Clinical Characteristics of Severe Japanese Encephalitis: A Case Series from South Korea

Jun-Sang Sunwoo,¹ Soon-Tae Lee,^{2,3} Keun-Hwa Jung,^{2,3} Kyung-Il Park,⁴ Jangsup Moon,^{2,3} Ki-Young Jung,^{2,3} Manho Kim,^{2,3,5} Sang Kun Lee,^{2,3} and Kon Chu^{2,3*}

¹Department of Neurology, Soonchunhyang University School of Medicine, Seoul, South Korea; ²Department of Neurology, Comprehensive Epilepsy Center, Seoul National University Hospital, Seoul, South Korea; ³Program in Neuroscience, Seoul National University College of Medicine, Seoul, South Korea; ⁴Department of Neurology, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, South Korea; ⁵Protein Metabolism Medical Research Center, Seoul National University College of Medicine, Seoul, South Korea

Abstract. Japanese encephalitis (JE) virus is a major cause of devastating viral encephalitis, especially in Asia. Although a successful vaccination program led to its near-elimination over three decades in South Korea, the incidence of JE has increased since 2010. The present study investigated the clinical manifestations, laboratory findings, and factors affecting neurological outcomes of reemerging JE. We retrospectively reviewed medical records of laboratory-confirmed JE patients who presented with acute encephalitis syndrome at three tertiary hospitals between 2010 and 2015. A total of 17 patients with JE were identified. Their median age was 51 years, and 10 (58.5%) were men. The most common symptoms and signs were fever (94.1%), altered consciousness (94.1%), and headache (80.2%). Hyporeflexia (47.1%), seizures (35.2%), abnormal brainstem reflex (23.5%), and flaccid weakness (17.6%) were also noted. Brain imaging revealed thalamic lesions in all patients, with the hippocampus, midbrain, basal ganglia, and cerebral cortex affected to varying degrees. Sixteen patients (94.1%) required management in the intensive care unit with mechanical ventilation due to neurological deterioration. At the time of discharge, 11 (64.7%) had poor recovery, defined as Glasgow coma scale scores of less than 8, and remained ventilator dependent. Comparison between the two outcome groups indicated that midbrain involvement ($P = 0.028$) and rapid deterioration ($P = 0.005$) were associated with severe neurological sequelae. Given that JE is a vaccine-preventable disease, vaccination for adults should be considered in response to the reemergence of JE.

INTRODUCTION

Japanese encephalitis (JE) is one of the most important viral encephalitis in many countries within Asia, including South Korea.¹ The global incidence of JE is estimated to be approximately 67,900 new cases per year, with an overall incidence of 1.8 per 100,000.² JE virus (JEV) is a mosquito-borne flavivirus related to dengue, West Nile, and Zika viruses.³ Although most JEV infections are nearly or completely asymptomatic, clinically apparent JE results in high case fatality rates of 20–30% and severe neurological deficits in 30–50% of survivors.⁴ After a short, nonspecific prodrome, patients typically present with fever, altered sensorium, headache, and seizures.^{5,6} Clinical manifestations also include flaccid paralysis and parkinsonian movement disorders.⁷ JEV is primarily transmitted by *Culex tritaeniorhynchus* mosquitoes within a zoonotic cycle where water birds and pigs serve as major vertebrate hosts for viral maintenance and amplification.¹ In this regard, close proximity to rice fields and pigsties is considered a risk factor for JE in agricultural countries.⁸ Furthermore, mosquito vector activities are largely affected by the climatic environment; thus, temperate regions such as South Korea and Japan have seasonal patterns of JE epidemics characterized by marked summertime peaks.^{9,10}

South Korea was an historically high-incidence area for JE, with several thousand cases occurring annually through the late 1960s.¹¹ Afterward, extensive use of insecticides decreased mosquito vectors in rice paddies and a long-standing national immunization program led to the near-elimination of JE in South Korea.⁹ Only 55 cases were

reported between 1984 and 2009. However, the number of JE cases notably increased in 2010, when 26 new cases were confirmed, including seven deaths.¹² This increased JE incidence has continued, reaching a peak of 40 cases in 2015. A total of 129 JE cases were reported between 2010 and 2015, with a case fatality rate of 21.3%.^{13,14} However, the clinical characteristics of recently reemerging JE in South Korea have not yet been reported. Herein, we describe the clinical presentations, laboratory findings, and clinical factors affecting outcomes after the acute stage of JE.

MATERIALS AND METHODS

JE case definition. The laboratory-confirmed JE cases were defined as cases that met both clinical criteria for acute encephalitis syndrome (AES) and laboratory criteria for JE according to the World Health Organization recommendation.¹⁵ Clinically, AES refers to the acute onset of fever and at least one of altered mental status and newly developed seizures. Laboratory confirmation of JEV infection requires one of the following: 1) presence of JEV-specific IgM antibody in serum or cerebrospinal fluid (CSF) samples in the absence of IgM to other flaviviruses; 2) detection of a more than 4-fold increase in JEV-neutralizing antibody between acute and convalescent stages.¹⁶ Laboratory tests and confirmation were done by the Korea Centers for Disease Control and Prevention (KCDC; Cheongju-si, South Korea). Regarding the laboratory diagnosis of JE, we follow the decision of KCDC.

Laboratory procedures for diagnosis of JE. For laboratory diagnosis of JE, all samples from patients were transferred to the KCDC and serological tests were performed as previously described.¹² Anti-JEV IgM antibodies were tested by using the JE-Dengue IgM Combo enzyme-linked immunosorbent assay (ELISA) (Panbio, Australia) and JE

* Address correspondence to Kon Chu, Department of Neurology, Seoul National University Hospital, 101, Daehak-ro, Jongno-gu, Seoul, South Korea 03080. E-mail: stemcell.snu@gmail.com

Detect IgM ELISA kits (InBios, Seattle, WA) according to the manufacturer's protocols. Anti-JEV IgG antibodies were detected by using the JE Detect IgG ELISA kit (InBios). To detect JEV-specific neutralizing antibodies, the plaque reduction neutralization test (PRNT) was conducted as previously described.¹⁷

Data collection. To identify laboratory-confirmed JE cases between 2010 and 2015, we searched the electrical medical record systems of three tertiary hospitals affiliated with Seoul National University. We included only patients who were hospitalized at the acute stage of encephalitis and diagnosed with JE during the hospitalization. All patients presenting with AES underwent laboratory investigations, including blood and CSF cultures, viral polymerase chain reactions (PCR), and serological tests for infectious causes of encephalitis: herpes simplex virus (HSV) type 1 and 2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, influenza, adenovirus, enterovirus, JC virus, measles, human immunodeficiency virus, human herpes virus 6 and 8, syphilis, scrub typhus, *Mycoplasma*, *Legionella*, *Mycobacterium*, *Chlamydia*, *Brucella*, *Borrelia*, *Cryptococcus*, *Aspergillus*, and *Pneumocystis*. None of JE-confirmed cases in this study had coinfections. We retrospectively reviewed the patient medical records to investigate the clinical manifestations of JE together with laboratory and neuroimaging findings and clinical outcomes. For patients referred from other facilities, we also reviewed clinical information obtained from the previous hospitals where the patient was admitted. In terms of residential areas, urban areas were defined as Seoul, the capital city, and six metropolitan cities according to the administrative divisions of South Korea. The remaining provinces were defined as rural areas. For all laboratory-confirmed JE cases, vaccination history was investigated through the medical records and the electronic vaccination registry operated by KCDC. Additionally, we investigated vaccination history by directly asking patients or their relatives. Functional status was measured by the modified Rankin scale (mRS) and Glasgow coma scale (GCS), and poor outcomes were defined as GCS scores of less than 8 or ventilator-dependent status. Then, we compared good outcome and poor outcome groups in terms of demographic, laboratory, and neuroimaging findings.

Statistical analysis. Statistical differences between the two outcome groups were analyzed by the Fisher's exact or Mann-Whitney *U* tests according to the nature of the variables. We used IBM SPSS Statistics for Windows, version 21.0 (Armonk, NY) for statistical analyses; the significance level was set at a two-tailed *P* value of less than 0.05.

Ethics statement. This study was approved by the institutional review board (IRB) of Seoul National University Hospital (H-1606-074-771). Informed consents were not obtained from the subjects because this was a retrospective chart review study. The IRB granted a waiver of informed consent for this study. The information obtained from medical records was de-identified to protect the privacy of subjects.

RESULTS

Demographic characteristics. We identified 17 patients who fulfilled the clinical and laboratory criteria for JE during the study period. Their median age was 51 years (range,

15–87), and 10 (58.5%) patients were men. Ten (58.8%) patients lived in rural areas. Seven (41.2%) patients lived in urban areas: four in Seoul, two in Incheon, and one in Daegu. When the cases were stratified by age, JE was most common in patients aged 50–59 years (41.2%), followed by those aged 40–49 years (23.5%) and those aged over 60 (17.6%), whereas patients younger than 30 years accounted for only 11.8% of the study population. All cases occurred in August (41.2%), September (47.1%), and October (11.7%), in line with the marked summer epidemics of JE in South Korea.^{9,16} Primary or booster vaccination against JEV was not evident in any cases. Five patients had history of chronic diseases such as hypertension and diabetes mellitus, whereas immune-compromising conditions were not found in any cases. Neither proximity to a pigsty nor history of international travel before the clinical onset of JE was identified in any patients.

Clinical features. The median time from symptom onset to initial hospital visit was 3.5 days (range, 1–13); five patients were referred from other hospitals. The most common symptoms and signs at initial presentation were altered mental status (94.1%), fever (94.1%), and headache (80.2%). The specific manifestation of altered mental status was confusion in four (25%), stupor in four (25%), and coma in eight (50%), and the median GCS score was 8 (range, 3–15) at the time of admission. Seizures occurred in six (35.2%) patients: generalized tonic-clonic seizure in all patients, simple partial seizure in one, and complex partial seizure in one patient. Neurological examination revealed diminished deep tendon reflex in eight (47.1%) patients, abnormal brainstem reflex in four (23.5%), and flaccid paralysis in three (17.6%). Flaccid weakness typically affected the lower extremities, and the weakness spread to involve four extremities in one patient. Upper motor neuron signs such as extensor plantar response and ankle clonus were noted in two (11.8%) patients. Rigidity was found in three (17.6%) patients.

Laboratory findings. Blood tests at the time of admission revealed leukocytosis (white blood cell [WBC] count > 10,000/ μ L) in five (29.4%) patients and C-reactive protein elevation (> 0.5 mg/dL) in 10 patients (58.8%). Thirteen (76.5%) patients were positive for anti-JEV IgM antibody in the first serum sample tested (Table 1). The remaining patients seroconverted by the follow-up test. Anti-JEV IgM antibody in CSF was positive in nine (75%) of 12 patients tested. Data for antibody titer were available for 13 patients, and all showed a titer increase, with a median 4-fold change (range, 2–32). CSF samples were obtained from all 17 patients, and the median time from symptom onset to lumbar puncture was 3 days (range, 1–11 days). CSF pleocytosis was evident in 100% of patients, with a median WBC count of 126/mm³ (range, 25–630/mm³); the median lymphocyte ratio on WBC differential was 69% (range, 18–90%). Protein elevation (> 45 mg/dL) was noted in 16 (94.1%), with a median value of 95 mg/dL; CSF glucose was normal, with a median CSF to serum ratio of 0.55.

Neuroimaging and electroencephalography. Brain magnetic resonance imaging (MRI) demonstrated bilateral medial thalamic T2 high-signal lesions in all patients (Table 2). Extrathalamic lesions involved the hippocampus in 15 (88.2%), midbrain in 12 (70.6%), and basal ganglia in 9 (52.9%) patients. As shown in Figure 1, the temporal lobe

TABLE 1

Patient demographics and results of serological tests for Japanese encephalitis virus

Patient no.	Age	Sex	Serum IgM Ab		CSF IgM Ab	JEV-specific Ab titer (1:n)	
			Initial	Follow-up		Initial	Follow-up
1	15	F	+	+	N/A	16	64
2	21	M	–	+	–	–	N/A
3	38	M	+	+	+	32	512
4	40	M	+	+	N/A	256	512
5	42	M	+	+	N/A	16	128
6	43	F	–	+	+	16	512
7	47	M	–	+	+	–	256
8	50	F	–	+	–	–	256
9	51	F	+	+	–	16	256
10	52	M	+	+	+	N/A	512
11	54	M	+	+	+	16	128
12	57	M	+	+	+	256	512
13	58	M	+	+	+	128	512
14	59	M	+	+	+	16	64
15	71	F	+	+	N/A	512	1,024
16	73	F	+	+	+	16	32
17	87	F	+	+	N/A	128	256

Ab = antibody; CSF = cerebrospinal fluid; JEV = Japanese encephalitis virus; N/A = not available.

lesions particularly involved the hippocampus, including its tail portion, whereas midbrain lesions typically affected the substantia nigra. Electroencephalography (EEG) was performed in all patients; epileptiform discharges were identified in six (35.3%) patients. Among them, two had clinical seizures, whereas the remaining four had no witnessed seizures. Of six patients with epileptiform discharges, four patients had EEG findings suggestive of nonconvulsive status epilepticus (NCSE), including lateralized periodic discharges or rhythmic delta activities with evolving patterns. In cases without epileptiform discharges, EEG showed generalized irregular slow activities with varying degrees of amplitude, which suggested diffuse cerebral dysfunction.

Clinical course and outcomes. All but one (94.1%) of the patients with JE required management in the intensive care unit (ICU), including mechanical ventilation and tracheostomy, mainly for deteriorating consciousness and consequent respiratory failure. The clinical course of neurological deterioration

was fulminant; the median time from symptom onset to nadir was 5 days (range, 3–17 days), and the median GCS score at the nadir was 3 (range, 3–8). General supportive treatment was the primary management strategy in all cases. At the time of discharge, the median mRS score was 5 (range, 1–5), indicating severe neurological sequelae following JE in most cases. The 11 (64.7%) patients with poor outcome were bedridden (i.e., mRS score 5) and remained ventilator-dependent. In contrast, six patients (35.3%) with good outcomes recovered consciousness, with final GCS scores ranging between 10 and 13, which led to successful weaning from mechanical ventilation. The median length of ICU and hospital stays was 21 and 43 days, respectively. All patients survived to discharge. In univariate analysis, the factors related with poor outcomes included midbrain-involving lesions on MRI ($P = 0.028$) and rapid neurological progression to nadir ($P = 0.005$; Table 3). Otherwise, highest antibody titers, CSF profiles, and EEG findings did not differ between the two outcome groups.

DISCUSSION

In South Korea, laboratory investigation and diagnosis for JEV are performed by KCDC through the national surveillance system. Therefore, laboratory confirmation of JE in this case series was made based on well-established protocols and criteria of KCDC rather than arbitrarily determined by the authors.¹⁷ The presence of IgM antibodies in serum alone can be problematic for JE diagnosis in regions where other flaviviruses cocirculate.¹⁸ However, dengue and West Nile viruses are not endemic in South Korea unlike southeast Asian countries.^{19,20} In eight patients, the presence of CSF JEV antibody was not confirmed. However, serum antibody titers increased more than 4-fold or up to significantly high titers ($\geq 1:256$) in the follow-up test, which supports true JEV infection. All of the patients had MRI features typical of JE such as bilateral thalamic hyperintensities, although neuroimaging findings were not used as selection criteria. Furthermore, all cases occurred during the seasonal outbreak of JE in South Korea and

TABLE 2

Anatomical distribution of brain lesions on magnetic resonance imaging

Patient no.	Thalamus	Hippocampus	Midbrain	Basal ganglia	Neocortex	Cerebellum	Meningeal enhancement
1	+						+
2	+	+	+	+	+		+
3	+	+	+				+
4	+	+	+	+			+
5	+	+	+		+		+
6	+	+	+	+			
7	+	+	+	+	+		
8	+	+	+	+	+	+	+
9	+	+	+	+	+	+	+
10	+	+					
11	+	+					
12	+	+	+	+	+		
13	+	+					+
14	+	+	+	+			+
15	+	+	+	+	+		
16	+						
17	+	+	+				
Total	17 (100%)	15 (88.2)	12 (70.6)	9 (52.9)	7 (41.2)	2 (11.8)	9 (52.9)

FIGURE 1. Axial fluid-attenuated inversion recovery magnetic resonance imaging of Japanese encephalitis. A case demonstrating typical MRI findings including bilateral hyperintensities in the (A) medial thalamus, (B) hippocampal tail, and (C) body. (D) Midbrain lesions involving the substantia nigra as well as hippocampal tail lesions are noted in another case. (E) A case showing extensive brain lesions. High-signal lesions involving the medial frontal cortex, insular cortex, caudate nucleus, basal ganglia, thalamus, and hippocampal tails are noted. (F) In addition, hyperintensities in the substantia nigra are seen.

underwent comprehensive tests to rule out other etiologies of acute encephalitis. Taken together, it is suggested that our JE cases indicated true JEV infection rather than false positives due to antibody cross-reactivity or asymptomatic infection.

The results of the present study showed that recent JE in South Korea predominantly affected the adult population over 40 years of age. This finding is consistent with national surveillance data that 89.9% (116 of 129) of JE cases between 2010 and 2015 were more than 40 years of

TABLE 3
Clinical features of Japanese encephalitis according to outcomes

Variables	Good outcome (N = 6)	Poor outcome (N = 11)	P value
Age, years	56 (15–73)	50 (21–87)	0.591
Male	3 (50)	7 (63.6)	0.644
Seizures	2 (33.3)	4 (36.4)	1
Hyporeflexia	3 (50)	5 (45.5)	1
Abnormal brainstem sign	0 (0)	4 (36.4)	0.237
Laboratory			
CSF WBC (/mm ³)	144 (25–630)	126 (38–480)	0.961
CSF protein (mg/dL)	90.7 (31–132.4)	104 (43–134.2)	0.961
CSF/serum glucose ratio (%)	52.6 (35.9–59.2)	57.5 (42.3–64.4)	0.263
Highest serum JEV Ab titer (1:n)	320 (32–1,024)	256 (64–152)	0.875
Brain MRI lesions			
Thalamus	6 (100)	11 (100)	1
Hippocampus	4 (66.7)	11 (100)	0.11
Midbrain	2 (33.3)	10 (90.9)	0.028*
Basal ganglia	2 (33.3)	7 (63.6)	0.335
Cerebral cortex	1 (16.7)	6 (54.5)	0.304
Cerebellum	0 (0)	2 (18.2)	0.515
Meningeal enhancement	3 (50)	6 (54.5)	1
EEG			
Epileptiform discharges	4 (66.7)	2 (18.2)	0.109
NCSE	3 (50)	1 (9.1)	0.099
Disease progression			
GCS at nadir	3.5 (3–8)	3 (3–3)	0.098
Time to nadir (days)	6.5 (5–17)	4 (3–6)	0.005*

CSF = cerebrospinal fluid; EEG = electroencephalography; GCS = Glasgow Coma Scale; JEV Ab = Japanese encephalitis virus antibody; MRI = magnetic resonance imaging; NCSE = nonconvulsive status epilepticus. Data are presented as a median (range) or a number (%).

* $P < 0.05$.

age.^{13,14} Before implementation of the vaccination program, JE was a predominantly childhood disease, in which more than 80% of cases were children under 15 years of age.⁹ Similarly, the nationwide immunization targeting children led to a shift in the age distribution of JE cases from children to adults in other Asian countries, including India, Japan, and Taiwan.^{21–23} This age-shifting phenomenon may suggest successful vaccination for children, resulting in a relative increase of adult JE cases. Further epidemiological and serological studies are required to elucidate the exact cause of reemerging JE in South Korea. Moreover, given that JE is a vaccine-preventable disease, public health policies on the necessity of primary and booster vaccination for adults should be considered.

Decreased tendon reflex and flaccid limb paralysis were noteworthy features of JE, although they occurred in a minority of cases. Anterior horn cell involvement in a subgroup of JE patients has been well established.^{18,24} In the current study, three patients showed acute flaccid paralysis with encephalitis symptoms, and decreased tendon reflex was present in eight patients. A previous study reported that tendon reflex changes were associated with poor prognosis,²⁵ although the association was not significant in our data. Together with West Nile virus, JEV is one of the primary viruses that can cause both AES and poliomyelitis-like flaccid paralysis.²⁶ Thus, JE should be considered in the differential diagnosis of acute encephalitis associated with hyporeflexia or flaccid motor weakness.

The clinical profiles and outcomes of JE have been described in previous studies particularly from Southeast Asia. A decreased level of consciousness or deep coma was consistently identified as a poor prognostic factor across the studies.^{27–29} In our study, likewise, the median GCS score (3) at the nadir in the poor outcome group was less than that of the good outcome group (3.5), although the difference was not statistically significant. Since all cases experienced deep coma with GCS scores falling below 8, it was difficult to quantitatively demonstrate differences in the extent of unconsciousness between the two groups. Instead, focusing on the speed of the deterioration of consciousness, we found that JE patients with poor outcomes deteriorated more rapidly into a comatose state. However, patients with good outcomes also reached the lowest level of consciousness within a median of 6.5 days, indicating that patients with JE mostly experienced worsening consciousness within the first week after symptom onset. A reduced level of consciousness is a well-known clinical feature of JE,¹⁸ but there has been little information on its time course during the acute stage. A study from Vietnam showed that the median time to full coma was 5 days,⁵ which is consistent with the results from our cases. The largest case series from India also reported that GCS scores during the acute phase declined from 15 to 5 within 2 days.⁶ Taken together, severe and rapid consciousness deterioration is a common clinical course during the acute phase of JE. Careful monitoring for alteration of consciousness is required for early stage management.

Regarding MRI findings of JE, thalamic lesions with concurrent hippocampal involvement were noted in most patients. Although medial thalamic lesions were the most consistent findings of JE, extrathalamic lesions including the basal ganglia, hippocampus, midbrain, cerebellum, and

cerebral cortex were also reported in previous studies.^{30–32} Interestingly, the posterior hippocampus was preferentially involved in our JE cases (88.2%). Temporal lobe involvement in JE was also reported in neuroimaging study from India.³³ In agreement with our results, JE typically affected the posterior hippocampus, whereas the temporal neocortex and insular were usually spared.³³ In line with this, CSF PCR assays for HSV were all negative in our cases. JEV enters the brain through a hematogenous route.³⁴ The blood supply to the body and tail of the hippocampus arises from the posterior circulation such as the posterior cerebral and posterior choroidal arteries, whereas anterior choroidal and anterior temporal arteries from the anterior circulation supply the blood to the hippocampal head.^{35,36} Considering that the blood supply to the thalamus also originated from the posterior circulation system, the arterial supply anatomy may partly explain the concurrent involvement of the thalamus and the posterior hippocampus in JE. Further imaging studies with pathological evaluations are required to validate our observation that reemerging JE is characterized by predominant involvement of the posterior hippocampus.

There has been little information concerning the correlation between neuroimaging findings and clinical outcomes^{29,37}; to our knowledge, the current study is the first to suggest the association between midbrain involvement and poor outcomes in JE. It is presumed that midbrain lesions represented the rostro-caudal extension of JEV-associated pathology from the thalamus, which might be attributed to both direct viral invasion through the axonal transport and neuronal death secondary to overactivated inflammatory responses.³⁸ Abnormal brainstem signs and breathing patterns, which were related with poor outcomes in other studies, could be understood in the same context of the midbrain involvement in MRI.¹⁸

In this study, clinical seizures occurred in six (35.3%) JE cases. The other four (23.5%), who had no witnessed seizures, revealed epileptiform discharges on EEG. Previous studies reported that JE was associated with seizures in approximately 40% particularly during the acute stage of encephalitis.^{5,39} Although the presence of seizures itself did not have a prognostic significance, repeated seizures or status epilepticus was significantly associated with a poor outcome.⁵ Further, approximately 30% of seizures were reported to have subtle motor phenomena, making its diagnosis challenging without EEG recordings. In line with this, we identified four cases (23.5%) with NCSE; two of them had no witnessed seizures. Viral encephalitis can cause NCSE,⁴⁰ but little is known about NCSE in JE. The extent to which epileptic activities in NCSE contribute to the additional neuronal damage remains controversial and varies with the type and etiology of NCSE.⁴¹ However, considering the lack of specific antiviral treatments and the high rate of severe neurological sequelae in JE, early detection and management of NCSE might be an important treatment strategy to improve the outcome by controlling the secondary complications. The survival rate of our JE cases was 100% at hospital discharge, suggesting better mortality outcomes than those of previous studies.^{23,28,29} In addition to seizure management, appropriate critical care including mechanical ventilation and hemodynamic support might have contributed to avoiding early mortality of JE in this study.

The current study has several limitations. Because of the nature of a hospital-based study, a small number of JE cases were included. In this regard, our observations cannot be generalized to all JE cases in South Korea. The tertiary hospital setting might also contribute to a high rate of unfavorable outcomes through a selection bias toward severe cases. Lack of multivariate analysis hindered identification of independent predictors for JE outcomes. Furthermore, although parkinsonian movement disorders have been well established in JE, detailed information on abnormal movements was not available in many cases due to the limitation of retrospective design of this study. A multicenter study with larger populations and longer follow-up is warranted to address these limitations.

In conclusion, midbrain lesions and rapid consciousness worsening appear to be associated with severe neurological sequelae in this study. Given its recent reemergence in South Korea, JE should be considered a possible cause of acute encephalitis, particularly in the summer season. In addition, since the initial presentations of JE might be nonspecific, a high index of suspicion and subsequent serological evaluation are critical for prompt diagnosis. Physicians should also pay careful attention to consciousness deterioration, seizures, and respiratory failure during the acute phase to minimize secondary complications.

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Authors' addresses: Jun-Sang Sunwoo, Department of Neurology, Soonchunhyang University School of Medicine, Seoul, South Korea, E-mail: ultrajs4@gmail.com. Soon-Tae Lee, Keun-Hwa Jung, Jangsup Moon, Ki-Young Jung, Manho Kim, Sang Kun Lee, and Kon Chu, Department of Neurology, Seoul National University Hospital, Seoul, South Korea, E-mails: staelee@gmail.com, jungkh@gmail.com, jangsup.moon@gmail.com, jungky10@gmail.com, kimmanho@snu.ac.kr, sangkun2923@gmail.com, and stemcell.snu@gmail.com. Kyung-Il Park, Department of Neurology, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, South Korea, E-mail: ideopki@gmail.com.

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