Acute Necrotizing Encephalopathy in Korean Infants and Children: Imaging Findings and Diverse Clinical Outcome

Ji Hye Kim, MD[1]
In-One Kim, MD[2]
Myung Kwan Lim, MD[3]
Man Soo Park, MD[4]
Choong Gon Choi, MD[5]
Hye Won Kim, MD[6]
Jee Eun Kim, MD[6]
Soo Jin Choi, MD[6]
Young Hwan Koh, MD[6]
Dal Mo Yang, MD[6]
Sung Wook Choo, MD[1]
Myung Jin Chung, MD[1]
Hye-Kyung Yoon, MD[1]
Hyun Woo Goo, MD[5]
Munhyang Lee, MD[7]

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[1]Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine; [2]Department of Radiology, Seoul National University College of Medicine; [3]Department of Radiology, Incheon Medical Center, College of Medicine, Inha University; [4]Department of Radiology, Asan Kang Nung Hospital; [5]Department of Radiology, Asan Medical Center, University of Ulsan College of Medicine; [6]Department of Radiology, Gachon Medical School, Ghil Medical Center; [7]Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine

Address reprint requests to:
Ji Hye Kim, MD, Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-dong, Kangnam-gu, Seoul 135-710, Korea.
Tel. (822) 3410-0511
Fax. (822) 3410-0084
e-mail: jhkate.kim@samsung.com

Objective: The purpose of our study was to describe acute necrotizing encephalopathy in Korean infants and children, and we sought to evaluate the prognostic factors.

Materials and Methods: Acute necrotizing encephalopathy was diagnosed in 14 Korean infants and children. We retrospectively analyzed the neuroimaging findings including the follow-up changes. The clinical course of the disease was graded, and we evaluated prognostic factors including age, serum level of the aminotransferase, hemorrhage, and localized atrophy of the brain.

Results: This encephalopathy predominantly affected the bilateral thalami (n=14), pons (n=12), and midbrain (n=10) in a symmetrical pattern. Hemorrhage was observed in eight patients (57%). On the follow-up images (n=12), the brain lesions were reduced in extent for all patients, and generalized atrophy was seen in six patients. Localized tissue loss was observed in five patients and a complete resolution occurred for one patient. All the patients survived and two recovered completely; mild (n=6) to severe (n=6) neurological deficits persisted in the remaining 12 patients. The significant prognostic factors identified in this study were the presence of hemorrhage ($p = 0.009$) and localized atrophy ($p = 0.015$).

Conclusion: Acute necrotizing encephalopathy in Korean patients showed the characteristic patterns of the post-infectious encephalopathy as described in the literature. The high survival rate and the relatively favorable clinical course observed for the present study suggest a more diverse spectrum of disease severity than was previously described. The presence of hemorrhage and localized tissue loss on MR images may suggest a poor prognosis.

Acute necrotizing encephalopathy (ANE) represents a peculiar type of encephalopathy characterized by bilateral symmetrical lesions that are predominantly observed in the thalami and brain stem of infants and children. It has been described by Japanese pediatricians, and it is regarded as a novel disease entity based on clinico-pathological data (1, 2). Although there is some argument on specific terminology (3), the term acute necrotizing encephalopathy has been widely accepted since it was first proposed by Mizuguchi et al. (1). ANE occurs following a systemic viral infection, and death or irreversible neurological sequelae have been described as the typical result of this disease. However, the etiology and pathogenesis of the disease remain mostly unknown. ANE has been predominantly reported in Japan and Taiwan in the Far East, and although Korea is geographically close to these countries, only three Korean cases have been reported (4, 5). Thus, we have conducted the first large series study on ANE in Korea.

The purpose of this multi-institutional study was to describe the radiological findings and the clinical course of ANE in Korean infants and children, and we sought to evaluate the clinico-radiological prognostic factors related to this disease.

MATERIALS AND METHODS

Fourteen infants and children with ANE that was diagnosed in six Korean institutions over the past 10 years were the study subjects. The diagnoses were based on the criteria proposed by Mizuguchi et al. (6) (Table 1). The ages of the 14 patients ranged from 5 months to 12 years with a median age of 26 months, and there were 8 boys and 6 girls. The clinical findings during their hospital admission are summarized in Table 2. Presenting symptoms included fever and seizure followed by impairment of consciousness; this was often precipitated by seizures in all patients except for one (patient 3) who stayed alert throughout the clinical course. All of the patients had experienced preceding symptoms, and they all had signs of upper respiratory tract infection (n=11) or acute viral gastroenteritis (n=3). The

Table 1. Diagnostic Criteria of Acute Necrotizing Encephalopathy Proposed by Mizuguzi (modified from reference 11)

1. Acute encephalopathy following viral disease, with seizure and deterioration of consciousness.
2. Absence of CSF pleocytosis. CSF protein is commonly increased.
3. Neuroimaging findings of symmetric, multifocal brain lesions involving the bilateral thalmi, upper brain stem tegmentum, periventricular white matter, internal capsule, putamen and cerebellum.
4. Elevation of serum aminotransferase level to a variable degree. No increase in blood ammonia.
5. Exclusion of any resembling disease.
   A. Clinical differential diagnosis; toxic shock syndrome, hemolytic uremic syndrome, Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke.
   B. Radiological (or pathological) differential diagnosis; Leigh encephalopathy, glutaric acidemia, methyl malronic aciduria, infantile bilateral strial necrosis, Wernicke encephalopathy, carbon monoxide poisoning, acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, arterial or venous infarct, severer hypoxic or traumatic injury.

Table 2. Summary of the Clinical Findings of 14 Patients

Case No	Age/ Gender	Viral Infection	Presentation of Encephalopathy	S-AST/ALT (IU/L)	CSF Profile	Antiviral Antibody/PCR	Outcome
1	5 Mo/M	URI, 3DA	Seizure, stuporous	89/45	WNL	ND	Spastic quadriplegia, rigidity
2	5 Yr/M	URI, 4DA	Seizure, comatose	242/1000	WNL	ND	Stuporous, rigidity
3	5 Mo/F	URI, 7DA	Seizure	88/43	WNL	Negative for HSV, TORCH	Recovered
4	10 Mo/F	URI, 15DA	Seizure, stuporous	80/28	WNL	ND	Spastic quadriplegia
5	5 Mo/M	URI, 14DA	Seizure, drowsy	36/35	WNL	ND	Recovered
6	6 Yr/M	AGE, 7DA	Seizure, comatose	159/216	WNL	ND	Coma
7	19 Mo/M	URI, 10DA	Seizure, lethargic	88/174	Protein, 240 mg/dl	Negative for Coxackie, JBV, HSV1, Echovirus	Increased DTR, ankle clonus
8	4 Yr/F	URI, 10DA	Seizure, stuporous	68/45	WNL	ND	Left motor weakness
9	10 Yr/M	URI, 14 DA	Stuporous to drowsy	66/21	WNL	ND	Drowsy to alert, increased DTR
10	28 Mo/M	URI, 10DA	Seizure, lethargic, deviated left eye	38/103	WNL	Negative for HSV	Alert, eye deviation
11	12 Yr/F	AGE, 13DA	Seizure, comatose	62/15	Protein, 61 mg/dl	ND	Stupor
12	3 Yr/F	URI, 4DA	Seizure, drowsy	153/162	Protein, 179 mg/dl	Positive for Influenza A	Drowsy to alert, eye blinking, left arm clonus
13	10 Mo/M	AGE, 2DA	Seizure, drowsy, decerebrated rigidity	102/42	Increased protein	Negative for HSV, enterovirus	Severe motor deficit
14	6 Mo/F	URI, 4DA	Seizure, mental change, rigidity of extremity	54/21	Increased protein	Negative for HSV, enterovirus	Alert, less rigid extremity

Note.—URI = upper respiratory infection, AGE = acute viral gastroenteritis, S-AST/ALT = serum level of aspartate/alanine aminotransferase, WNL = within normal limit, JBV = Japanese B encephalitis virus, HSV = herpes simplex virus, Mo = months, Yr = years, DA = days ago, ND = Not performed, DTR = deep tendon reflex

time interval between the most recent viral infection and the onset of encephalopathy varied from 3 to 15 days with a mean period of 8 days. None of the patients had been recently immunized.

The serum levels of the aspartate aminotransferase and alanine aminotransferase were found to be elevated to variable extents in 13 patients. The serum ammonium levels were not elevated in any of the 10 patients tested. Cerebrospinal fluid (CSF) analysis was done for 12 patients and none of them exhibited pleocytosis. A mild increase in the protein level of the CSF was noted in 5 patients. Serum anti-viral antibody and polimerase chain reaction (PCR) analysis for viral DNA were performed for 6 patients; all of them were negative except for one in whom inflenza A virus was cultured from the CSF and nasal secretions (patient 12). Stains and cultures for bacteria in the CSF were all negative.

All the patients underwent an MR examination between one and seven days from the encephalopathy onset, and a total of 28 MRIs and 3 CT scans were obtained. Because the cases were collected from multiple institutes, MR imaging were performed on various equipment, including 1.5-T, 1.0-T and 0.5-T superconducting systems (Siemens AG, Erlangen, Germany/ General Electric Medical Systems, Milwaukee, U.S.A.), and the images included spin echo T1-, T2-weighted images and fluid attenuated inversion recovery sequences having combinations of axial, sagittal and coronal image planes. Post-contrast enhancement images were obtained for eight patients. The slice thickness used was usually 5 mm.

The neuroimaging findings were analyzed in terms of the distribution and pattern of the lesions, the presence of hemorrhage and temporal evolution. We classified the patients into favorable and severe sequelae groups accord-

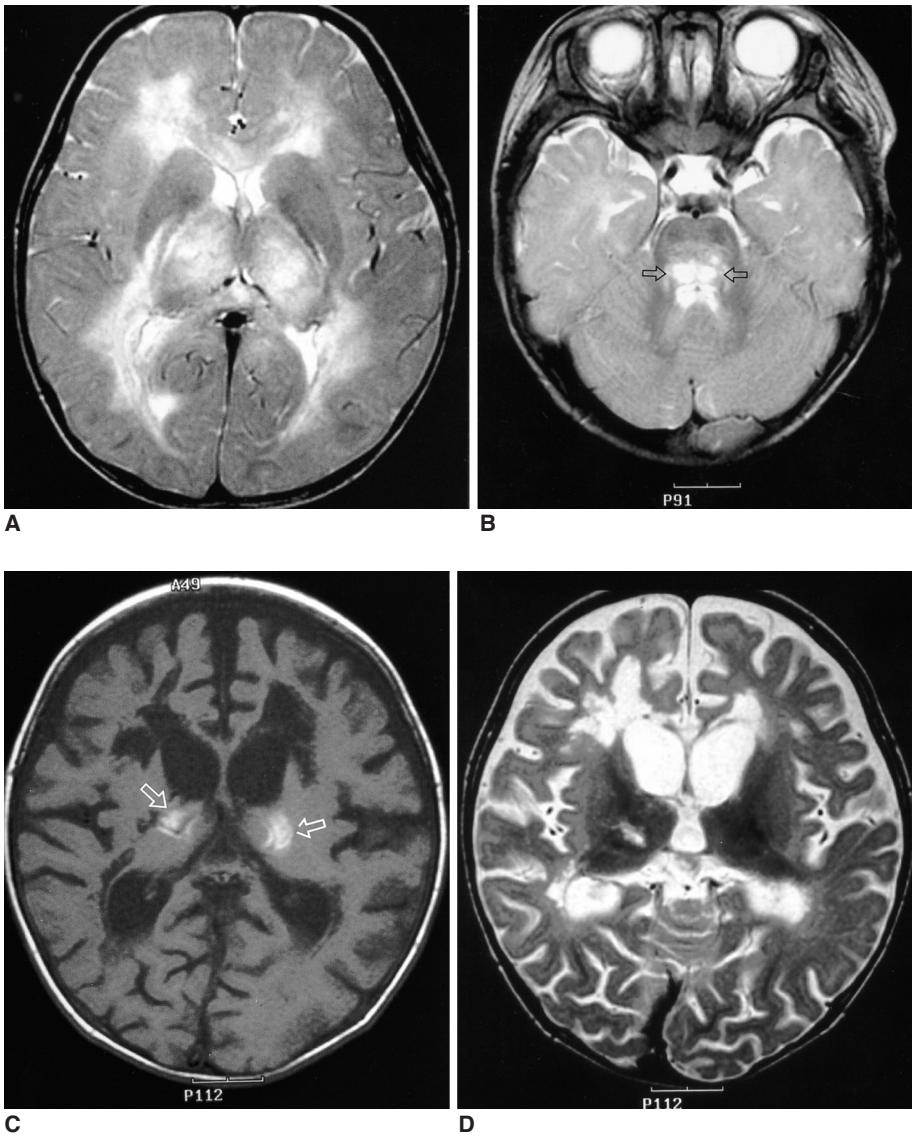

Fig. 1. MRIs of a 10-month-old girl (patient 4) who was left with severe sequelae.
A, B. Initial MR images obtained on the day following the hospital admission. T2-weighted axial images (**A, B**) show increased signal intensity in the thalami, the posterior internal capsule, putamen, periventricular white matter and the tegmen of the pons (arrows).
C, D. Follow-up MR images obtained after one month of initial study. The T1-weighted image (**C**) shows shrunken thalami, localized low signal intensity that was similar to the cerebrospinal fluid in the periventricular white matter, and generalized atrophy of the cerebral hemispheres. The patches of bright signal intensity in the bilateral thalami (open arrows) suggest a subacute stage of hemorrhage. The localized bright signal intensity in the periventricular white matter and in the right thalamus on T2 weighted images (**D**) suggest the cystic evolution.

ing to the clinical outcome, where the favorable group included those patients who recovered completely or had only mild sequelae. Mild sequelae were defined as a restored gait and speech abilities in spite of the residual neurological deficits (6). The remaining subjects were included in the severe sequelae group. Several prognostic factors were evaluated with respect to the patient outcome: 1) age < 2 years, 2) elevated serum levels of aspartate aminotransferase or alanine aminotransferase of >100 IU/liter, 3) presence of hemorrhage, and 4) localized tissue loss on follow-up MR images. Statistical analysis was performed using Fisher's exact test in a 2 ×2 table. A *p*-value of < 0.05 was regarded as statistically significant.

RESULTS

Neuroimaging findings

The neuroimaging findings are summarized in Table 3. The major involved sites were the thalami (n=14), pons (n=12), midbrain (n=10), and internal capsule (n=7) in a bilateral symmetrical pattern (Figs. 1, 2). The brainstem involvement was predominantly tegmental (Figs. 1B, 3B) in eight patients, and both the ventral and dorsal brainstems were involved for four patients. The temporal lobe (n=4), external capsule (n=4), cerebral deep white matter (n=3), cerebellum (n=2), putamen (n=2), frontal lobe (n=1), and caudate nuclei (n=1) were also involved in some patients. The observed lesions were initially edematous with T1 and T2 prolongation. There were hyperintense thalamic lesions noted on the T1-weighted images in eight patients on the initial images (n=5) or on the follow-up images (n=3, Fig. 1D); this suggested that there was a subacute stage of hemorrhage, which was also seen in the pons in one patient. These hemorrhagic lesions showed variable T2 signal intensity. Contrast enhancement was performed for eight patients and enhancement

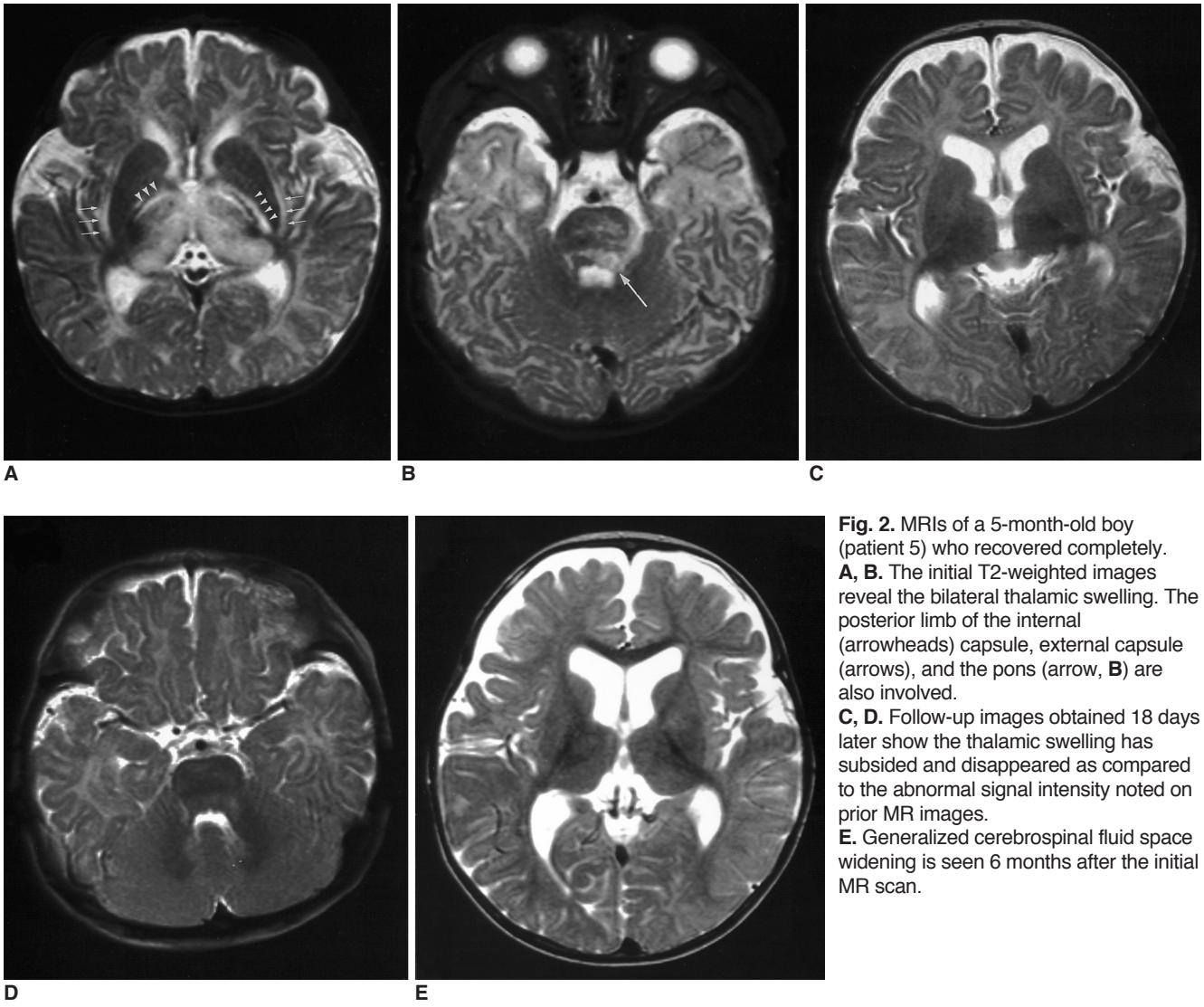

Fig. 2. MRIs of a 5-month-old boy (patient 5) who recovered completely.
A, B. The initial T2-weighted images reveal the bilateral thalamic swelling. The posterior limb of the internal (arrowheads) capsule, external capsule (arrows), and the pons (arrow, **B**) are also involved.
C, D. Follow-up images obtained 18 days later show the thalamic swelling has subsided and disappeared as compared to the abnormal signal intensity noted on prior MR images.
E. Generalized cerebrospinal fluid space widening is seen 6 months after the initial MR scan.

occurred in four of them, usually on the follow-up images (n=3).

Follow up images were obtained for 12 patients from day 7 to day 180 after the first MR scan. The lesion swelling had subsided and the extent of the abnormal signal intensity decreased in all the patients (Figs. 1, 2). For patient 5, along with the clinical recovery, the brain lesions having abnormal signal intensity disappeared on the follow-up MR images obtained 18 days after the first images were taken, and the last MR imaging taken 6 months after the initial scan revealed a generalized CSF space widening (Fig. 2). Shrunken thalami (n=3) or localized cystic encephalomalacia (n=2, Figs. 1C, D) were noted on the relatively long-term follow-up images. Generalized CSF space widening was noted for 6 patients (Figs. 1C, D, 2E), and it was considered to be atrophy.

Patient outcome

All the patients survived and two of them (14%) completely recovered. Mild neurological deficit remained

Table 3. Summary of Radiological Findings of 14 Patients

No.	Scan time*	Distribution of the Lesions	Hemorrhage	Temporal Evolution	Interval of Scans
1	5 D	Bilat. thalami, IC, CN	Thalami	Decreased extent, residual hemorrhage, localized tissue loss & generalized atrophy	4 D, 5 Mo
2	4 D	Bilat. thalami, pons, midbrain, IC, EC	Thalami, pons	Decreased extent, strong enhancement, generalized atrophy	4, 25 D
3	1 D	Bilat. thalami, pons	None	Decreased swelling & extent	9 D
4	1 D	Bilat. thalami, pons, midbrain, IC, PVWM, temporal lobe	Thalami (delayed **)	Decreased extent, new thalamic hemorrhage, mild enhancement, localized & generalized atrophy	28 D
5	1 D	Bilat. thalami, pons, midbrain, IC, EC, frontal & temporal lobes	None	Resolved lesions & generalized CSF space widening	18 D, 6 Mo
6	3 D	Bilat. thalami, pons, midbrain, IC, putamen, PVWM, cerebellum	Thalami	Decreased extent, mild enhancement, localized tissue loss & generalized atrophy	1, 3 Mo
7	2 D	Bilat. thalami, pons, midbrain, IC, EC, temporal lobe, cerebellum	None	NA	NA
8	5 D	Bilat. thalami, pons, midbrain	None	Decreased extent, generalized atrophy	3 Mo
9	6 D	Bilat. thalami, pons, midbrain	None	NA	NA
10	4 D	Bilat. thalami, pons, midbrain, IC, PVWM, temporal lobe	None	Decreased extent	13 D
11	7 D	Bilat. thalami, pons, midbrain	Thalami (delayed **)	Decreased extent, new thalamic hemorrhage, dense enhancement, localized atrophy	23 D
12	1 D	Bilat. thalami, putamen, pons, midbrain	Thalami (delayed **)	Residual lesion, hemorrhage	23 D
13	2 D	Bilat. thalami, pons, PVWM	Thalami	Residual atrophy of lesions and hemorrhage	3 Mo
14	4 D	Bilat. thalami, EC	Thalami	Improved lesion	1 W

Note.—*Scan time = time interval between scan time and onset of the neurological symptoms.
**delayed = hemorrhage was first appeared on follow-up MR images.
D = days, Mo = months, W = week, NA = Not applicable, Bilat. = bilateral, IC = internal capsule, EC = external capsule, PVWM = periventricular white matter, CN = caudate nuclei

Table 4. Significance of Prognostic Factors

Patient Outcome	Prognostic Factors: Favorable	Prognostic Factors: Severe Sequelae	p Value
Age < 2 years	4	3	1
Elevated aspartate / alanine aminotransferase	3	3	1
Presence of hemorrhage	2	6	0.009
Local tissue loss	0	5	0.015

Table 5. Outcome of the Patients with Acute Necrotizing Encephalopathy Described in the Literature and This Study

	Literature Cases (6–25)	Cases in This Study
Survival with sequale		
None/mild	32 (35%)	8 (57%)
Moderate/severe	37 (40%)	6 (43%)
Death	23 (25%)	0 (0%)
Total	92 (100%)	14 (100%)

in six patients (43%) and moderate to severe neurological deficits or mental alterations persisted in six patients (43%). For the prognostic factors that we tested, we found that hemorrhage (p = 0.009) and localized tissue loss (p = 0.015) were associated with a poor prognosis.

DISCUSSION

ANE has been recently established as a disease entity and it predominantly affects infants and young children in Japan and Taiwan. Despite the fact that these countries and Korea are in close geographical proximity, the first case in Korea was reported as recently as 2003 (4). However, we were able to identify another 12 patients in six institutions over the last 10 years, and this suggests that most ANE patients have remained unreported in Korea. Nevertheless, it is not known whether the cause of this racial or geographic predilection is related to genetic or environmental factors. Having considered the recent cases from outside the Far East (7, 8–14), it appears that the geographic distribution of this malady could be wider than was previously thought.

The outcome of ANE is generally grave, although the prognosis has improved recently. We reviewed the outcomes of the 92 reported cases in the literature (6–26) that occurred in countries other than Korea, and we found that 65% of the patients died or were left with severe neurological sequelae. In contrast to the literature cases, all of the patients in our study survived and 57% completely recovered or were left with only mild deficits (Table 5). There are several other reported cases with good outcomes in the literatures (10, 14, 18, 26, 27). Those patients with good outcomes, including several cases in the present study, could be categorized as having a "mild" form of ANE, as has been described by Yoshigawa et al. (26). The pathologic process of ANE is presumed to be reversible in the less severely affected patients who proceed on to a complete clinical recovery and disease resolution, as was demonstrated by the MRI findings.

It is interesting that all our patients with severe neurological sequelae had hemorrhagic lesions on the MR images (Fig. 1), and the presence of localized atrophy or cystic encephalomacia seemed to be related to the severe sequelae. In addition, it is known that older patients, non-Japanese children and those patients with low values of serum aminotranferase, and also those patients without brainstem lesions tended to recover well (6). However, the patients' age and serum aminotranferase levels were not found to be significantly correlated with the clinical outcome in the present study. This was possibly due to the relatively small number of cases, which undoubtedly is a limitation of this study.

The distributions of lesions detected on CT or MRI scans in the present study were typical of ANE as described in the literature; the locations included thalami, upper brainstem tegmentum, cerebral white matter, internal capsule, putamen and the cerebellar medulla. Hemorrhage usually occurred in the thalami, and it was occasionally accompanied by brainstem hemorrhage. The cerebral white matter may be involved, although hemorrhage was seldom seen. The involved brain was often initially edematous, and it subsequently became atrophic. The temporal evolution of brain lesions on the MR images ranged from cystic encephalomalacia (n=2, Fig. 1) to complete resolution (n=1, Fig. 2), and this could indicate a more diverse spectrum of this disease's severity.

In clinical practice, ANE should be differentiated from viral encephalitis and the other types of parainfectious encephalopathies. Viral encephalitis may have a specific site of symmetrical brain involvement including the thalami, hypothalami, basal ganglia, or brainstem, and probably this is the result of a specific route of infection or from a molecular interaction between a viral protein and a receptor on the host cells (28). Of these, Japanese encephalitis virus involves the bilateral thalami; this disease is an endemic encephalitis spread by mosquitoes and it occurs only during a specific season. Unlike ANE, the thalamic lesions in Japanese encephalitis are not necessarily symmetrical, and brainstem involvement is relatively uncommon. Moreover, other brain areas such as the hippocampus, basal ganglia, substantia nigra, cerebellum, cerebral cortex and white matter are the frequently involved areas (29, 30).

Radiological findings are very helpful for differentiating the other types of postinfectious encephalopathies such as Reye syndrome or acute disseminated encephalomyelopathy (ADEM). However, the ANE having a favorable outcome may not be easily differentiated from ADEM with bilateral thalamic involvement (31, 32), although the involvement of other sites and the response to steroid therapy for patients with ADEM may be helpful. It's also interesting that the high apparent diffusion coefficient (ADC) of ADEM and the decreases in the ADC value in ANE on the diffusion-weighted images have been reported to suggest the different nature of the edema (20). The other radiological differential diagnoses that must be considered before arriving at a final diagnosis of ANE are; the acute form of infantile bilateral striatal necrosis, thrombosis of the internal and great cerebral vein, central pontine/extrapontine myelinolysis, Wernike encephalopathy, urea encephalopathy and Leigh encephalopathy. The other brain disorders that should be clinically excluded are

listed in Table 1.

In summary, ANE in Korean patients was found to be a post-infectious brain disorder predominantly involving the bilateral thalami and the brainstem, the disease will occasionally be accompanied by hemorrhage. The high survival rate with a relatively favorable clinical course and the various neuroimaging evolution patterns observed in the present study also suggest that there is a mild form of ANE and a more diverse spectrum of disease severity. The presence of hemorrhage and localized tissue loss on MR images may suggest a poor prognosis.

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