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Original Article

Clinical manifestations of Japanese encephalitis in southern Taiwan

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Background and purpose: Japanese encephalitis virus infection is a sporadic infectious disease in Taiwan. Despite progress in laboratory examinations and imaging studies, diagnosis of Japanese encephalitis remains underestimated. This study was conducted to identify clinical symptoms and laboratory findings that may assist in early identification of this disease.

Methods: This retrospective study included all patients diagnosed with Japanese encephalitis at Kaohsiung Veterans General Hospital from January 2000 through December 2007. Epidemiologic data, predisposing factors, neurological and non-neurological signs and symptoms, laboratory data, and treatment were analyzed. Outcomes and neurological complications were evaluated.

Results: Eleven patients had Japanese encephalitis, and 10 had sufficient information for enrolment into the study. Nine patients presented with non-significant constitutional symptoms of fever, nausea, or headache. Other signs and symptoms included rhinorrhea, sore throat, abdominal pain, cough, myalgia, or arthralgia. Eight patients had lymphocytic pleocytosis with elevated protein and borderline low glucose levels in the cerebrospinal fluid. Leptomeningeal enhancement and low density lesions were the most common computed tomography findings. T2 hyperintensity lesions and leptomeningeal enhancement were seen in 5 patients. Two patients presenting with acute flaccid paralysis had high intensity lesions on the thalamus and basal ganglion. There were no correlations between clinical, laboratory, and imaging findings. None of the patients had neurological sequelae.

Conclusions: Presentations, laboratory examination, and clinical signs are not specific for Japanese encephalitis. Sporadic cases are usually seen from May to August, which are associated with monsoon rains. Hence increased awareness of this disease is recommended during these periods.

Key words: Encephalitis, Japanese; Flavivirus; Signs and symptoms; Taiwan

Introduction

Japanese encephalitis (JE) is an endemic disease in South and East Asia [1,2], resulting in approximately 50,000 cases and 10,000 deaths per year, and usually affects children [2]. Since 1968, when a mass vaccination program against JE was implemented in Taiwan, the incidence rate has fallen considerably [3,4]. A definitive diagnosis made by viral isolation from blood or other specimens is usually difficult because viremia is transient and the viral load is low [5,6]. Detection of RNA by polymerase chain reaction and immunoglobulin by enzyme-linked immunosorbent assay (ELISA) from the cerebrospinal fluid (CSF) or serum are the usual methods of diagnosis [5,6]. The disease is typically an acute neurological syndrome, characterized by fever, convulsions, headache, focal neurological signs, and decreased consciousness. However, most infections are asymptomatic and the true prevalence is underestimated. Unfortunately,

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there is a high prevalence of neurological sequelae (up to 50%) in patients who survive JE [1]. Therefore, initial clinical manifestations of viral encephalitis and a complete medical history for early diagnosis are important for prompt supportive therapy to avoid neurologic sequelae. This study was conducted to identify clinical symptoms and laboratory findings that may assist in early identification of this disease.

Methods

The medical records of patients reported to the Centers of Disease Control (CDC) in Taiwan due to suspected JE who presented to Kaohsiung Veterans General Hospital (KVGH), Kaohsiung, Taiwan, from January 2000 through December 2007 were retrospectively reviewed. Only patients with a definitive diagnosis of JE were included in the analysis. Patients were diagnosed by detectable immunoglobulin M (IgM) in CSF or blood, or evidence of seroconversion of IgM and IgG in the convalescence stage by the ELISA method (Table 1). The data reviewed included the patients' baseline characteristics, systemic disease, animal contact, travel history, clinical presentations, and laboratory results. The therapeutic regimen and medications were also reviewed. The correlations between acute flaccid paralysis or imaging findings and laboratory or CSF studies were analyzed by Mann-Whitney *U* test. Eight paired CSF studies were also analyzed by Mann-Whitney *U* test to detect parameter trend. A p value of <0.05 was considered to be statistically significant.

Results

Demographics and clinical characteristics

117 patients were diagnosed with acute encephalitis and suspected JE virus infection during the 7-year period. These patients were reported to the CDC and 11 were confirmed to have JE. There were 5 men and 6 women, with a male-to-female ratio of 1:1.2. Their ages ranged from 20 to 71 years (mean, 40.6 years) [Fig. 1]. Only 10 medical charts were available for complete analysis. All patients presented to the KVGH between May and November (Fig. 2), albeit in different years.

Predisposing conditions

Information regarding animal contact and recent travel was not available for 2 patients. None of the patients had a history of travel to an endemic area. Six patients had a history of animal contact, including recent exposures to birds, pigs, and cows. No significant underlying conditions of diabetes mellitus, cardiovascular disease, cerebrovascular disease, renal insufficiency, or liver dysfunction were identified. No predisposing condition was significantly correlated with the diagnosis of JE.

Clinical manifestations

The initial manifestations of JE for most patients presenting to the emergency room included fever for at least 5 days (9/10; median, 7.0 days; interquartile range, 2 days; range, 5-15 days), headache (6/10), and nausea (6/10). Other prodromal symptoms included dizziness, nausea, convulsions, myalgia, sore throat, and cough. No patients presented with skin rash, arthralgia, diarrhea, or palpable lymphadenopathy. One of 10 patients had positive Kernig's sign and 2 had positive Brudzinski's sign. The Glasgow coma scale ranged from 4 to 15 (median, 10). New-onset neurologic signs were seen in 7 patients. Four patients had decreased muscle tone, 1 had diplopia, 1 had upward eyeball deviation, and 1 had focal tremor with extrapyramidal features. No patients had palpable hepatomegaly or splenomegaly. Two patients had gastrointestinal bleeding during their hospital admission.

Laboratory manifestations

The laboratory studies showed white blood cell (WBC) counts ranging from 6620 to 17,890/mm^3 (mean ± standard deviation [SD], 12,499 ± 4018/mm^3); hemoglobin from 116 to 172 g/L (mean ± SD, 14.2 ± 2.0 g/L), platelet counts from 125,000 to 244,000/mm^3 (mean ± SD, 194,800 ± 45,497). There was no statistically significant correlation between the hematologic and biochemical laboratory results and the neurological presentations of JE.

Cerebrospinal fluid study

All patients underwent a lumbar puncture during admission and 8 patients had a repeat spinal tap during their hospital stay (Table 2). The opening pressure ranged from 50.0 to 285.0 mm H_2O (mean ± SD, 156.7 ± 79.5 mm H_2O) and the closing pressure ranged from 20.0 to 185.0 mm H_2O (mean ± SD, 110.0 ± 61.0 mm H_2O). The CSF WBC counts of the 11 patients ranged from 9.0/mm^3 to 1560.0/mm^3 (mean ± SD, 315.4 ± 440.1/mm^3; median, 180/mm^3)and were mainly lymphocyte predominant. Red blood cells were seen in all CSF samples and ranged from 13.0/mm^3

Table 1. Demographics, clinical manifestations, serologic study, and magnetic resonance imaging study of Taiwanese patients with

Patient no.	Month of admission	Age/sex	First assessment		Second assessment	
			Serum immunoglobulin G/M	Cerebrospinal fluid immunoglobulin G/M	Serum immunoglobulin G/M	Cerebrospinal fluid immunoglobulin G/M
1	November	22/M	–/–	–/–	+/+	NA/NA
2	June	40/F	+/+	NA/NA	+/+	NA/NA
3	August	32/M	–/+	NA/NA	–/+	NA/NA
4	June	43/M	–/+	+/–	+/+	NA/NA
5	June	41/F	–/–	–/–	–/+	NA/NA
6	July	64/F	–/+	–/–	–/–	NA/NA
7	July	52/F	–/+	NA/NA	–/+	NA/NA
8	May	34/F	NA/+	NA/NA	NA	NA/NA
9	May	20/F	NA/NA	NA/+	–/+	NA/NA
10	July	71/M	–/+	–/+	+/+	NA/NA
11	July	28/M	+/+	–/+	–/–	+/+

Abbreviations: M = male; F = female; NA = not available.

to 8480.0/mm^3 (mean ± SD, 1283.3 ± 2741.1/mm^3; median, 270/mm^3). The mean CSF protein level was 110.1 mg/dL and the mean glucose level was 55.4 mg/dL, with an average CSF/serum glucose ratio of 0.5. Repeat spinal tap was done for 8 patients. The mean CSF WBC count ranged from 2.0 to 440.0/mm^3 (mean ± SD, 119.3 ± 140.3/mm^3), which was mainly lymphocyte predominant (89% to 100%). The second spinal tap revealed a CSF protein level of 56 to 752 mg/dL (mean ± SD, 193.3 ± 250.3 mg/dL) and glucose level ranged from 72.0 to 131.0 mg/dL (mean ± SD, 92.6 ± 18.4 mg/dL) with a CSF/serum glucose ratio of 0.46 to 0.76 (mean ± SD, 0.63 ± 0.13). No significant trend was observed between the first and repeat CSF

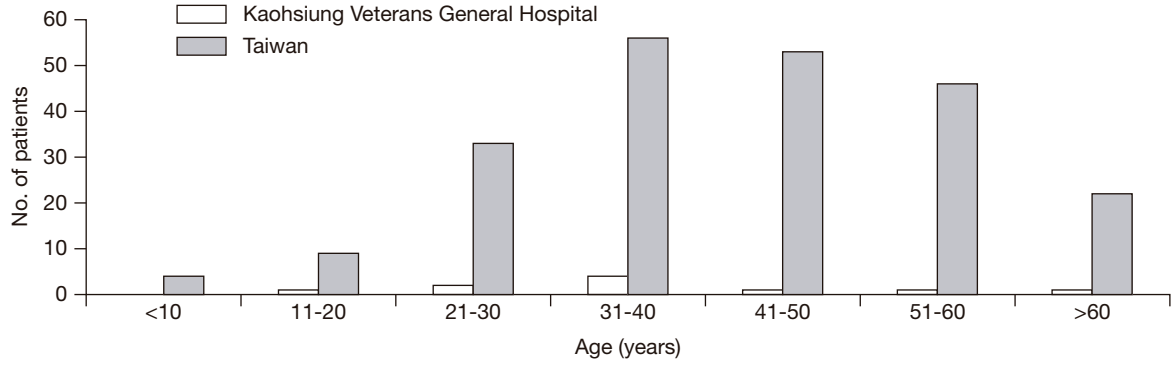

Fig. 1. Age distribution of patients with Japanese encephalitis from 2000 through 2007.

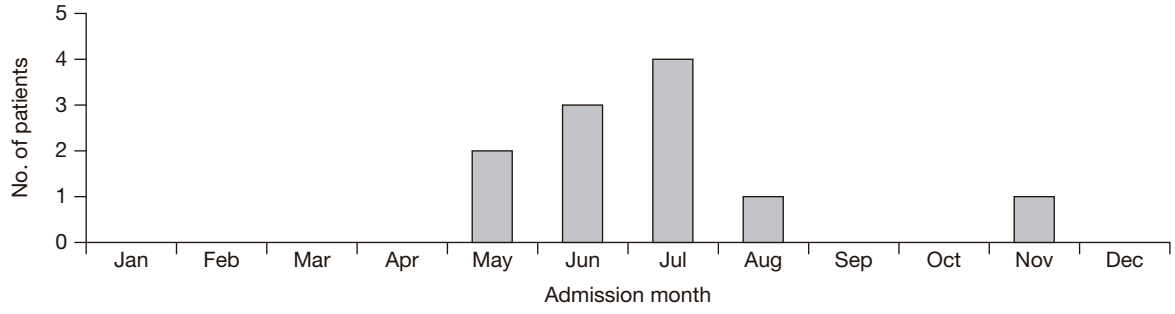

Fig. 2. Distribution of patients with Japanese encephalitis according to month of admission.

Japanese encephalitis.

Kernig's sign/ Brudzinski's sign	Decreased muscle tone	Focal neurologic signs	Brain magnetic resonance imaging
–/–	+	NA	Not done
–/–	–	Focal seizure	Hyperintense on T2 image of the midbrain, left periventricular white matter, left occipital horn, brain edema over left inferior turbinate
–/–	–	Diplopia	Not done
+/–	–	Extrapyramidal symptom	Bilateral cerebral hemisphere leptomeningeal enhancement
–/–	+	Upward eyeball deviation	Hyperintense on T2 image of the basal ganglion, thalamus, central white matter, hippocampus
–/–	–	NA	Not done
–/+	+	Seizure	Hyperintense on T2 image of the bilateral thalamus and cerebral hemisphere, leptomeningeal enhancement
–/–	–	NA	Brain edema on the bilateral inferior turbinate
–/–	–	NA	Negative
–/–	–	NA	Hyperintense on T2 image of the periventricular white matter
–/+	+	NA	Not done

studies. Only CSF protein levels were correlated with clinical neurological symptoms ($p = 0.03$).

Radiological manifestations

Computed tomography (CT) of the brain was undertaken for 9 patients, and intracranial abnormalities were seen in 4 patients. One patient had small bilateral periventricular low density lesions compatible with subcortical arteriosclerotic encephalopathy, and 1 patient had swelling of both cerebral hemispheres compatible with meningoencephalitis. An old cerebral infarct was seen in 1 patient and 1 patient had an intracranial aneurysm.

Magnetic resonance imaging (MRI) of the brain was done for 7 patients (Table 1). Abnormalities were seen in 6 patients. Four patients had increased signal intensity on T2 images and the area involved varied from periventricular white matter, bilateral thalamus, basal ganglion, central white matter, hippocampus, and midbrain. The other 2 patients had subtle leptomeningeal enhancement in the bilateral cerebral hemispheres and enlargement of the bilateral inferior turbinates. Only 1 patient with abnormal MRI findings had abnormalities on CT scan. Four of 5 patients with abnormal MRI findings had clinical focal neurologic signs. Patients with normal MRI results had no new-onset focal neurologic signs.

Electroencephalographic examination

Electroencephalographic examination was done for 1 patient, which revealed diffuse slowing of background activity over the bilateral hemispheres and severe slow activity on both frontotemporal areas. CT and MRI scans of the brain disclosed bilateral hemisphere swelling.

Management and treatment

All 10 patients received intravenous steroid therapy, which was given for 5 to 18 days (median, 10 days). Only 1 patient received steroid and glycetose without any antimicrobial therapy. Seven patients received glycetose therapy for suspected increased intracranial pressure. Five patients received more than 2 categories of antimicrobial agents initially. Eight patients received acyclovir therapy due to an initial diagnosis of aseptic meningitis.

Prognosis

One patient developed bacterial pneumonia complicated by respiratory failure during hospital admission. The patient was extubated and discharged after 30 days in hospital. All patients were followed up for more than 1 month. No patients had residual neurologic sequelae during follow-up in the outpatients clinic.

Discussion

The 10 patients with JE were diagnosed between May and November. 223 patients were diagnosed by the CDC throughout Taiwan during the study period. The number of confirmed patients ranged from 20 to

Table 2. Cerebrospinal fluid studies of patients with Japanese encephalitis.

Patient no.	First assessment						
	Sample collection day	White blood cells (/mm^3)	Neutrophils/ lymphocytes/ monocytes (%)	Red blood cells (/mm^3)	Protein (mg/dL)	Glucose (cerebrospinal fluid/serum) [mg/dL]	Lactate (mg/dL)
1	[a]	310	30/70/0		22	57/-	
2	1	80	0/100/0	270	164	53/96	
3	1	433	4/92/4	13	120	60/106	
4	1	90	2/98/0	590	54	66/102	11.7
5	1	290	1/99/0		109	63/115	
6	1	25	6/89/5	1555			
7	2	9		8480	141	66/148	
8	1	1560	44/51/5	240	172	59/122	
9	1	180	2/98/0	348	98	67/168	
10	1	420	75/25/0	30	126	44/116	22.0
11	1	72	19/81/0	24	95	59/-	14.5

[a]One day before visiting the emergency room.

35 each year from between 2000 and 2007 [8]. The highest number of patients was diagnosed between May and October, and the number usually peaked in July. This period is compatible with the rainy season in Taiwan, and may be associated with prolonged mosquito larval development. Most patients lived in eastern Taiwan, followed by central and southern Taiwan. These areas have more livestock breeding and agricultural industries. No patients were reported from the offshore islands of Taiwan within the 7-year study period. There were also more patients in rural areas than in urban areas.

The patients' age ranged from 20 to 71 years. No data regarding vaccination history was seen in any medical records. JE vaccination was available in Taiwan in 1967 and mandatory vaccination of all children has been underway since 1968. Four patients were born after 1968. In Taiwan, the incidence rate for JE before mandatory vaccination was relatively high at around 2/100,000 population. Since 1968, the incidence rate has declined gradually. Before the mandatory vaccination era, most patients with confirmed JE were children and adolescents, with few adult patients. However, the distribution reversed after the vaccination program began. According to recent notifiable infectious diseases statistics from CDC, approximately 90% of patients with confirmed JE were older than 20 years. In Taiwan, vaccination against JE is performed using inactivated vaccine derived from the Nakayama-NIH strain of JE virus-infected mouse brain or the inactivated freeze-dried Beijing strain [4,5]. These vaccines provide 96.8% protection when at least 2 doses are given [8]. This may explain the inefficient antibody protection for older patients, resulting from the absence of a booster dose after initial vaccination. Hence, some patients born after the mandatory vaccination era are infected by JE virus occasionally.

JE virus infection is usually asymptomatic with clinical manifestations seen in only 0.1% to 1.0% of infected patients [1,9,10]. Patients usually present with fever, chills, headache, and myalgia, accompanied by vomiting. In children, the common clinical manifestations are nausea, vomiting, and convulsions [6,11]. Fever, headache, and dizziness were the usual symptoms of patients in this study. Only 3 patients presented with meningism, which was less frequent than other central nervous system infections such as bacterial meningitis [12-17], tuberculous meningitis [16], and viral meningitis [15] in previous reports of JE [18]. Only 2 patients had convulsions, in contrast to studies showing that children often present with convulsions [7,19]. Decreased muscle tone was more frequently observed in these patients (4 of 10 patients) than in previous reports of infected children [7,19]. Decreased muscle tone may be related to the unusual presentation of acute flaccid paralysis in JE. Other constitutional symptoms usually associated with virus infections such as rhinorrhea, sore throat, cough, lymphadenopathy, skin rash, myalgia, and arthralgia were less frequently observed in these patients.

Leukocytosis is often noted in JE, with neutrophil counts ranging from between 51% and 90% [20]. Spinal tap often shows an elevated CSF opening pressure, elevated WBC, elevated protein, and normal CSF glucose level. In this study, the patients' hematological examination showed leukocytosis without other significant abnormalities. CSF studies showed elevated

Second assessment						
Sample collection day	White blood cells (/mm^3)	Neutrophils/ lymphocytes/ monocytes (%)	Red blood cells (/mm^3)	Protein (mg/dL)	Glucose (cerebrospinal fluid/serum) [mg/dL]	Lactate (mg/dL)
1	25	2/98/0	1	69	92/153	16.5
2	128	2/96/2	59	147	131/283	22.1
3	48	2/89/9	384	56	72/114	25.6
4	2		16,800			
5	41	0/100/0	270	173	91/120	30.1
2	440	100/0/0	90,000	752	120/-	
2	150	2/95/3	14	92	86/122	
3	120	5/92/3	480	64	83/-	23.5

WBC and protein level in 9 patients. The glucose levels were normal to low (mean ± SD CSF/serum glucose ratio, 0.5 ± 0.1). Only CSF protein levels were correlated with clinical neurological symptoms, and other CSF parameters had no statistical correlation with any clinical symptoms.

Hypodense lesions in the thalamus, midbrain, or basal ganglia are usually seen in CT scan of the brain of patients with JE. Brain edema is sometimes noted. The common cranial MRI findings include hypointense lesions in the thalamus on T1 image and hyperintense lesions on T2 image [21]. Abnormalities were seen in CT scans of the brain of 4 of 9 patients. Two patients had multiple low density lesions described as subcortical arteriosclerotic change and an old infarct in the brain parenchyma, 1 had brain swelling, and 1 had an aneurysm in the cavernous sinus. The findings for the first 2 patients can indicate a positive radiologic lesion for JE. Abnormalities in MRI were seen in 6 of 7 patients. The most common findings included multiple T2 hyperintense lesions in the brain parenchyma (4/7), brain edema (2/7) and leptomeningeal enhancement (2/7). Previous reports showed that the common MRI abnormalities were noted in the basal ganglion, midbrain, pons, and cerebral cortex [21]. Most patients (4/6) with abnormal MRI findings had focal neurological abnormalities. Among the 4 patients with a clinical presentation of acute flaccid paralysis, 2 underwent brain MRI, which revealed T2-hyperinterse lesions on the bilateral basal ganglia and thalamus. Five patients without decreased muscle tone underwent MRI, but similar findings were not observed in the basal ganglion or the thalamus (Table 1). The thalamus is a functional area for motor control; input connection from the basal ganglion, limbs, and somatosensory signals; and output signal to the basal ganglion and the cortex. Impaired thalamus function presents with motor-sensory dysfunction or decreased level of consciousness. The basal ganglion is a group of nuclei with the function of general motor control, eye movement, and cognitive function. Injury to the basal ganglion may induce cognition impairment, hypokinesia, myoclonus, or tics. The abnormalities in these areas may explain the presentation of acute flaccid paralysis. All 4 patients with positive MRI findings had a negative CT examination. Therefore, MRI was superior to CT for detecting JE intracranial lesions, as in a previous report [21].

Specific antiviral therapy is not available for JE. Supportive care and symptomatic treatment are the major therapies for these patients. Hoke et al demonstrated no statistically significant benefit for high-dose dexamethasone for JE-infected patients [12]. All of the patients in this study received dexamethasone therapy without associated side effects such as immunosuppression, psychiatric disturbances, or dependence with withdrawal syndrome.

No patients had any neurological sequelae recorded during follow-up. This result is different from previous reports of JE in children [2]. In the report of Diagana et al, recovery from neurological defects was slow for children [4]. Residual sequelae were also frequently noted [2]. Intellectual impairment was noted in approximately one-third of infected children. Speech disturbance and motor deficits are also commonly noted [20].

This study has limitations. The study was retrospective and only a small number of patients were evaluated. However, since mandatory vaccination has been available for more than 30 years, it is unlikely that a large number of patients would be available for evaluation in Taiwan. This was intended as a single-center experience of JE in southern Taiwan. Other limitations are the absent records of clinical manifestations and laboratory results from patients' medical records.

In conclusion, JE is predominantly a disease of adults since the mass vaccination program began in Taiwan. In contrast to children, adults experience fewer convulsive symptoms and meningism, and fewer neurologic sequelae. MRI is often correlated with neurological symptoms and is more sensitive than CT. These authors recommend that MRI should be done earlier for patients with suspected JE infection.

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