Clinical Infectious Diseases

MAJOR ARTICLE

A Nationwide Survey of Pediatric-onset Japanese Encephalitis in Japan

Etsuro Nanishi,[1] Takayuki Hoshina,[1,2] Masafumi Sanefuji,[1] Ryo Kadoya,[3] Katsuhiko Kitazawa,[4] Yukie Arahata,[4] Tetsuya Sato,[5] Yoshimichi Hirayama,[6] Katsuki Hirai,[7] Masaaki Yanai,[8] Kaori Nikaido,[9] Akihiko Maeda,[10] Hiroyuki Torisu,[11] Kenji Okada,[12] Yasunari Sakai,[1] and Shouichi Ohga[1]

[1]Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, [2]Department of Pediatrics, School of Medicine, University of Occupational and Environmental Health, Japan, [3]Department of Pediatrics, Japanese Red Cross Yamaguchi Hospital, [4]Department of Pediatrics, Asahi General Hospital, [5]Department of Pediatrics, Aki General Hospital, [6]Department of Pediatrics, Naha City Hospital, [7]Department of Pediatrics, Japanese Red Cross Kumamoto Hospital, [8]Department of Pediatrics, Kumamoto Regional Medical Center, [9]Department of Pediatrics, Fukuyama Medical Center, [10]Department of Pediatrics, Kochi Prefectural Hatakenmin Hospital, [11]Department of Pediatrics, Fukuoka Dental College Medical and Dental Hospital, and [12]Department of Nursing, Fukuoka Nursing College, Japan

Background. Japanese encephalitis (JE) is the leading cause of viral encephalitis with high mortality and morbidity in Asia. In Japan, however, the active recommendation of JE vaccine was retracted in 2005 because of the potential risk of acute disseminated encephalomyelitis. We aimed to determine the recent incidence of childhood-onset JE after the domestic change of vaccination policy in Japan, and to analyze the clinical features of affected children.

Methods. A retrospective nationwide survey was conducted for pediatric patients with JE in Japan from 1995 to 2015. The national surveillance system was used to identify the pediatric patients with JE. Follow-up questionnaires were sent to analyze their clinical and neuroimaging profiles.

Results. Among a total of 109 patients registered to the national surveillance, 10 (9%) were less than age 15 years. The annual incidence rate of childhood-onset JE was higher during 2005–15 than that during 1995–2004 (4.3×10^{-3} vs 1.1×10^{-3} per 100 000, respectively; $P = .04$). Endemic regions overlapped with prefectures that farmed pigs harboring antibodies against JE virus with high prevalence. Detailed clinical data were collected from 9 patients. None of them died, but 5 of 9 patients (56%) had neurological sequelae after recovery. One patient who was partially vaccinated with 2 doses of JE vaccine fully recovered from a coma. The age of 3 years or less was associated with unfavorable neurological prognosis.

Conclusions. Our data provide evidence for the importance and prophylactic effect of the JE vaccine in young children in the endemic area.

Keywords. Japanese encephalitis; childhood; vaccination.

Japanese encephalitis (JE), a mosquito-borne flavivirus infection, is the leading cause of vaccine-preventable viral encephalitis in Asia. JE virus is endemic in most parts of Asia to the Western Pacific region, and over 3 billion people in 24 countries have JE virus transmission risks [1]. Approximately 68 000 cases occur each year, and 75% of them are children younger than 15 years of age [2]. Although the majority of JE virus infections manifests as self-limited febrile illness, the mortality rate of children with encephalitis rises as high as 16%–34%, causing more than 10 000 deaths per year [1, 3–5]. Furthermore, approximately half of the children who survived the acute phase of JE are reported to develop the long-term sequelae of motor disability, cognitive dysfunctions, and epilepsy [1, 3, 4].

Currently, there is no specific treatment for JE, and the treatment mainly consists of supportive care. Although the mortality and morbidity may largely depend on the socioeconomic status of the country and the quality of intensive care that is available for patients in the endemic area, there is limited information about the outcome of childhood JE in developed countries with adequate medical resources.

Japan had licensed an inactivated mouse brain-derived vaccine in 1956 and thereafter incorporated it into the routine childhood immunization program. The scheduled vaccination program successfully led to a decline in the incidence of JE; however, the active recommendation of the vaccine was discontinued in 2005 because the vaccine's neural tissue substrate raised concern about the possibility of vaccine-related neurological adverse events such as acute disseminated encephalomyelitis (ADEM). The vaccination rate had precipitously dropped until the reinstatement of the active recommendation for receiving a new, inactivated Vero cell-derived vaccine in 2010, which was approved in 2009.

In Japan, physicians are mandated to report all JE patients to the national surveillance [1]. Taking these conditions into account, we aimed at investigating the recent incidence of pediatric JE in Japan, with a particular attention on the difference before and

Received 30 June 2018; editorial decision 4 September 2018; accepted 18 September 2018; published online September 24, 2018.

Correspondence: T. Hoshina, Department of Pediatrics, School of Medicine, University of Occupational and Environmental Health, Japan, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan (hoshina@med.uoeh-u.ac.jp).

Clinical Infectious Diseases® 2019;68(12):2099–104

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DOI: 10.1093/cid/ciy816

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after the change of the vaccination policy. The nationwide survey was thus conducted to analyze the annual incidence, regional difference, and the neurological outcomes of JE in childhood.

METHODS

Study Design and Subjects

A retrospective nationwide survey was conducted for children who were diagnosed with JE from January 1995 to December 2015 in Japan. The case definition used for the surveillance was that a patient with encephalitis syndrome with any positive result of a specific immunoglobulin M (IgM) antibody, real-time polymerase chain reaction (PCR), isolation of JE virus from the cerebrospinal fluid (CSF) or serum, or significant increase of serum antibody titers measured with neutralization, hemagglutination inhibition (HI), or complement fixation method [1].

A total of 10 patients <15 years of age received the diagnosis of JE in the surveillance registry during the study period. Nine of the 10 hospitals that managed the patients were identified. Questionnaires were sent to all 9 hospitals, and the following information was obtained for each patient: (a) age, sex, and resident area; (b) history of vaccination against JE; (c) any underlying disease; (d) signs, symptoms, laboratory data, and image findings of JE; (e) virus detection methods; (f) details of the treatment course; and (g) outcome. The neurological outcomes were evaluated on presence or absence of impairments at the time of discharge from the hospital ("short-term") and those lasting more than 6 months after discharge ("long-term"). The outcomes were then classified into 1 to 5 grades: (1) death; (2) severe (disability that would make the child dependent on others); (3) moderate (disability that affects function, but would not render the child dependent); (4) minor (mild effects on the function or personality change); and (5) full recovery, according to the Liverpool outcome score [5, 6].

Endpoints and Public Health Data

The primary endpoint was the incidence rate of pediatric JE in Japan before and after the change of the vaccination policy. The secondary endpoints were the outcomes, and the associations between symptoms, clinical findings, or treatments and long-term outcomes. The incidence rate was the number of JE cases per 100 000 populations, which was calculated using the census population data obtained from the Ministry of Health, Labor, and Welfare of Japan. The vaccination rates of JE during the years of 1995 to 2015 were obtained from the Ministry of Health, Labour, and Welfare of Japan [7]. The geographic map on serum titers of HI antibody against JE virus among farmed young pigs were adopted from the published data of National Institute of Infectious Diseases [8].

Statistical Analysis

Wilcoxon test or Student *t*-test was used to analyze the continuous variables, and likelihood ratio test was used to analyze the categorical variables. The *P*-value of <.05 was considered statistically significant. All statistical analyses were performed using the JMP Pro software program (ver. 11.0.0. SAS Institute, 2001, Cary, NC, USA).

Ethics

The present study was approved by the Institutional Review Board of Kyushu University (no. 26–368).

RESULTS

The Change in the Vaccination Rate and the Incidence Rate of JE in Japan

We found that 83% to 93% of children had received the first dose of JE vaccine before 2005 (Figure 1). In turn, when the government withheld the active recommendation, the vaccination rate drastically dropped to 4% in 2006. The vaccination

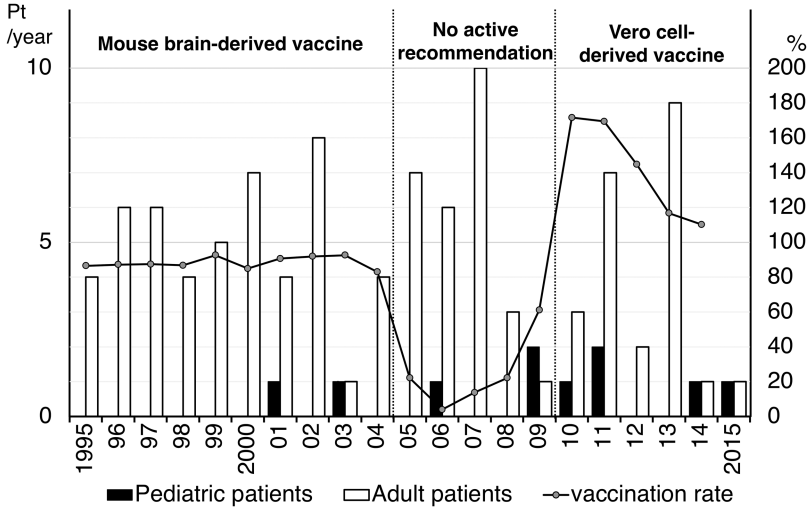

Figure 1. The vaccination rate and number of patients with JE during the study period in Japan. Vaccination rate is those of the first dose of JE vaccine, which was obtained from the Ministry of Health, Labor, and Welfare of Japan (http://www.mhlw.go.jp/topics/bcg/other/5.html). Abbreviation: JE, Japanese encephalitis.

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rate was recovered back to 171% when the Vero cell-derived products were available in 2010.

Only 2 (3.9%) out of 51 reported JE patients was <15 years of age during 1995–2004, whereas 8 (13.8%) children of 58 reported JE patients was identified during 2005–15. The annual incidence rate of childhood-onset JE was higher during 2005–15 than that during 1995–2004 (4.3×10^{-3} vs 1.1×10^{-3} per 100 000, respectively; $P = .04$) (Table 1). In contrast, there was no difference among the incidence rate of adult JE between the periods (4.5×10^{-3} vs 4.1×10^{-3} per 100 000, respectively; $P = .62$).

Demographic Characteristics

Demographic data of 9 children with JE were summarized in Table 2. The age at the onset of JE was median 6 years, ranging from 10 months to 11 years. The male-to-female ratio was 1.25. These patients developed JE in July (n = 1, 11%), August (n = 5, 55%), September (n = 2, 22%), or in October (n = 1, 11%). Notably, only one 7-year-old girl was partially vaccinated with 2 doses of JE vaccine, whereas the other 8 patients were unvaccinated against JE. We found that 8 of the 9 patients were reported from the prefectures located in the western Japan (Fukuoka, Kumamoto, Yamaguchi, Hiroshima, Kochi, and Okinawa). Most of the patients resided in the endemic area, where the proportion of young pigs with the positive result of HI antibodies to JE was high (Figure 2). Two out of 10 affected children lived in rural areas close to pigsties, whereas we were unable to confirm whether the remaining 8 children lived in urban area or nearby the risk areas for JE virus infection. These data indicated the correlation between the high-frequency exposure of children to the JE virus infection and the incidence rate of JE.

Clinical Findings During the Acute Phase of JE

Clinical and neurological features of 9 children affected by JE were recorded on admission and were summarized in Table 2. The median days of illness on the admission was 4 days, ranging from 1 to 7 days. All cases presented with fever of 37.9 °C or higher. Meningeal signs were noted only in 5 of 9 patients (56%). Seizure occurred in 3 patients (33%, patients 2, 3 and 4), and 2 of them marked the scores of 6 or less with Glasgow coma scale (patients 3 and 4). Including these 2 patients, altered consciousness ("coma" or "lethargy") was recorded for 7 of 9 patients (78%) before admission, and for 2 after hospitalization (22%, patients 5 and 6). During the acute phase of JE, 3 patients (patients 1, 4, and 5) showed focal neurological signs of "oculomotor paralysis" or "hemiplegia." However, including these 3 patients, broad cerebral damages were suspected from their accompanying signs of "coma," "tetraplegia," and "cognitive dysfunctions." Mechanical ventilation was used in 3 patients who developed coma or respiratory failure (patients 1, 3, and 4).

Table 1. Incidence Rates of Pediatric and Adult Patients With Japanese Encephalitis in Japan

	1995–2004	2005–2015	*P*-value
Pediatric, 0–14 years of age	0.0011	0.0043	.04
Adult, ≥15 years of age	0.0045	0.0041	.62

Incidence rate was calculated by the number of confirmed JE cases per 100 000 populations.

Laboratory and Virology Tests

All patients showed leukocytosis in the peripheral blood (median, 15 100 /μL; range, 10 000–33 980 /μL) on admission (Table 3). Serum C-reactive protein levels differed among patients (median, 0.6 mg/dL; range, 0.04–8.5 mg/dL). CSF samples were obtained from all patients, and the median days of illness when lumbar puncture was performed was 4 days (range, 1–8). Pleocytosis was evident in 7 patients (median, 82 /μL; range, 0–1560 /μL), and the median ratio of polymorphonuclear cells were 41% (range, 7%–65%). The median level of protein in CSF was 31 mg/dL (range, 0–56 mg/dL). No patient showed decrease in glucose of CSF (63–145 mg/dL).

The diagnosis of JE in 3 patients was made with the positive result of PCR in CSF, elevated JE-specific IgM antibody in CSF, or serum during the acute phase of the disease (Table 3). The other 3 patients received the diagnosis of JE with the ≥4-fold increase of HI antibody titers in paired sera. The remaining 3 patients were positive for both tests. The diagnostic methods did not differ among patients with different severity.

Neuroimaging Studies

Brain magnetic resonance imaging (MRI) were taken for all 9 patients (Table 3). At least 1 parenchymal lesion was detected in 7 patients, whereas no lesions were identified in 2 patients (patients 6 and 7). All of these lesions were most sensitively detected with diffusion-weighted image as high-intense signals and were less sensitively depicted with T2-weighed and fluid-attenuated inversion recovery (FLAIR) images.

Cortical lesions proved to be the most frequent abnormality in MRI and were found in 6 patients (67%, patients 2–5, 8, and 9). Among them, 1 patient developed diffuse hemispheric lesions (patient 3). Thalamic lesions were shown in 4 patients (44%, patients 1, 4, 8, and 9), and 3 of them involved the cerebral cortex or other regions. The brain lesions extended to the basal ganglia and splenium of corpus callosum in patient 5 and 8, respectively.

Treatments and Outcomes

Corticosteroids or intravenous immunoglobulin (IVIG) were applied to the acute-phase treatments for 5 patients because immune-mediated acute encephalopathy or ADEM was suspected (Table 4, patients 1, 3–5, and 8). Four patients received corticosteroid therapy. Three of them underwent high-dose methylprednisolone therapy during the early phase of illness. The remaining patient received dexamethasone. IVIG was used in 3 patients. Six out of 9 patients received intensive cares under

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Table 2. Demographic and Clinical Characteristics of Pediatric Patients With JE in Japan

	Demographic Characteristics				Clinical Characteristics on admission						
Pt	Age	Sex	Onset Month	Vaccination Against JE	Day of Illness	Fever, °C	Meningeal Signs	Seizure	GCS	Neurological Manifestation During the Acute Phase	Reported Year
1	10 mo	M	Aug.	None	4	38.6	–	–	11	Lethargy, tetraplegia, oculomotor paralysis, bulbar paralysis	2015
2	1 yr	F	Aug.	None	7	39.8	–	+	NA	Lethargy, impaired speech	2009
3	1 yr	M	July	None	1	39.0	–	+	3	Coma, tetraplegia	2011
4	3 yrs	M	Sep.	None	4	38.8	+	+	6	Coma, hemiplegia, conjugate deviation, impaired speech	2006
5	6 yrs	F	Sep.	None	3	39.9	–	–	15	Lethargy, hemiplegia, impaired speech	2010
6	7 yrs	M	Aug.	None	3	39.2	+	–	15	Lethargy	2009
7	7 yrs	F	Oct.	Twice	1	37.9	–	–	Unknown	Lethargy	2003
8	10 yrs	M	Aug.	None	5	39.5	+	–	9	Coma, cognitive dysfunction, hypertonic muscle	2011
9	11 yrs	F	Aug.	None	4	40.4	+	–	13	Lethargy, tremor, cognitive dysfunction, hyperreflexia	2001

Abbreviations: GCS, Glasgow coma scale; JE, Japanese encephalitis; NA, not applicable.

the control of respiratory support and intracranial pressure, in combination with anticonvulsive and antimicrobial therapies. Therapeutic hypothermia was introduced in 2 who developed coma (patients 3 and 4).

The duration of hospitalization was median 20 days, ranging from 13 to 103 days. No patients died during the acute phase and the ≥6 months of follow-up period in this study. Four of 9 patients (44%) fully recovered without neurological impairments at the time of discharge from the hospital (Table 4). The long-term outcomes were assessed for all but 1 patient who had no sequelae at discharge. Five patients experienced motor or cognitive impairments at discharge. Among them, 1 patient had only minor neurological disability with mild hemiparesis at discharge and reached a complete recovery in 3 months. We found that 3 of these 4 patients with long-term neurological impairments were aged 3 years or younger (patients 1, 3, and 4). Patients aged 3 years and younger showed moderate to severe sequelae more frequently than those more than 3 years of age (75% vs 0%).

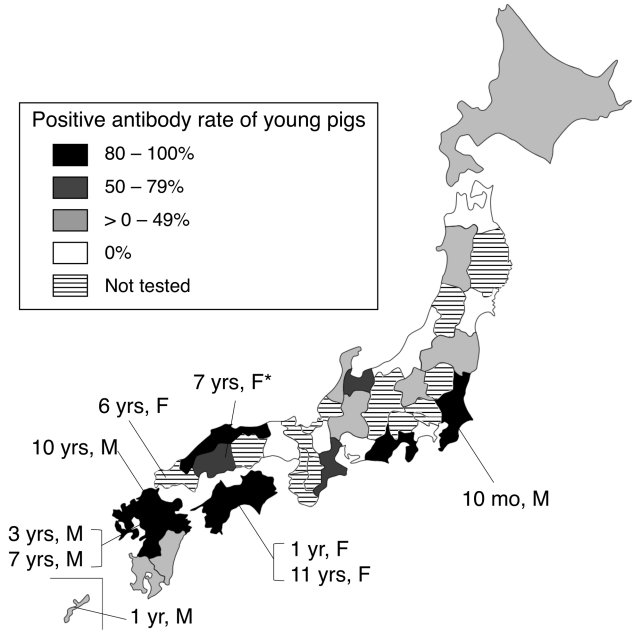

Figure 2. The distribution of pediatric patients with JE and the positive HI antibody rate among young pigs in each prefecture. Serum HI antibody titers against JE virus in young pigs were measured in 2016. The data were obtained from the National Institute of Infectious Diseases (https://www.niid.go.jp/niid/images/iasr/2017/08/450r07f01.gif). Abbreviations: HI, hemagglutination inhibition; JE, Japanese encephalitis. *The patient received 2 doses of JE vaccine before the onset of JE.

DISCUSSION

We identified a total of 10 pediatric patients with JE using the national surveillance system of Japan during the years of 1995 to 2015. Although the incidence of adult JE has been considered to be stationary in Japan, the incidence rate of pediatric cases with JE significantly increased after the domestic change of the vaccination policy. Among 9 patients with detailed clinical information, none had been immunized with JE vaccine except for one who was partially vaccinated with 2 doses of JE vaccine. No patients died during the study period, but more than half of the patients had considerably long-lasting neurological sequelae, particularly in infants and young children.

The regular immunization program had mainly contributed to the decline in the prevalence rate of JE in Japan. Nonetheless, the content of brain components in the vaccine product had raised concerns about the possibility of vaccine-related neurological side effects, such as ADEM [9]. In Japan, 13 cases of JE vaccine-related ADEM were recognized as a health hazard from 1991 to 2005 [10]. Immediately after the 14th case of ADEM was reported, the Ministry of Health, Labour, and Welfare of Japan discontinued the active recommendation for receiving the mouse brain-derived vaccine in 2005. On the other hand, over 80% of pigs in the farms of endemic regions were infected with

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Table 3. Laboratory Findings, Virus Detection Method, and Abnormalities in MRI During the Acute Phase of Illness

	Peripheral Blood		CSF					
Pt	WBC, /μL	CRP, mg/dL	WBC, /μl	PMNs, %	Protein, mg/dL	Glucose, mg/dL	Virus Detection Method	Abnormal Brain MRI
1	15 100	0.04	43	7	33	70	PCR (day 4, CSF) HI (day 4 → 13, <1:10 → 1:80)	Bilateral thalamus, day 4
2	15 170	1.0	355	44	27	88	HI (day 7 → 50, 1:20 → 1:160)	Frontal cortex, day 9
3	18 000	0.6	0	NA	NP	145	PCR (day 1, CSF)	Diffuse cerebral hemispheres, day 19
4	33 980	8.4	45	65	46	142	HI (day 4 → 11, <1:10 → 1:320)	Bilateral thalamus, and left temporal cortex, day 4
5	16 500	8.5	136	41	25	66	PCR (day 3, CSF) Specific IgM (day 6, CSF and serum) HI (day 6 → 18, 1:10 → 1:40)	Bilateral basal ganglia, and left frontal cortex, day 5
6	11 600	0.3	981	20	56	67	Specific IgM (day 5, CSF) HI (day 5 → 19, 1:10 → 1:640)	None, day 8
7	11 200	0.04	0	NA	<10	79	PCR (day 1, CSF)	None, day 2
8	10 000	0.2	82	54	29	68	Specific IgM (day 6, CSF and serum)	Right thalamus, left frontal cortex, and splenium of corpus callosum, day 6
9	11 870	2.1	1560	38	53	63	HI (day 4 → 11, 1:10 → 1:160)	Left thalamus, and occipital cortex, day 4

Abbreviations: CRP, C-reactive protein; CSF, cerebrospinal fluid; HI, hemagglutination inhibition; MRI, magnetic resonance imaging; NA, not applicable; NP, not performed; PCR, polymerase chain reaction; PMN, polymorphonuclear cells; WBC, white blood cell.

JE virus, and the annual infection rate in children without vaccination was 2.6% in recent Japan [11]. Vector-breeding grounds or pig-farming areas have never been expanded in recent Japan. The constant rate in the incidence of adult JE suggested that these environmental factors remained unchanged during the 2 decades of study periods. These data also supported evidence that the surveillance and reporting systems were sustained at the constant quality. It was therefore likely that the interval without available JE vaccine rendered the growth of population of unvaccinated children in Japan and consequently increased the number of children affected by JE in subsequent years.

There is no specific treatment for JE. The efficacy of dexamethasone, interferon-alpha, oral ribavirin, IVIG, or minocycline were evaluated in randomized controlled trials, which failed to reduce the mortality and neurological sequelae [6, 12–15]. The mortality rate of childhood JE was as high as 16% to 34% in the former reports from India and Southeast Asia [5, 6, 12, 13, 16, 17]. In contrast, no patients died in this study. The high accessibility and the quality of supportive care might have contributed to the low mortality in Japanese children. However, the fact that more than half of the patients suffered from motor or cognitive impairments demonstrated the importance of universal vaccine prevention against the sporadic occurrence of JE in developed countries.

The World Health Organization (WHO) concluded that no causal relationship exists between ADEM and the mouse

Table 4. Treatment and Clinical Outcomes of Patients

Pt	Duration of Hospitalization, Days	Treatment	Sequelae at Discharge	Long-term Sequelae
1	103	High-dose methylprednisolone	Severe (tetraplegia, dysphagia, intellectual disability)	Persisted
2	19		None	None
3	65	High-dose methylprednisolone, IVIG, induced hypothermia	Severe (tetraplegia, disturbance of consciousness, epilepsy)	Persisted
4	42	Dexamethasone, induced hypothermia	Moderate (right hemiparesis, intellectual disability)	Persisted
5	13	IVIG	Minor (mild right hemiparesis)	None
6	14		None	None
7	14		None	None
8	20	High-dose methylprednisolone, IVIG	Minor (higher brain dysfunction)	Persisted
9	90		None	Not applicable

Sequelae were classified into (1) severe, disability that would make the child dependent on other; (2) moderate, disability that affects function but would not render the child dependent; and (3) minor, mild effect on the function or personality change.

Abbreviation: IVIG, intravenous immunoglobulin.

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brain-derived vaccine in 2010 [18]. Independent studies supported this conclusion, wherein the annual incidence of ADEM remained unaltered throughout the observation period, 2005–2009 [19, 20]. In the current study, 3 out of 10 pediatric cases with JE were less than 3 years of age, and younger age correlated with unfavorable neurological prognoses. As recommended by WHO, the primary inoculation of JE vaccine should be started at 6–9 months of age in endemic setting [10, 21]. Accordingly, Japan Pediatric Society revised their recommendation in 2016 and proposed that children in the endemic area should receive their primary immunization at 6 months of age. It was also noteworthy that immunogenicity of the Vero-cell-derived products for children under the age of 3 years was equivalent to those more than 3 years of age [18].

There are several limitations in this study. First, our study included only the JE patients who had been reported to the national surveillance system. This retrospective analysis possibly caused an error of underestimating the number of patients because the reporting efforts may influence negatively on the actual counts of patients. However, these factors were considered constant throughout the study periods. We therefore regarded the change in incidence and mortality rates as all trustworthy. Second, a considerable number of patients were diagnosed with the HI method. Although the HI method is the only commercially available method for the diagnosis of JE virus infection in Japan, it takes several weeks until the antibody titers rise to the detectable level. Therefore, we might have missed the most severe patients who had died within the first days of illness. Because JE cannot be distinguished clinically from other causes of encephalitis, all cases with acute encephalitis syndrome should be prospectively tested to reveal the precise clinical features of childhood JE in Japan.

In conclusion, we conducted the nationwide study for elucidating the incidence and severity of childhood JE in recent Japan. Although the incidence and mortality rates were lower than that of developing countries, many affected children had long-lasting neurological sequelae. JE remains a threat without herd immunity because the animal reservoir cannot be eradicated from the environments. The results of this study demonstrated the value of the universal vaccination program in the endemic setting.

Notes

Acknowledgments. We thank all the patients, their families, and members of the staff in the institutions for the treatment of patients; we also thank Chiaki Miyazaki, Kei Nishiyama, Yoshito Ishizaki, and Toshiro Hara for the valuable advice and generous support.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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