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Original Article

Epidemiology of Pediatric Acute Encephalitis/Encephalopathy in Japan

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We studied the etiology of pediatric acute encephalitis/encephalopathy (pAEE) using epidemiological data obtained from a nationwide survey in Japan. Two-step questionnaires were sent to the pediatric departments of hospitals throughout the country in 2007, querying the number of the cases during 2005-2006 as the first step, and asking for the details of clinical information as the second step. In all, 636 children with pAEE (age ≤ 15 years) were enrolled. For the known etiology of pAEE (63.5% of the total cases), 26 microbes and 2 clinical entities were listed, but the etiology of 36.5% remained unknown. Influenza virus (26.7%), exanthem subitum (12.3%), and rotavirus (4.1%) were the most common, and the incidence of pAEE peaked at the age of 1 year. This trend was common among all etiologies. Among the neurological symptoms observed at the onset of pAEE, seizures were observed more often in patients aged ≤ 3 years, although abnormal speech and behavior were also common in older children. Undesirable outcomes (death and neurological sequelae) occurred at high rates in patients with any known etiology other than mycoplasma. In conclusion, these findings provide comprehensive insight into pAEE in Japan.

Key words: childhood, encephalitis, encephalopathy, etiology, Japan, pAEE

Pediatric acute encephalitis/encephalopathy (pAEE) is defined as a condition with an acute onset of impaired consciousness following an infection in childhood. During the winter of 1998-1999, an outbreak of pAEE associated with influenza occurred in Japan. After that outbreak, we conducted a national survey of the prevalence and clinical features of pAEE and the associated outcomes and prognostic factors [1]. In all, 202 cases were analyzed, of which 148 were diagnosed as having influenza-associated pAEE based on virological evidence. Influenza-associated pAEE developed mainly in children aged ≤ 5 years, either on the day that influenza signs appeared or on the following day. Major signs included impaired consciousness, convulsions, cough, and vomiting. In many patients, multiple-organ failure developed. The rates of mortality (31.8%) and disability (27.7%) were high.

Since that time, pAEE has become widely recognized, arousing the attention of pediatricians worldwide because influenza-associated pAEE strongly affects children's health management. Although various microbial pathogens other than influenza virus have been reported as causative agents of pAEE [2], the epi-

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demiological data for pAEE in Japan remain limited [3]. Therefore, we conducted the next nationwide survey by sending questionnaires to pediatric departments throughout Japan in 2007. We analyzed the epidemiological data of 2005-2006 with an emphasis on pAEE etiology.

Patients and Methods

Nationwide survey of pAEE cases during 2005-2006. A nationwide survey of pAEE was conducted at the beginning of 2007 by the Department of Pediatrics of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan with financial support from the Japanese Ministry of Health, Labour and Welfare. Two-step questionnaires were used to determine the number of cases and clinical features of pAEE over a 2-year period between January 2005 and December 2006. The first questionnaire was mailed to the chiefs of pediatric departments in hospitals with pediatric wards throughout Japan, querying whether any patient had been hospitalized for pAEE in their hospitals.

In the survey, pAEE was defined as a condition with an acute onset of impaired consciousness following an infection. The second questionnaire, sent later to hospitals that reported pAEE cases, included queries about the following details: the prefecture in which the hospital was located; patient age; sex; onset date; survival and neurological outcome; causative microbiological agent; presence/absence of diagnosis of acute disseminated encephalomyelitis (ADEM); history of vaccination, febrile seizure, epilepsy, and traumatic brain injury; symptoms at onset including seizure, consciousness disturbance, abnormal behavior or speech, and fever; laboratory findings; and imaging and encephalography data.

The microbiological causative agent was defined based on either (1) a positive result of a culture, antigen test, or viral DNA or RNA polymerase chain reaction (PCR) test, or (2) by significant increases in specific antibodies. We included the clinical diagnosis of exanthem subitum (ES)-associated encephalopathy as an exception. Of the 2,848 hospitals that received the first questionnaire, 1,339 (47.0%) responded. The second questionnaire was sent to 354 hospitals. Responses were received from 248 hospitals. In all, 717 pAEE cases were reported, including 70 ADEM cases.

Study population and data analysis. We first excluded all 70 ADEM cases because the pathology and epidemiology of ADEM are well established; it is regarded as a distinct pathological entity [4,5]. We subsequently excluded 11 cases of patients older than 15 years, and we included the remaining 636 patients with pAEE who were aged ≤15 years. We extracted the following patient data: age; sex; survival and neurological outcome; causative microbiological agent; the symptoms at the onset including seizure, consciousness disturbance, abnormal behavior or speech, and fever. The study was approved by the Ethics Committee of the Graduate School of Medicine, Dentistry and Pharmaceutical Sciences of Okayama University, Japan (Ken 1609-016).

Statistics. After conducting a descriptive analysis, we first examined the distributions of neurological symptoms (including consciousness disturbance, seizure, and abnormal speech or behavior) and fever, in all patients and in the patients separated by age group. Earlier reports indicated that nearly half of the cases show the development of pAEE in infancy and toddler years (0-3 years of age) [1,3]. We therefore divided the patients into 2 age groups: 0-3 and 4-15 years of age at the onset of neurological symptoms. We tested the differences in the data of the 2 groups by using chi-squared tests.

We next evaluated the distributions of symptoms separated by causative microbiological agents. Finally, to assess the impact of these microbiological agents on patient prognosis, we assessed the associations using a logistic regression model, adjusting for age (continuous). In the model, we estimated the odds ratios (ORs) of 2 types: first, we estimated the ORs for survival (*i.e.*, death vs. survival) and then we estimated the ORs for severe sequelae (*i.e.*, death or neurological sequelae vs. intact survival). We used a category of "other" causative microbiological agents as a reference in the model to compare the ORs among seven main causes of pAEE. Stata ver. 14 software (Stata Corp., College Station, TX, USA) was used for all analyses. A value of $p < 0.05$ was accepted as significant. We also estimated the 95% confidence intervals (CIs) using logistic regression analysis.

Results

Table 1 summarizes the sex and etiology of the pAEE cases. The male to female ratio was 1.24. In all,

Table 1 Sex and etiology of the pAEE cases ($n = 636$)

		n (%)
Sex		
	Male	350 (55.0)
	Female	283 (44.5)
	Unknown	3 (0.5)
Etiology		
	Influenza virus	170 (26.7)
	Exanthem subitum	78 (12.3)
	Rotavirus	26 (4.1)
	Mycoplasma	23 (3.6)
	Adenovirus	18 (2.8)
	Mumps virus	14 (2.2)
	Herpes simplex virus	13 (2.0)
	Escherichia coli associated with hemolytic-uremic syndrome	8 (1.3)
	Salmonella	6 (0.9)
	Enterovirus	6 (0.9)
	Respiratory syncytial virus	5 (0.8)
	Norovirus	4 (0.6)
	Varicella zoster virus	4 (0.6)
	Measles virus	4 (0.6)
	Epstein-Barr virus	4 (0.6)
	Human metapneumovirus	3 (0.5)
	Streptococcus pyogenes	3 (0.5)
	Sepsis	2 (0.3)
	Pertussis	2 (0.3)
	Haemophilus influenzae	2 (0.3)
	Coxsackievirus	2 (0.3)
	Bartonella	1 (0.2)
	Rubella	1 (0.2)
	Parvovirus	1 (0.2)
	Bacillus cereus	1 (0.2)
	Campylobacter	1 (0.2)
	Echovirus	1 (0.2)
	Cytomegalovirus	1 (0.2)
	Unknown	232 (36.5)

26 causative agents and two clinical entities (ES and sepsis) were defined as the etiology of pAEE. Among the 170 patients with influenza, 86 (50.6%) were reportedly infected with influenza A and 42 (24.7%) with influenza B. Among the 78 patients with a diagnosis of ES, 27 (34.6%) were diagnosed by an increase of specific antibodies to human herpesvirus (HHV)-6; 31 (39.7%) patients were diagnosed by HHV-6 DNA PCR, one patient (1.3%) was diagnosed by HHV-7 DNA PCR, and 19 (24.4%) patients were diagnosed based only on clinical findings.

Fig. 1 portrays the age distribution and association with the etiology of pAEE. A peak of the incidence was found among the patients aged 1 year (Fig. 1A). Regarding the month-age distribution, bimodal peaks were found in the patients aged 0 and those around 12-15 months of age (Fig. 1B). Influenza-associated encephalopathy had a wide age distribution with a peak incidence among patients aged 12 months, ES-associated encephalopathy occurred exclusively in infants, especially those aged around 12 months (Figs. 1A, B). Rotavirus, adenovirus, and mumps virus caused encephalopathy mainly in infants and toddlers, whereas mycoplasma-associated encephalopathy occurred mainly among school-age children (Fig. 1A). Herpes simplex virus (HSV)-associated pAEE constituted a core element of the first peak of incidence at the age of 0 month (Fig. 1B).

Table 2 presents the association between age and neurological symptoms at onset. Seizures were visible significantly more frequent in the younger age group, whereas abnormal speech and behavior were observed significantly less frequently ($p < 0.05$, respectively) than in the older age group. Fever was observed in > 90% of the patients, irrespective of age.

Table 3 presents the association between symptoms and causative pathogens. Although seizures were observed with a high incidence in younger patients (< 3 years) with nearly all causes, HSV-associated pAEE had a lower incidence than pAEE associated with other causes. At older ages (4-15 years), although seizure was a main symptom, abnormal speech and behavior also constituted common symptoms for etiologies including influenza, rotavirus, mycoplasma, adenovirus, and mumps virus.

Of the 636 pAEE patients, 43 (6.8%) died, 565 survived (88.8%), and the survival outcomes of 28 patients were unknown. Although 344 (60.9%) of the 565 patients who survived manifested no neurological sequelae, 215 (38.1%) of them did have neurological sequelae but the medical records of six of them did not include information related to neurological sequelae.

Table 4 presents the association between etiology and outcome of the 602 pAEE patients with known outcomes. The patients with main causes other than mycoplasma had considerably high rates of undesirable outcomes (*e.g.*, death and survival with neurological sequelae). Compared with the pAEE cases with "other" causes, no significantly different probability of undesirable outcome was found among the patients with the seven main causes.

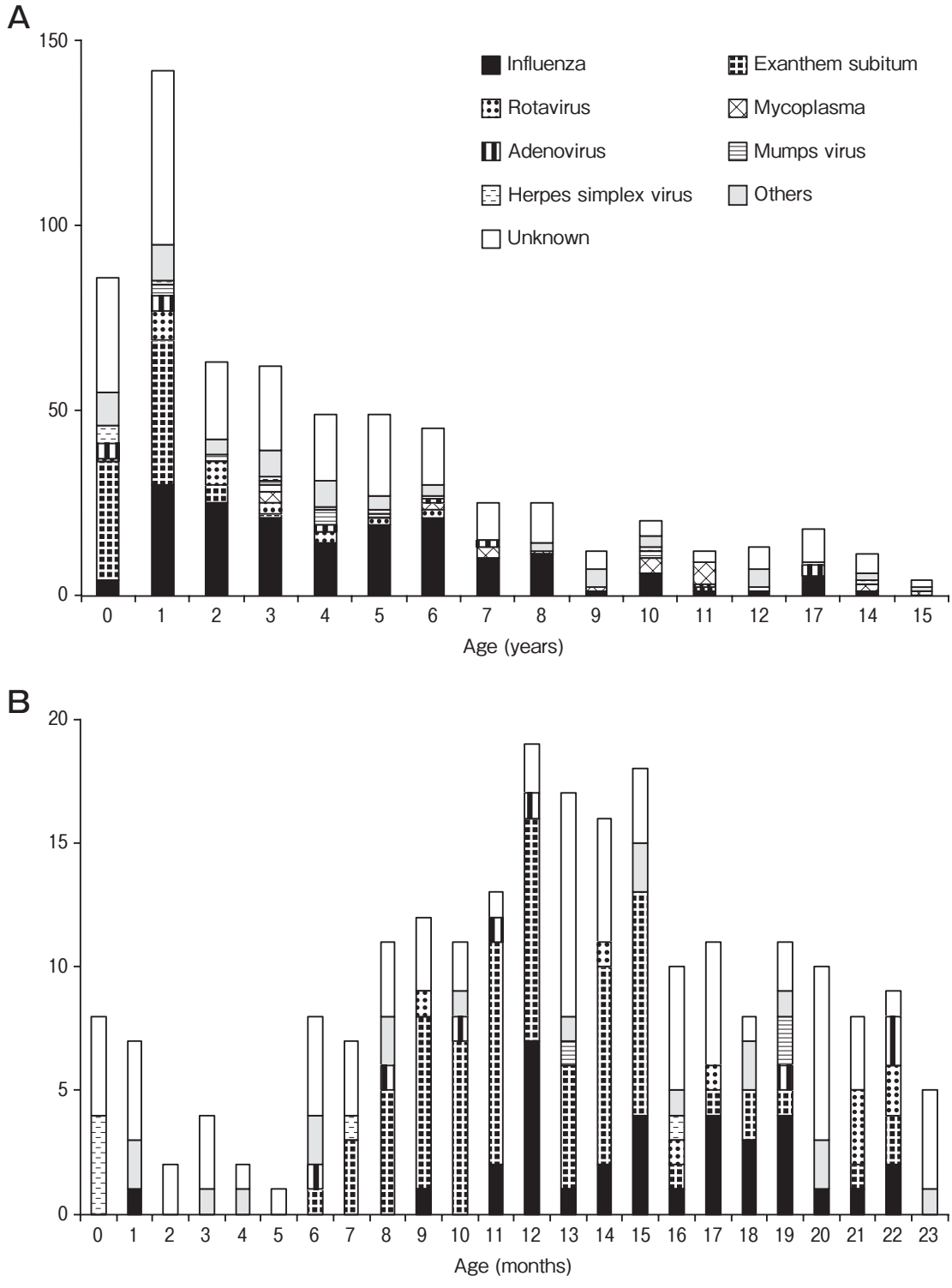

Fig. 1 Age distribution of pAEE patients by year (A) and month (B). Causes are shown in stacked bar charts.

Table 2 Neurological symptoms and fever at the onset of pAEE

Symptom	Total (%) ($n=636$)	Age 0–3 years (%) ($n=353$)	Age 4–15 years (%) ($n=283$)	p value*
Disturbance of consciousness	553 (88.5)	310 (89.9)	243 (86.8)	0.232
Seizure	481 (76.2)	305 (87.1)	176 (62.6)	<0.001
Abnormal speech and behavior	174 (28.0)	50 (14.5)	124 (44.6)	<0.001
Fever	581 (92.5)	324 (93.4)	257 (91.5)	0.365

Percentages are calculated among patients with information for each symptom.
*P values between the 2 age groups.

Table 3 Association of symptoms with the etiology of pAEE

Symptoms		Influenza	ES	Rotavirus	Mycoplasma	Adenovirus	Mumps virus	HSV	Others	Etiology unknown
All age groups		($n=170$)	($n=78$)	($n=26$)	($n=23$)	($n=18$)	($n=14$)	($n=13$)	($n=62$)	($n=232$)
	Consciousness disturbance	150 (90.9)	66 (84.6)	22 (88)	21 (91.3)	16 (88.9)	13 (92.9)	8 (66.7)	55 (88.7)	202 (88.6)
	Seizure	132 (78.6)	74 (94.9)	21 (80.8)	8 (34.8)	11 (61.1)	11 (78.6)	7 (53.9)	41 (66.1)	176 (76.9)
	Speech and behavior changes	62 (36.9)	8 (10.3)	5 (19.2)	9 (42.9)	8 (44.4)	6 (42.9)	2 (18.2)	14 (22.6)	60 (26.8)
	Fever	166 (99.4)	74 (96.1)	22 (88)	21 (91.3)	18 (100)	14 (100)	12 (92.3)	52 (83.9)	202 (88.2)
Age 0–3 years		($n=80$)	($n=77$)	($n=18$)	($n=3$)	($n=10$)	($n=6$)	($n=7$)	($n=30$)	($n=122$)
	Consciousness disturbance	68 (90.7)	66 (85.7)	17 (94.4)	3 (100)	8 (80)	6 (100)	4 (66.7)	27 (90)	111 (92.5)
	Seizure	70 (89.7)	74 (96.1)	16 (88.9)	2 (66.7)	7 (70)	6 (100)	4 (57.1)	22 (73.3)	104 (86)
	Speech and behavior changes	19 (24.4)	7 (9.1)	1 (5.6)	0 (0)	3 (30)	1 (16.7)	1 (20)	3 (10)	15 (12.7)
	Fever	77 (98.7)	74 (97.4)	16 (94.1)	3 (100)	10 (100)	6 (100)	6 (85.7)	25 (83.3)	107 (89.2)
Age 4–15 years		($n=90$)	($n=1$)	($n=8$)	($n=20$)	($n=8$)	($n=8$)	($n=6$)	($n=32$)	($n=110$)
	Consciousness disturbance	82 (91.1)	0 (0)	5 (71.4)	18 (90)	8 (100)	7 (87.5)	4 (66.7)	28 (87.5)	91 (84.3)
	Seizure	62 (68.9)	0 (0)	5 (62.5)	6 (30)	4 (50)	5 (62.5)	3 (50)	19 (59.4)	72 (66.7)
	Speech and behavior changes	43 (47.8)	1 (100)	4 (50)	9 (47.4)	5 (62.5)	5 (62.5)	1 (16.7)	11 (34.4)	45 (42.5)
	Fever	89 (100)	0 (0)	6 (75)	18 (90)	8 (100)	8 (100)	6 (100)	27 (84.4)	95 (87.2)

Percentages are calculated among patients with information for each symptom.
ES, exanthem subitum; HSV, herpes simplex virus.

Table 4 Association of outcomes with the etiology of pAEE ($n=602$)

Outcomes	Influenza ($n=158$)	ES ($n=72$)	Rotavirus ($n=26$)	Mycoplasma ($n=22$)	Adenovirus ($n=17$)	Mumps virus ($n=14$)	HSV ($n=13$)	Others ($n=61$)	Etiology unknown ($n=219$)
Death*	11 (7.0)	2 (2.8)	1 (3.9)	0 (0)	2 (11.8)	1 (7.1)	1 (7.7)	5 (8.2)	20 (9.1)
Survival with neurological sequelae*	39 (24.7)	31 (43.1)	10 (38.5)	3 (13.6)	6 (35.3)	4 (28.6)	4 (30.8)	20 (32.8)	98 (44.8)
Survival without neurological sequelae*	108 (68.4)	39 (54.2)	15 (57.7)	19 (86.4)	9 (52.9)	9 (64.3)	8 (61.5)	36 (59.0)	101 (46.1)
Death vs. survival**	0.82 (0.27–2.48)	0.25 (0.05–1.37)	0.4 (0.04–3.62)	NE	1.39 (0.24–7.97)	0.83 (0.09–7.77)	0.91 (0.1–8.61)	1 (reference)	1.09 (0.39–3.05)
Death and neurological sequelae vs. intact survival**	0.63 (0.34–1.18)	0.83 (0.4–1.7)	0.88 (0.34–2.25)	0.34 (0.09–1.3)	1.16 (0.39–3.49)	0.75 (0.22–2.53)	0.88 (0.25–3.11)	1 (reference)	1.63 (0.91–2.93)

*Data shown as number (%).
**Data shown as odds ratio (95% confidence interval). The odds ratio was adjusted for age.
ES, Exanthem subitum; HSV, Herpes simplex virus; NE, not estimated.

Discussion

Our analyses revealed influenza and ES as the 2 main causes of pAEE and that the age distribution had a peak at 1 year of age. These findings accorded with those of an earlier report [3]. We further examined the precise month-age distribution up to 24 months. The number of patients with pAEE increased after 6 months of age, as observed for general febrile illness [6]. Age predilection was observed in pAEE associated with HSV (at 0 month) and ES (8-15 months). This information could be helpful regarding the choice of laboratory examinations for diagnosis.

We observed that the neurological symptoms at the onset of pAEE were associated with patient age. As anticipated from the age-dependent incidence of febrile

seizures [7], seizures were observed more often in the younger patients (≤3 years old). Abnormal speech and behavior were more frequent in the older patients (≥4 years old). These findings seemed to reflect the brain development process [7]. We also identified differences in neurological symptoms at the onset among the causes of pAEE. The seizure incidence was lower in the HSV-associated pAEE cases compared to the other causes, which might be associated with the age predilection (at 0 month); the diagnosis of neonatal seizure is rather difficult [8]. As has been examined intensively and acknowledged widely [9], abnormal speech and behavior are associated with influenza, although comparable rates were observed for pAEE associated with mycoplasma, adenovirus, and mumps virus.

Our present findings indicate that the rates of mortality and severe neurological sequelae of pAEE were high, as reported earlier from a Japanese study [3]. Moreover, the rates of undesirable outcomes were dependent on the pAEE etiology. The mortality rate of influenza-associated pAEE was reported initially to be as high as around 30% [1]. However, the corresponding rate was found to be 7.0% in the present study, nearly equal to those in recently published reports [10, 11]. This dramatic decrease might be attributable to the widespread use of the treatment guidelines from the Japanese Ministry of Health, Labour, and Welfare [12]. The mortality rate and the rates of severe neurological sequelae of pAEE associated with ES and rotavirus in the present study were nearly identical to those of earlier studies [13, 14]. It might be of interest to ascertain whether the introduction of rotavirus vaccine [15] will alter the outcomes.

It is also noteworthy that we detected no significantly different odds of undesirable outcomes (*e.g.*, death and neurological sequelae) among the seven main etiologies. This finding likely indicates that the etiology alone is not a prognostic factor of pAEE; syndrome classification might contribute more to the outcomes [3]. In addition, the measurement of brain injury markers such as S-100B and tau protein in cerebrospinal fluid samples might have predictive ability for clinical outcomes in patients with pAEE [16].

This study has several limitations. First, as with many surveys in Japan, the response rate to the questionnaire was not high enough to rule out possible non-response bias. Second, the survey used for this study was outdated. Third, the etiology was inferred according to the diagnosis by physicians, among whom the diagnostic microbiological testing for pAEE was not standardized.

Several rapid antigen detection kits recently became available in Japan for the detection of human metapneumovirus [17], norovirus [18], and respiratory syncytial virus [19]. Moreover, the loop-mediated isothermal amplification method is now available for the detection of *Mycoplasma pneumoniae* [20] and *Bordetella pertussis* [21]. In the current clinical setting, diagnostic microbiological testing is much more facilitated and specified than in years past. In addition, syndrome classification has been introduced with advantages in the prediction of clinical outcomes [3]. Future studies of the epidemiology of pAEE must adopt viewpoints of both etiology and syndrome classification.

In conclusion, we documented the epidemiological distribution of pAEE in Japan over a 2-year period between January 2005 and December 2006. We anticipate that the results of the current analysis will provide further support for the management and daily clinical care of patients with pAEE.

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