed, but influenza antigens were not detected in the brain, including areas such as the cerebrum, hippocampus, cerebellum, brain stem, basal ganglia, and thalamus. In blood vessels, including those outside the brain, microemboli and hyalinization of the small vessels were observed. Plasma influxes from vessels to the visceral parenchyma were found in 3 patients. In 2 patients, hemophagocytosis was observed, which suggests the activation of macrophages by hypercytokinemia.

In 18 patients, we attempted to detect influenza RNA in CSF specimens by use of RT-PCR, but specimens from only 3 patients yielded positive results. Detection of the herpes simplex virus by PCR was attempted for 20 patients, but no virus DNA was detected. Virus isolation from CSF specimens was attempted for 21 patients, but all samples were negative for other viruses. In the present study, patients were not assessed for the infection with human herpesvirus 6 and human herpesvirus 7, which were recently shown to be detectable in CSF from patients with influenza encephalopathy [22].

DISCUSSION

During the winter of 1998–1999, when Sydney-type H3N2 influenza was pandemic, there was an outbreak of encephalitis/encephalopathy in Japan. During the same period, cases of meningitis associated with influenza were reported in the United Kingdom [23]. We conducted a national survey that included all hospitals and pediatric clinics and analyzed 148 cases of influenza-associated encephalitis/encephalopathy. To

Table 4. Association between platelet count and prognosis for 148 patients with influenza-associated encephalitis/encephalopathy.

Platelet count, cells/μL	No. (%) patients, by outcome				
	Normal resolution	Mild sequelae	Severe sequelae	Death	Total
$<5 \times 10^4$	2 (6.9)	2 (6.9)	1 (3.4)	24 (82.8)	29 (100)
$\geqslant 5 \times 10^4$ and $<10 \times 10^4$	8 (28.6)	3 (10.7)	5 (17.9)	12 (42.9)	28 (100)
$\geqslant 10 \times 10^4$ and $<15 \times 10^4$	15 (68.2)	6 (27.3)	0 (0.0)	1 (4.5)	22 (100)
$\geqslant 15 \times 10^4$	33 (55.0)	16 (26.7)	7 (11.7)	4 (6.7)	60 (100)

Table 5. Association between serum aspartate aminotransferase (AST) level and prognosis for 148 patients with influenza-associated encephalitis/encephalopathy.

	No. (%) of patients, by outcome				
Serum AST level, IU/L	Normal resolution	Mild sequelae	Severe sequelae	Death	Total
>1000	3 (9.4)	2 (6.5)	3 (9.7)	23 (74.2)	31 (100)
>500 and ⩽1000	5 (45.5)	0 (0.0)	0 (0.0)	6 (54.5)	11 (100)
⩾100 and ⩽500	15 (36.6)	12 (29.3)	3 (7.3)	11 (26.8)	41 (100)
<100	34 (55.7)	14 (23.0)	7 (11.5)	6 (9.8)	61 (100)

the best of our knowledge, this is the first nationwide clinical survey of influenza-associated encephalitis/encephalopathy. We found that the disease developed mainly in children aged <5 years, with onset either on the day that influenza signs appeared or on the next day. Patients often developed multiple-organ failure and either died or suffered severe disability. Thrombocytopenia and severely elevated levels of transaminases were factors associated with a poor prognosis.

Reye syndrome, which is closely associated with the administration of aspirin, is one of the best-known encephalopathies associated with epidemics of influenza [6–8]. There are several differences between Reye syndrome and the cases of influenza-associated encephalitis/encephalopathy seen in the present study. First, classical Reye syndrome is usually associated with type B influenza [24]. Second, only a small percentage of our patients had hypoglycemia and/or hyperammonemia, which are characteristic of classical Reye syndrome. Third, aspirin was administered to only 2 of our patients. However, it should be noted that some nonsalicylate antipyretic drugs—for example, diclofenac sodium and mephenamate—might be associated with the development of influenza-associated encephalitis/encephalopathy or affect the severity of the disease. Case-control studies are currently under way to clarify the relationship between these drugs and influenza-associated CNS diseases.

The pathogenesis of influenza-associated encephalitis/encephalopathy is unclear. Whether the influenza virus invades the brain parenchyma is still a controversial issue. Fujimoto et al. [13] reported that viral RNA was frequently detected in the CSF by RT-PCR. However, recent reports have indicated that viral RNA is not detected in the CSF of most patients with influenza-associated encephalitis/encephalopathy [18, 25]. In the present study, only a small number of patients had CSF samples that tested positive for viral RNA. Findings of pathologic examination, including the lack of detectable viral antigen in brain tissues, also have suggested that direct viral invasion and inflammation are unlikely to be the causes of this disease. Disease progression appears to be too rapid for the virus to invade the CNS directly and to replicate in CNS tissue, causing brain damage. The observed absence of viral antigen in affected tissues and the rapid progression of disease differentiate this disease from herpes simplex encephalitis, which is caused by direct invasion by and cytopathic effects of herpes simplex virus [26, 27].

In influenza-associated encephalitis/encephalopathy, elevated concentrations of several cytokines, such as soluble TNF receptor–1, IL-1β, and IL-6, have been observed in serum and CSF [18, 28]. Elevated levels of serum transaminases and LDH, vascular damage throughout the body, and the rapid progression to multiple-organ failure suggest that hypercytokinemia and injury to blood vessels or vascular endothelia may play important roles in the pathogenesis of influenza-associated encephalitis/encephalopathy [29]. These characteristics are often seen in virus-associated hemophagocytic syndrome or systemic inflammatory response syndrome. Kawasaki disease, which is characterized by systemic inflammatory responses or vascular injury, is often seen in Japan. Japanese people might have genetic backgrounds that facilitate the development of systemic inflammatory responses or hypercytokinemia; they might, therefore, have a tendency to develop influenza-associated encephalitis/encephalopathy. These speculations may explain why epidemic encephalitis was not seen throughout the world during the pandemic of influenza A (H3N2). Another possibility is that the virus strain that spread in Japan might have been more virulent with respect to the CNS or might have been prone to induce systemic inflammation. Further investigation into the molecular pathogenesis and epidemiology of this disease is necessary to better our understanding and to enable the development of effective strategies to manage outbreaks.

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