Table 1
Laboratory data in groups A and B

	Elemental ($n = 11$)	Non-elemental ($n = 20$)	Normal range	p
Age (years)	6.89 ± 6.17	4.90 ± 3.40		
Sex (M/F)	6/5	12/8		
UA (mg/dl)	1.53 ± 0.81	3.31 ± 1.37	2.5–5.8	<0.01
IP (mg/dl)	2.94 ± 1.41	4.49 ± 1.18	2.4–4.5	<0.05
K (mEq/l)	3.57 ± 0.96	4.16 ± 0.43	3.5–4.8	<0.05
Na (mEq/l)	139.5 ± 2.58	140.3 ± 2.94	140–146	n.s.
Cre (mg/dl)	0.35 ± 0.12	0.32 ± 0.10	0.4–0.8	n.s.
FEUA (%)	32.70 ± 28.65	17.41 ± 24.00	4–14	n.s.
% TRP (%)	87.73 ± 13.29	86.27 ± 20.96	60–90	n.s.
FENa	0.915 ± 1.202	0.644 ± 0.555	<1.0	n.s.
Urine pH	7.364 ± 0.67	7.39 ± 0.65	5.5–7.0	n.s.
β2 MG (mg/l)	22.23 ± 29.31	11.03 ± 29.20	<0.27	n.s.
TP (g/dl)	6.67 ± 0.60	6.54 ± 0.70	6.6–8.0	n.s.
Hb (g/dl)	12.52 ± 1.70	12.44 ± 1.15	10.9–14.3	n.s.
Cal (kcal/kg/day)	52.72 ± 12.19	59.58 ± 16.74		n.s.
Protein intake (g/kg/day)	2.32 ± 0.42			

Each value is expressed as mean ± SD. M, male; F, female; UA, uric acid; IP, inorganic phosphate; Cre, creatinine; FEUA, fractional excretion of uric acid; FENa, fractional excretion of sodium; %TRP, percent tubular reabsorption of phosphate; β2-MG, β2-microglobulin; TP, total protein; Hb, hemoglobin; Cal, calorie.

throughout total parenteral nutrition. The amino acids for parenteral nutrition are associated with the renal tubular reabsorption of uric acid. However, it is unclear whether the mechanism of hypouricemia is the same between parenteral nutrition and elemental enteronutrition. The deficiency of molybdenum (required as cofactor for uric acid synthesis) was reported extremely rarely as a cause of hypouricemia, during total parenteral nutrition [9]. Although we had not measured the serum level of molybdenum, we should also examine the molybdenum level when we see the hypouricemic patients.

An elemental enteral diet was known to influence pancreatic secretion [10], intestinal mucosal atrophy [11], bacterial translocation [12], and changes in the gastrointestinal microflora [13,14] like parenteral nutrition. The mechanism underlying this gastrointestinal influence of an elemental diet remains unclear. Janne et al. [11] reported colonic mucosal atrophy induced by an elemental diet in rats. Both mitotic and DNA synthetic activities decreased in the colonic mucosa during administration of the elemental diet. So, they concluded that atrophy of the colonic mucosa was probably mediated by a reduction in the proliferative activity of the stem cells in the mucosal glands. Another cause of intestinal villus atrophy with an elemental diet might be a lack of dietary fiber [15,16]. Chun et al. [15] reported that pectin feeding results in hyperplasia of the small intestinal mucosa and significant increases in the enzyme activities of the brush border membrane of the ileum. Soluble dietary fiber, such as pectin, added to an enteral diet has an effect on the proliferative activity of the colonic mucosa and improves the intestinal mucosal impairment. Although almost all reports concerning villus atrophy due to an elemental diet were based on animal experiments, Hosoda et al. [17] reported that intestinal mucosal atrophy was caused by an elemental diet in humans. The use of a pectin-supplemented enteral diet is recommended in severely disabled children to avoid intestinal atrophy.

The pathological findings for the gastrointestinal tract of severely disabled children after a long-term elemental diet were not known. However, Iai and Yamada [2] reported intestinal mucosal atrophy in an elderly severely disabled person after 25 years of enteral nutrition. This finding supports the fact that intestinal atrophy occurs in severely disabled children after prolonged elemental nutrition. Although there were no significant differences in calories, total protein, and hemoglobin between the two groups, and apparent malnutrition was not present in these two groups, some absorption disturbance of nutrition and subclinical malnutrition due to intestinal mucosal atrophy were suspected to cause hypouricemia.

To eliminate the influence of VPA [3], we included patients who were taking VPA in this study. It is ideal to select severely disabled children who have not taken VPA at all to compare the uric acid levels between two groups. However, we had such a small number of severely disabled children receiving elemental diet who had not taken VPA, that we had to include patients taking VPA to equal the condition of the patients.

In conclusion, although the exact mechanism remains obscure, prolonged elemental enteral nutrition might be a cause of hypouricemia in severely disabled children. The components of an elemental diet, secondary intestinal villus atrophy, changes in the microflora, and the underlying condition needing the elemental diet were suspected to have some relationship with hypouricemia in severely disabled

children receiving elemental nutrition. However, we will need to clarify the weight of these multi-factors by further investigations.

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Original Article

Febrile convulsion during the acute phase of Kawasaki disease

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Abstract

Background: Although seizures occur in association with meningitis or encephalitis in Kawasaki disease, febrile convulsions in Kawasaki disease are considered to be extremely rare. The aim of the present study is to elucidate the incidence of febrile convulsion in the acute phase of Kawasaki disease, in Niigata City General Hospital, Niigata, Japan.

Methods: The study included 177 patients with Kawasaki disease. Patients ranged in age from 2 months to 10 years (mean age 26.89 ± 22.44 months). The study included 105 males and 72 females. The clinical records of Kawasaki disease patients were examined retrospectively.

Results: Febrile convulsions were not recognized in these 177 patients throughout the course of the disease, despite the presence of a high grade fever and their young age. However, eight of the 177 patients had experienced simple febrile convulsions during other febrile illness except for those with Kawasaki disease. In the acute phase of Kawasaki disease, only two patients showed generalized convulsion associated with prolonged consciousness disturbance and pleocytosis in the cerebrospinal fluid.

Conclusion: The incidence of febrile convulsions in the acute phase of Kawasaki disease might be extremely low, confirming the results of previous reports. Kawasaki disease is characterized by systemic vasculitis and is sometimes complicated by intracranial vasculitis. The incidence of electroencephalographic abnormalities and pleocytosis in the cerebrospinal fluid is higher in patients with Kawasaki disease. However, the reason why febrile convulsions did not occur in the acute phase of Kawasaki disease remains unknown, despite the presence of central nervous system involvement.

Key words febrile convulsion, Kawasaki disease.

Kawasaki disease is an acute febrile disorder of unknown etiology. Central nervous system complications in Kawasaki disease are uncommon: however, aseptic meningitis, encephalitis, cerebral infarction, subdural effusion, ataxia, facial nerve palsy and seizures have been rarely reported in children with this disease. Although the etiology of the central nervous system involvement remains obscure, systemic vasculitis, including the central nervous system, might play a role. According to previous reports of Kawasaki disease,[1–8] seizures occur in association with meningitis or encephalitis. Febrile seizures in Kawasaki disease are considered to be extremely rare. When febrile seizures occur, they usually affect patients under 5 years of age, and are accompanied by a high grade fever. Thus, to elucidate the incidence of febrile convulsion in the acute phase of Kawasaki disease, we retrospectively examined the clinical records of Kawasaki disease patients admitted to Niigata City General Hospital, Niigata, Japan.

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Methods

The study included 177 patients admitted to Department of Pediatrics, Niigata City General Hospital, between January 1991 to April 2002, for the treatment of Kawasaki disease. The patients ranged in age from 2 months to 10 years (mean age 26.89 ± 22.44 months). The study included 105 males and 72 females.

Results

Febrile convulsions were not recognized in our 177 patients throughout the course of the disease, despite the presence of a high grade fever and their young age. However, eight of the 177 patients had experienced simple febrile convulsions during febrile illness except for those with Kawasaki disease. In the acute phase of Kawasaki disease, only two patients showed generalized convulsion associated with prolonged consciousness disturbance and pleocytosis in the cerebrospinal fluid. A 2-month-old boy developed generalized tonic convulsions lasting 15 min following prolonged unconsciousness.

The cerebrospinal fluid examination revealed a total cell count of 85/μL, and protein at 42 mg/dL. His serum sodium concentration was 117 mEq/L. Another 2-month-old boy developed prolonged generalized tonic convulsions and was on mechanical ventilation. His cerebrospinal fluid had a total cell count of 27/μL, with protein at 45 mg/dL. His serum sodium concentration was 122 mEq/L. Thirteen days of consciousness disturbance followed initiation of neurological symptoms.[9] Two patients recovered completely without any neurological sequelae.

Table 1 Incidence of febrile convulsion in Kawasaki disease in previously reported cases

Study	Incidence of FC	Other CNS complications
Otsuka *et al.*[1]	1/155 (0.64%)	Meningitis 6/155
Asou *et al.*[2]	8/498 (1.6%)	Four CNS involvements
Kajitani *et al.*[3]	1/402 (0.24%)	One MCLS/FC197
Nanbo *et al.*[4]	0/152 (0%)	Six FC after MCLS
Terasawa *et al.*[5]	0/540 (0%)	Six CNS involvements
Present study	0/177 (0%)	Two seizures with other etiology

FC, febrile convulsion; CNS, central nervous system; MCLS, mucocutaneous lymph node syndrome.

Discussion

In previous reports of seizures associated with Kawasaki disease (Table 1), the incidence of febrile convulsions was reported to be 1/155,[1] 8/498,[2] 1/402,[3] 0/152[4] and 0/540,[5] retrospectively. Nanbo *et al.* also reported that febrile convulsions did not occur in 152 Kawasaki disease patients, however, febrile convulsions associated with other febrile illness occurred almost at the same rate as in other children.[4] Yokoyama *et al.* reported that febrile convulsions were recognized in one of 26 patients with Kawasaki disease who were examined by electroencephalography.[6] Mitsudome *et al.* also reported that febrile convulsions occurred in four of 62 patients with Kawaski disease, who were examined by electroencephalography.[7] In these two reports,[6,7] bias was present in that the electroencephalography examination was performed with the suspicion of central nervous system involvement. Thus, the incidence of febrile convulsion might be higher in these two reports than in other reports. Otaki *et al.* reported that patients with Kawasaki disease developed seizures associated with hyponatremia, similar to our two cases.[8] Our two patients who developed seizures were both 2 months old and presented with hyponatremia and pleocytosis in the cerebrospinal fluid. They have never been diagnosed as having febrile convulsion, and their clinical courses resembled acute encephalitis or encephalopathy.

The incidence of febrile convulsion was reported to be 5–10%. Febrile convulsions ranged from 6 months to 4 years, being approximate to the ages of the patients with Kawasaki disease. Although this study was not a statistical analysis, the incidence of febrile convulsions in the acute phase of Kawasaki disease might be extremely low confirming the results of previous reports. Kawasaki disease is characterized by systemic vasculitis, mainly involving the coronary arteritis and sometimes complicated by intracranial vasculitis. On histopathological investigation, aseptic chorio and/or leptomeningitis, severe edema, necrosis, localized status spongiosus and vascular change such as endoarteritis, periarteritis and perivascular cuffing were present in some of their patients.[10] The incidence of electroencephalographic abnormalities and pleocytosis in the cerebrospinal fluid is higher in patients of Kawasaki disease. Such a pathologic mechanism could also affect the central nervous system and be responsible for the neurologic symptoms. However, the reason that febrile convulsions did not occur in the acute phase of Kawasaki disease remains unknown, despite the presence of central nervous system involvement. Its mechanism might be related to the etiology of Kawasaki disease. If the mechanism is determined, it will be useful for developing preventive methods for febrile convulsions. Further investigation is necessary to elucidate these matters.

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Clinically mild encephalitis/encephalopathy with a reversible splenial lesion

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Abstract—*Objective:* To clarify whether patients with clinical diagnoses of encephalitis/encephalopathy with a reversible lesion in the splenium of the corpus callosum (SCC) share common clinical features. *Methods:* Possible encephalitis/encephalopathy patients with a reversible isolated SCC lesion on MRI were collected retrospectively. Their clinical, laboratory, and radiologic data were reviewed. *Results:* Fifteen encephalitis/encephalopathy patients with a reversible isolated SCC lesion were identified among 22 patients referred for this study. All 15 patients had relatively mild clinical courses. Twelve of the 15 patients had disorders of consciousness. Eight patients had seizures, and three of them received antiepileptic drugs. All 15 patients clinically recovered completely within 1 month (8 patients within a week) after the onset of neurologic symptoms. The SCC lesion was ovoid in six patients; it extended irregularly from the center to the lateral portion of SCC in the other eight patients. Homogeneously reduced diffusion was seen in all seven patients who underwent diffusion-weighted imaging. There was no enhancement in the five patients so examined. The SCC lesion had completely disappeared in all patients at follow-up MRI exams between 3 days and 2 months after the initial MRI (within 1 week in eight patients). *Conclusion:* The clinical features among the affected patients were nearly identical, consisting of relatively mild CNS manifestations and complete recovery within 1 month.

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MRI is accepted as a more sensitive technique than CT for the diagnosis of encephalitis/encephalopathy and is particularly useful for detecting early changes in the brain. An MRI finding of an ovoid reversible lesion in the central portion of the splenium of the corpus callosum (SCC) without any accompanying lesions has been reported in around 20 patients with epilepsy receiving antiepileptic drugs.[1-5] The MR finding is unusual but has been reported in a few patients with encephalitis/encephalopathy caused by various agents such as influenza virus,[6] rotavirus,[7] and O-157 *Escherichia coli*.[8] These patients had no history of seizures or administration of antiepileptic drugs. These previously reported cases of encephalitis/encephalopathy were clinically mild, and the patients recovered completely. We retrospectively reviewed the clinical, radiologic, and laboratory findings of 15 Japanese patients with encephalitis/encephalopathy with a reversible isolated SCC lesion to clarify whether they share common clinical features and whether their MRI findings are identical to those reported in the literature secondary to epilepsy.[1-5]

Patients and methods. Possible encephalitis/encephalopathy patients with a reversible isolated lesion involving the central portion of the SCC on MRI were collected retrospectively by sending out a questionnaire to the members of the Annual Zao Conference on Pediatric Neurology and to some members of the Japanese Society of Pediatric Neurology and Japanese Society of Neuroradiology. We reviewed MR scans and charts of these patients, including information about symptoms, clinical diagnosis, medications, treatments, prognosis, results of CSF analysis, and EEG. The diagnosis of encephalitis has been defined as acute onset of brain dysfunction such as seizures and disorders of consciousness with inflammatory changes such as pleocytosis of CSF. When there was no evidence of inflammatory change, we used the term "encephalopathy." A reversible isolated SCC lesion was defined, for the purposes of this study, as a lesion involving the central portion of the SCC without any accompanying lesions on the initial MRI, which disappeared on the follow-up study.

Results. We identified 15 encephalitis/encephalopathy patients with a reversible isolated SCC lesion among the 22 patients whose clinical records and MRI examinations were referred for this study. Three patients were excluded because they had lesions in the white matter or cerebellum as well as in the SCC. Three were excluded because they had no follow-up MRI study. One patient, who was taking oral antiepileptic drugs, had another potential cause for the splenial lesions and was eliminated as well. The clini-

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Table 1 Clinical data for encephalitis/encephalopathy with reversible central splenial lesion

Patient no.	Age/ sex	Pathogen	Initial symptom	Premedication	CNS manifestation (onset day)	CNS diagnosis	Therapy	Prognosis	CSF	EEG
1	3/F	Unknown	Diarrhea, vomiting	None	Seizure, motor deterioration (3)	Encephalitis	PB, Dex	CR (d 21)	CC, 34	Slow BA
2	2/M	Unknown	Fever	None	Seizure, drowsiness (3)	Encephalopathy	Diazepam	CR (d 6)	Normal	Slow BA
3	4/F	Unknown	Fever, diarrhea	None	Seizure, blindness (3)	Encephalopathy	Diazepam	CR (d 5)	NE	Slow BA
4	5/M	Influenza A	Fever	None	Seizure, delirium (2)	Encephalopathy		CR (d 3)	Normal	Slow BA
5	5/M	Adenovirus	Fever	Amantadine	Ataxia, drowsiness (3)	Encephalopathy	IVIGG	CR (1 mo)	Normal	Slow BA
6	7/M	Mumps	Fever, parotitis	None	Delirium (3)	Meningoencephalitis	IVIGG	CR (d 5)	Pleocytosis	Slow BA
7	59/F	Unknown	Fever	None	Vertigo (1), lethargy (2)	Encephalitis	ACV, antibiotics	CR (d 8)	CC, 500	Slow BA
8	18/F	Unknown	Fever	None	Seizure, delirium (2)	Encephalitis	PB, PSL	CR (1 mo)	CC, 17	Slow BA and spikes
9	10/M	Unknown	Fever, cough	None	Delirium (7), seizure (8)	Encephalitis	ACV, PHT, PSL	CR (d 17)	Normal	Slow BA
10	8/M	Mumps	Fever, vomiting	None	Headache (1), seizure, delirium (4)	Meningoencephalitis		CR (d 10)	CC, 119	Normal
11	4/F	Unknown	Fever	None	Seizure, delirium (2)	Encephalopathy	Antibiotics, diazepam	CR (d 5)	Normal	NE
12	25/F	VZV	Fever, vesicula	None	Headache, drowsiness, nausea (3)	Encephalopathy	ACV	CR (d 10)	NE	NE
13	9/F	Unknown	Fever	None	Neck stiffness (3), vertigo, tremor (7)	Meningoencephalitis	ACV, antibiotics, Dex	CR (d 21)	CC, 337	Slow BA
14	22/M	Unknown	Fever	None	Hallucination, delirium (6)	Encephalopathy	ACV, antibiotics, PSL	CR (d 11)	Normal	Slow BA
15	10/M	Unknown	Fever	None	Drowsiness (3)	Encephalopathy, rhabdomyolysis	Antibiotics, IVIGG	CR (d 14)	Normal	Slow BA

PB = phenobarbital; Dex = dexamethasone; CR = complete recovery; CC = cell count (/mm^3); BA = basic activity; NE = not examined; IVIGG = IV immunoglobulin G; ACV = acyclovir; PSL = prednisolone; PHT = phenytoin; VZV = varicella zoster virus.

cal records and radiologic examinations of the remaining 15 patients were reviewed by the authors and are the basis of this study. The findings of the 15 patients are summarized in tables 1 and 2.

The 15 patients (8 male and 7 female; age 2 to 59 years) developed normally until the onset of neurologic symptoms. Fever preceded neurologic symptoms in all 15 patients. Directly causative agents were identified by rapid antigen-detection assay, PCR, positive IgM, or longitudinally increased IgG in 5 of 15 patients. The pathogens included influenza A, mumps virus (two patients), varicella-zoster virus, and adenovirus. The onset of neurologic symptoms ranged from day 1 to 7 of the illness. Eight of the 15 patients had seizures. Other neurologic symptoms included disorders of consciousness (12 patients), vertigo (2 patients), motor deterioration, blindness, ataxia, tremor, and hallucinations. No patient needed mechanical ventilation. Three patients had received antiepileptic drugs (phenobarbital for two patients and phenytoin for another) at the time of MR studies. Analysis of CSF revealed pleocytosis in 6 of 13 examined patients but normal glucose and protein levels. EEG showed slow basic activity characteristic of encephalitis/encephalopathy in 12 of 13 examined patients. Though their treatments were variable (e.g., corticosteroids for five patients and IV IgG administration for three patients), all 15 patients clinically recovered completely within 1 month (8 patients within 1 week after the onset of neurologic symptoms) without sequel.

In 14 of the 15 patients, the initial MR study was performed within 4 days of the onset of neurologic symptoms. On axial images, the lesion was ovoid and in the center of the SCC in six patients (Patients 3, 4, 7, 8, 13, 14) (figure 1) and extended irregularly into the lateral portion of SCC in the other eight patients (figure 2). In Patient 12, a lesion in the central portion of the SCC was detected on sagittal T1- and T2-weighted images (axial T2-weighted image being unavailable). There was no obvious correlation between the shape of SCC lesion and the scan date, neurologic symptoms (presence or absence of seizures, date of complete recovery), or laboratory findings. The SCC lesion was, compared with the surrounding splenium, homogeneously hyperintense on T2-weighted images and isointense to slightly hypointense on T1-weighted images. Homogeneously reduced diffusion (hyperintensity on diffusion-weighted images and low apparent diffusion coefficient [ADC] values) was seen in all seven patients examined by diffusion-weighted imaging. There was no enhancement of the SCC lesion after gadolinium adminis-

Table 2 MRI data for patients with encephalitis/encephalopathy with reversible central splenial lesion

Patient no.	Initial MRI								Follow-up MRI	
	Scan date	Lesion	Shape	T2WI	T1WI	Gd	DWI	ADC	Scan date	Lesion
1	Day 3 (0)	SCC	Extended	H	sl L	NE	NE	NE	Day 6	None
2	Day 3 (0)	SCC	Extended	sl H	sl L	—	H	L	Day 60	None
3	Day 5 (2)	SCC	Ovoid	sl H	I	NE	NE	NE	Day 9	None
4	Day 3 (1)	SCC	Ovoid	sl H	I	NE	H	L	Day 13	None
5	Day 3 (0)	SCC	Extended	sl H	I	NE	H	L	Day 7	None
6	Day 4 (1)	SCC	Extended	sl H	I	NE	H	L	Day 8	None
7	Day 3 (2)	None								
	Day 5 (4)	SCC	Ovoid	sl H	sl L	—	H	L	Day 20	None
8	Day 3 (2)	SCC	Ovoid	sl H	I	—	NE	NE	Day 25	None
9	Day 8 (2)	SCC	Extended	sl H	I	NE	NE	NE	Day 12	None
10	Day 7 (3)	SCC	Extended	H	I	—	NE	NE	Day 14	None
11	Day 3 (1)	SCC	Extended	sl H	I	NE	NE	NE	Day 30	None
12	Day 10 (8)	SCC		sl H	I	NE	NE	NE	Day 40	None
13	Day 7 (4)	SCC	Ovoid	H	L	—	NE	NE	Day 15	None
14	Day 7 (1)	SCC	Ovoid	H	sl L	NE	H	L	Day 11	None
15	Day 4 (2)	SCC	Extended	sl H	sl L	NE	H	L	Day 8	None

Scan date (days after CNS manifestations). T2WI = T2-weighted image; T1WI = T1-weighted image; Gd = gadolinium enhancement; DWI = diffusion-weighted imaging; ADC = apparent diffusion coefficient; SCC = splenium of the corpus callosum; H = high intensity; sl L = slightly low intensity; NE = not examined; sl H = slightly high intensity; L = low intensity; I = isointensity.

tration in any of the five patients who received contrast material. MRI of Patient 7 showed normal findings at 2 days after the onset of neurologic symptoms but revealed an SCC lesion at 4 days (see figure 1). The SCC abnormalities of all 15 patients completely disappeared at follow-up MRI studies performed 3 days to 2 months after the first abnormal study (within 1 week in 8 of 15 patients). In at least six patients (Patients 1, 5, 8, 9, 13, 15), the SCC lesion disappeared before clinical recovery was complete.

Discussion. Despite different causative agents, the clinical features of the 15 patients with encephalitis/encephalopathy and an isolated reversible SCC lesion were nearly identical, consisting of relatively mild CNS manifestations and complete recovery within 1 month. Thus, we propose that this may represent a new clinicoradiologic syndrome with an excellent prognosis and that MRI is a key study in establishing the diagnosis.

As in any patient with encephalitis/encephalopathy and lesions in the white matter, acute disseminated encephalomyelitis (ADEM) should be considered in the differential diagnosis.[9] ADEM is monophasic postinfectious or postvaccinial inflammatory disorder, which is pathologically characterized by an acute perivenous lymphocytic infiltration with confluent demyelination. ADEM presents with seizures, focal neurologic signs, and alteration of consciousness, which develop days to weeks after the onset of presumed viral infections. CSF analysis reveals mild pleocytosis. Corticosteroids are accepted as useful treatment for ADEM, and recovery occurs

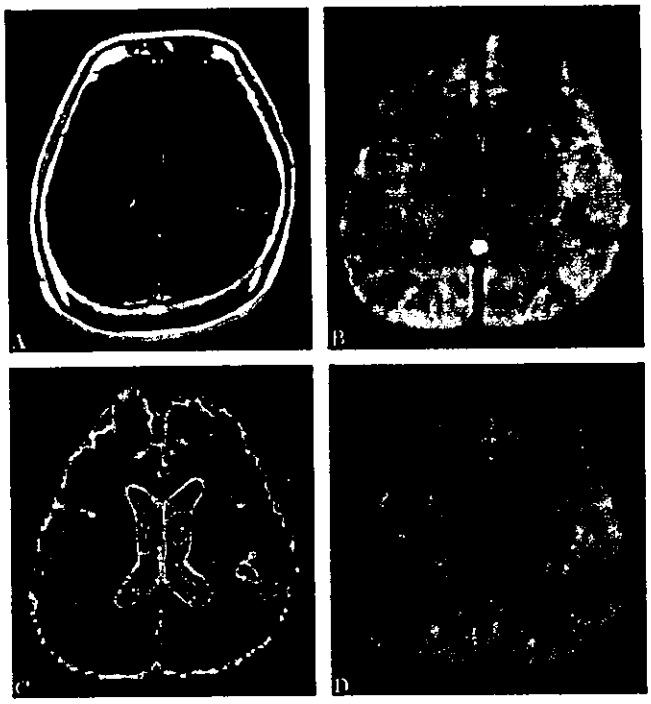

Figure 1. Case 7. MRI on day 5, showing an ovoid lesion in the mid-splenium of the corpus callosum on diffusion-weighted imaging (B) and apparent diffusion coefficient (ADC) map (C) with decreased ADC value and no enhancement on gadolinium-enhanced T1-weighted imaging (A). Follow-up study on day 20 showed no lesion on any sequence (D).

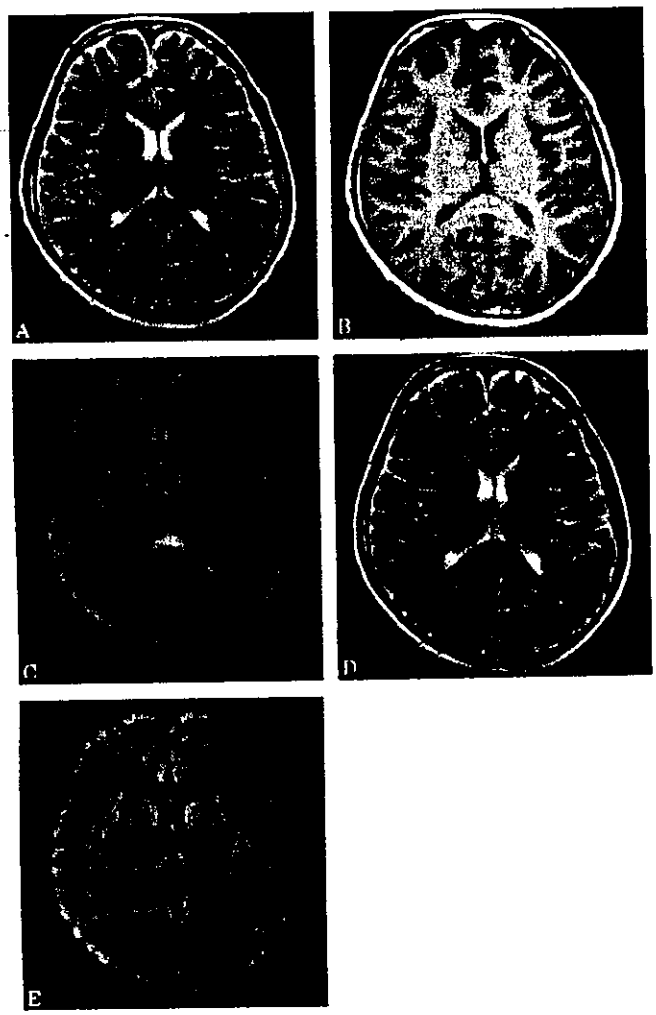

Figure 2. Case 15. MRI on day 4, showing a lesion extending into the lateral portion of the splenium of the corpus callosum (SCC) on T2- and T1-weighted imaging (A, B) and diffusion-weighted imaging (C). The lesion in the SCC disappeared on all sequences on day 8 (D, E).

within weeks.[9] In contrast, the patients in this report developed neurologic symptoms quickly after the onset of illness (day 1 to 7) and also recovered completely within 1 month (mostly within 1 week after neurologic manifestations). Directly causative agents were identified in 5 of the 15 patients, suggesting primarily infectious encephalitis/encephalopathy rather than postinfectious. Corticosteroids were not necessary in most of the patients.

MRI in ADEM usually shows multiple foci of T1 and T2 prolongation, typically bilateral and asymmetric, in the subcortical white matter.[10] Although the corpus callosum may be involved in ADEM, these patients nearly always have asymmetric callosal lesions in addition to other white matter lesions.[11] After contrast agent infusion, the lesions in ADEM will show variable enhancement depending on their acuity. The lesions usually evolve over weeks to months and disappear only after several months, as the imaging evolution of the disease lags behind the clinical evolution. Indeed, the white matter damage may be permanent. The SCC lesions in the patients in this report had no contrast enhancement, and most disappeared completely within 1 week before clinical recovery was complete. The splenial lesions in these patients, therefore, are clinically and radiologically unlikely to represent a manifestation of ADEM.

Other possible differential diagnoses of splenial lesions include ischemia, posterior reversible encephalopathy syndrome, diffuse axonal injury, multiple sclerosis, hydrocephalus, Marchiafava–Bignami disease, lymphoma, and extrapontine myelinolysis.[11] These are excluded clinically and radiologically in our patients.

One of the most interesting MRI findings in the patients in this study is that the SCC lesion has reversible, homogeneous reduced diffusion. The reversibility suggests that this finding is distinct from cytotoxic edema seen in cellular energy failure, such as acute infarction, which is nearly always irreversible. We postulate two possible mechanisms for the transiently decreased ADC of the lesions: intramyelinic edema and inflammatory infiltrate. Recently, high signal on diffusion-weighted imaging and decreased ADC values of white matter lesions have been observed in patients with Canavan disease, metachromatic leukodystrophy, and phenylketonuria.[12,13] A possible explanation proposed for this phenomenon is intramyelinic edema due to separation of myelin layers.[12,13] Interestingly, periventricular T2 abnormalities in phenylketonuria have been shown to be reversible with improvement in metabolic control.[13-15] Therefore, the transiently decreased ADC values of the SCC lesion suggest that reversible intramyelinic edema may be the operant factor. A diffusion-weighted imaging study of multiple sclerosis found decreased ADC values in 4 of 28 homogeneously enhancing multiple sclerosis lesions.[16] The authors postulated that the influx of inflammatory cells and macromolecules, combined with related cytotoxic edema, might have caused decreased ADC. Thus, the decreased ADC in the splenium may be a result of inflammation. With either cause, intramyelinic edema or inflammation, ADC may return to normal if the cause resolves quickly.

Why is the splenium involved as an isolated site? Although the splenium is the only region where the vertebrobasilar system supplies blood to the corpus callosum (which is primarily supplied by the carotid system),[17] the reversibility of the lesions and the absence of any other lesions in vascular distributions make it unlikely that the splenial abnormalities are the result of ischemia. Another possible pathogenesis of the splenial lesions might be related to the presence of elevated inflammatory cytokines, such as interleukin-6,[18,19] although the exact mechanism by which the splenium would be involved as an isolated site due to any of the causes is difficult to understand. One might propose that the viral antigens or receptors on the antibodies induced by the antigens have specific affinities for receptors on splenial axons

or the myelin sheaths surrounding them, but this is pure speculation.

Recently, an ovoid-shaped reversible splenial lesion has been reported in approximately 20 patients with epilepsy receiving antiepileptic drugs.[1-5] Homogeneously reduced diffusion was reported in some examined patients.[3-5] Toxic levels or rapid withdrawal of antiepileptic drugs or frequent seizures are presumed to be the cause of the lesion in these patients. The imaging features of the lesions in these epileptic patients are very similar to those in our encephalitis/encephalopathy patients; however, the shape of the lesion is somewhat different. In reported patients and one patient referred to us who was receiving antiepileptic drugs, the SCC lesions were ovoid or round in shape[1-5] except for one patient.[3] In contrast, the lesions were ovoid in six of our patients and irregularly extended into the lateral portion of the SCC in eight patients with encephalitis/encephalopathy. Among 15 patients with encephalitis/encephalopathy in this study, 7 patients had no seizures, and only 3 of the 8 patients with seizures received antiepileptic drugs. We conclude, therefore, that the lesions in our patients with encephalitis/encephalopathy did not result from seizures or antiepileptic drugs per se, though these two conditions may share the same unknown pathogenesis or have same spectrum.

It is unclear how common this finding might be in patients with mild encephalitis/encephalopathy. Because of the relatively high incidence of influenza-associated encephalitis/encephalopathy in Japan,[18,19] we have had the opportunity to obtain brain MRI in 15 children with relatively mild CNS symptoms; however, MRI studies are not commonly obtained in such patients, making it difficult to know how often SCC lesions might be seen in this patient population.

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LETTER TO THE EDITOR

The difficulties of diagnosing VPA-induced pancreatitis in children with severe motor and intellectual disabilities

A 5-year-old girl developed normally until 1 year of age, when she contracted influenza encephalopathy. She then became bed-ridden with spastic quadriplegia, mental retardation and epilepsy as sequelae. Oral administration of valproic acid (VPA) was begun because of intractable seizures. In March 2003, her seizures stopped completely after the VPA dosage was increased. However, she lost her appetite and her body weight decreased from 17.5 to 16.5 kg in one month. On April 10, she became inactive without fever, nausea or vomiting. Physical examination revealed no abnormal findings, including abdominal defense and tenderness. Laboratory examinations disclosed no abnormal findings. On April 11 she started vomiting and the next day she developed fever to 38 °C. On April 13, she developed acute respiratory failure and hypoxemia refractory to oxygenation. Chest XP showed bilateral diffuse infiltrations and she was put on mechanical ventilation. Laboratory data blood results were as follows: CRP 13.55 mg/dl, total protein 4.3 g/dl, GOT 45 IU, GPT 29IU, LDH 776 IU, Ca 7.5 mg/dl, FDP 98.0 μg/dl (nl < 5.0) and serum amylase 190 IU/l (nl < 130). However, no diagnosis could be established at that time. An abdominal CT showed marked swelling of the pancreas, and abdominal fluid (Fig. 1), and acute pancreatitis was diagnosed, probably due to VPA. VPA was stopped and treatment for pancreatitis was started. On April 16, laboratory examination disclosed a marked increase of pancreatic enzymes (lipase 76 IU/L (5-33), trypsin 4012 ng/ml (100-500) and elastase I19138 ng/dl (72-436)), but with only slightly increased serum amylase 153 IU/l. On May 9 laboratory data had normalized and an abdominal CT disclosed a marked improvement in pancreatic swelling. She recovered completely without any sequelae.

Acute pancreatitis has been reported as a rare adverse effect of VPA.[1] Many patients developed acute pancreatitis induced by VPA had neurological deficits, such as cerebral palsy and mental retardation.[1-4] Grauso-Eby et al.[2] reported that 55% of reported children with VPA-induced pancreatitis had neurological deficits. Patients with neurological deficits rarely complain of clinical symptoms such as abdominal pain. Abdominal defense and tenderness are also unclear. Our patient did not show any symptoms suggesting pancreatitis. Furthermore, severely disabled children often vomit due to gastro-esophageal reflux, and it has been reported that acute pancreatitis can be misdiagnosed as gastro-esophageal reflux.[4] The increased level of serum amylase was trivial in our patient. Almost half of the reported patients with VPA-induced pancreatitis had a trivial increase or normal levels of serum amylase.[1-3] The reason for this remains obscure. The diagnosis of pancreatitis without suggesting symptoms and elevation of serum amylase levels is difficult and only swelling of the pancreas on abdominal CT enabled us to diagnose acute pancreatitis in our patients. Other pancreatic enzyme tests, such as trypsin, elastase and lipase were also helpful for the diagnosis. In severely disabled children, we should keep in

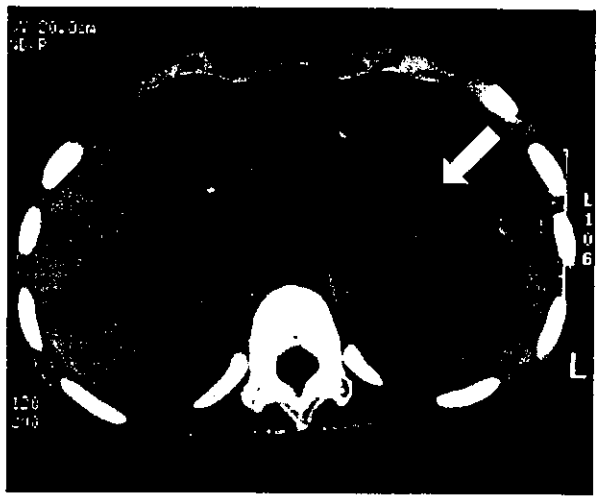

Figure 1 Abdominal CT finding. Abdominal CT disclosed diffuse markedly swelling of pancreas.

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mind VPA-induced pancreatitis as a cause of vomiting or unexplained symptoms, even if the serum amylase level is not or only slightly elevated.

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主題

精神・神経疾患

小児期発症急性脳炎・脳症の臨床的検討

吉川 秀人*・山崎佐和子
阿部 裕樹・渡辺 徹・阿部 時也

要旨

1990年から2003年までの14年間に新潟市民病院小児科に入院した急性脳炎・脳症の患児123例について検討した。月別では冬期間，特に1月に多かった。原因が明らかになったものではインフルエンザ21例，HHV6　7例，単純ヘルペス5例，マイコプラズマ8例などが多かったが59例は原因不明だった。予後により死亡群（20例），後遺症群（32例），治癒群(71例)に分類し予後因子を検討したところ，肝機能障害，播種性血管内凝固症，腎不全，横紋筋融解症の合併は予後不良因子であった。また，入院時検査値でCre，血小板数，FDP値が予後の推定に有用であった。治療法は，人工呼吸器管理，ステロイド剤，グリセオール，抗蛋白凝固阻止剤，アシクロビル等が用いられたが，治療法の有用性を実証するためには今後，さらに前方視的検討が必要であると思われた。

（小児科臨床　57：2223，2004）

KEY WORDS▶　急性脳炎，急性脳症，小児

はじめに

近年，インフルエンザ脳症の流行もあり，社会的にも小児期の脳炎・脳症には関心が集まっている。しかし，脳炎・脳症の病態は小児においては侵襲的な検査ができず，剖検も少ないことから未解明な部分が多い。治療法に関しても経験的なものが多く，必ずしもエビデンスに基づいた治療法が確立されているわけではない。当院においても個々の急性脳炎，脳症に関してはすでに報告[1)6)]されたものもあるが，その全体像については，十分に検討されておらず，いまだ不明な点も多い。今回，当院に入院した急性脳炎・脳症患児の臨床像をまとめ，予後因子を検討したので報告する。

対象と方法

1990年から2003年までの14年間に，新潟市民病院小児科に入院し治療を要した急性脳炎・脳症の患児123例を対象とした。急性脳炎・脳症の診断は，発熱，嘔吐，意識障害，けいれんなどの中枢神経症状を急激な経過で呈し，代謝異常症や中毒などを除外されたも

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のとした。病理学的には急性脳炎は脳実質の炎症，急性脳症は脳浮腫であるが，髄液細胞数で区別することは難しい症例も多く，急性脳炎・脳症とした。

これらの症例の原因，診断，病態，治療法を検討し，また予後との相関を検討した。予後により，死亡20例（16.2%）（A群），後遺症32例（26.0%）（B群），治癒71例（C群）に分類し，それぞれの年齢，性別，原因，血液生化学検査所見，髄液所見，合併症，治療について比較検討した。血液生化学検査所見は GOT，LDH，CK，TP，Na，Cre，WBC，Hb，plt，FDP，BS，NH_3について入院時検査値を比較検討した。髄液所見は，髄液細胞数，タンパク値，糖値について入院時検査値を比較検討した。値はすべて平均値±標準偏差（mean±SD）で表した。また肝機能障害，播種性血管内凝固症，腎不全，横紋筋融解症の有無と予後との間の関係も比較検討した。3群間の差は Kruskal-Wallis 検定を用いて検定した。いずれも $p<0.01$を有意とした。統計ソフトは StatView5.0 (SAS Institute Inc., Cary, NC) を用いた。

後遺症32例の内容は，痙性四肢麻痺＋重度精神遅滞12例，精神遅滞＋てんかん12例，精神遅滞のみ4例，てんかんのみ3例，右片麻痺のみ1例であった。

治療に関しては，人工呼吸器管理，ステロイド薬の使用（デキサメサゾンまたはメチルプレドニゾロンによるパルス療法），グリセオールの使用，抗蛋白凝固阻止剤の使用，免疫グロブリン製剤の使用，アシクロビルの使用，カテコラミンの使用，フェノバルビタールの使用について，3群間で比較検討した。

結　果

1）症例の臨床像（表1）：123症例は，男児66例，女児57例で，年齢は1カ月から14歳

表1　各群の患者背景および原因

	A群　死亡例	B群　後遺症例	C群　治癒例	計
症例数	20	32	71	123
男児	10	15	41	66
女児	10	17	30	57
年齢 (mean±SD)	43.4±48.7月	34.9±34.9月	63.6±46.0月	
けいれん	20	28	50	98
原因				
インフルエンザ	6	9	6	21
単純ヘルペス	1	3	1	5
HHV 6	1	2	4	7
麻疹		1		1
マイコプラズマ			8	8
風疹			7	7
水痘			2	2
パルボ B19			2	2
ムンプス			1	1
百日咳			1	1
川崎病			2	2
テオフィリン関連	1	1	5	7
不明	11	16	32	59

7カ月までであった。原因が明らかになったものは64例（52.0%）で，その内訳はインフルエンザ21例[4)6)]，マイコプラズマ8例，ヒトヘルペスウイルス6型　7例，単純ヘルペス5例，パルボB19　2例[1)]，麻疹脳炎1例，風疹脳炎7例，ムンプス脳炎1例，百日咳1例等で，59例は原因不明であった。死亡例では，原因不明が11例と多く，次いでインフルエンザが6例と多かった。月別では夏に少なく冬，特に1月に多い傾向が認められた(図)。1992年に風疹脳炎の流行，1997～2001年にインフルエンザ脳症の流行がみられたが[4)6)]，それ以外には大きな流行はみられなかった。亜型分類では，急性散在性脳脊髄炎5例，急性壊死性脳症10例，出血性ショック脳症3例，溶血性尿毒性症候群3例等であった，けいれんは98例で出現し治療を要したものは69例であった。合併症として肝機能異常47例，腎不全19例，播種性血管内凝固症30例，横紋筋融解症17例で併発し，いずれも死亡例，後遺症例，治癒例の順に高率に併発した（表2）。脳波で急性期に周期性片側性てんかん様放電を呈した症例が10例（インフルエンザ脳症4例，テオフィリン脳症2例，辺縁系脳炎2例，マイコプラズマ脳炎1例，原因不明の急性脳症1例）認められた[7)]。

2）予後因子の検討：肝機能障害，腎不全，播種性血管内凝固症，横紋筋融解症の有無と予後との関係では，4項目すべてで，有意差が認められた（表2）。3群間の入院時検査値の比較で有意差を認めた項目はGOT，LDH，Cre，血小板数，FDPの5項目であった（表3）。GOT，LDHは有意差は認められたが，後遺症例が一番高値であり予後判定には使用できないと思われた。これは後遺症例の中にGOT，LDH値が数千に達した症例が数例存在したためであると考えられた。有意差はなかったが，髄液タンパク，NH_3も死亡例において高い傾向が認められた。

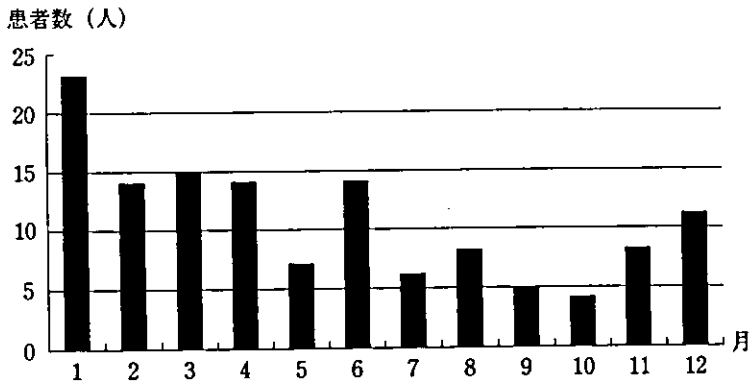

図　月別患者発生数

表2　各群における合併症の有無と予後との関係

	計	A群　死亡例	B群　後遺症例	C群　治癒例	
肝機能障害	47	19/20(95%)	13/32(40.6%)	15/71(21.1%)	p<0.0001
腎不全	19	12/20(50%)	2/32(6.3%)	5/71(7.0%)	p<0.0001
播種性血管内凝固症	30	16/20(80%)	7/32(21.8%)	7/71(9.8%)	p<0.0001
横紋筋融解症	17	10/20(50%)	4/32(12.5%)	3/71(4.2%)	p<0.0001

表3　各群における入院時検査値と予後との関係

		A群　死亡	B群　後遺症	C群　治癒	
GOT	IU/ℓ	285.0±225.2	727.5±1686.4	383.4±1736.4	p<0.01
LDH	IU/ℓ	1549.1±853.5	2109.1±3471.0	1150.0±2203.5	p<0.01
CK	IU/ℓ	715.8±981.3	1570.2±4974.1	279.1±651.6	n.s.
TP	g/dℓ	5.9±0.8	6.0±0.6	6.4±0.7	n.s.
Na	mEq/L	140.2±11.2	135.1±5.8	135.7±5.0	n.s.
Cre	mg/dℓ	1.2±0.8	0.42±0.2	0.58±0.7	p<0.01
WBC	/㎣	10210.5±5339.8	9854.4±5687.8	11597.0±6031.2	n.s.
Hb	g/dℓ	12.0±1.9	11.5±1.0	11.9±1.3	n.s.
plt	×10⁴/㎜	15.1±11.5	23.1±9.3	28.6±13.8	p<0.01
FDP	μg/dℓ	234.1±373.1	32.9±70.7	9.1±9.07	p<0.01
BS	mg/dℓ	197.1±76.8	161.7±70.0	156.8±75.2	n.s.
NH_3	μg/dℓ	128.1±129.0	64.4±57.5	66.1±46.1	n.s.
髄液細胞数	/3	77.8±142.1	89.0±198.4	70.6±110.3	n.s.
髄液蛋白濃度	mg/dℓ	86.2±70.1	88.5±29.1	85.8±31.2	n.s.
髄液糖濃度	mg/dℓ	164.1±182.4	30.7±36.1	38.0±38.2	n.s.

n.s.：not significant

表4　各群における治療法

	A群　死亡例	B群　後遺症例	C群　治癒例
人工呼吸器管理	20/20(100%)	11/32(34.3%)	11/71(15.4%)
ステロイド薬	13/20(65%)	20/32(62.5%)	30/71(42.2%)
グリセオール	20/20(100%)	31/32(96.8%)	51/71(71.8%)
抗蛋白凝固阻止剤	16/20(80%)	9/32(28.1%)	10/71(14.1%)
免疫グロブリン製剤	14/20(70%)	22/32(68.7%)	34/71(47.8%)
アシクロビル	8/20(40%)	19/32(59.3%)	39/71(54.9%)
カテコラミン	20/20(100%)	7/32(21.8%)	11/71(15.4%)
フェノバルビタール	6/20(30%)	20/32(62.5%)	28/71(39.4%)

3）治療（表4）は，人工呼吸器管理42例，ステロイド剤63例，蛋白分解酵素阻害剤35例，ガンマグロブリン70例，アシクロビル66例，グリセオール102例，カテコラミン38例，血漿交換7例，低体温療法4例，ウリナスタチン6例，アンチトロンビンIII 8例で施行された。いずれの治療法も予後が悪いほど，重症なほど，複数の治療を併用していた。けいれんに対しては通常のジアゼパム，フェニトイン以外では，ミダゾラム42例，リドカイン29例，バルビタール療法16例で施行された。

考　察

小児期に発症する急性脳炎・脳症の実態については，近年のインフルエンザ脳症流行に関しては全国調査等されてはいるものの，それ以外の急性脳炎，脳症の実態については不明な点が多い。

当院における急性脳炎・脳症の予後因子に関して，渡辺ら[2]は1974年から1992年10月までに入院した急性脳炎・脳症51例について検

討し報告した。原因ではヘルペス，百日咳，原因不明の予後が不良であり，発症年齢が3歳以下，意識障害がGCSで6以下，意識障害期間が5日以上，けいれん重積有り，回復期CT異常所見，急性期背景脳波活動が平坦あるいはデルタ波主体の場合，予後不良であった。死亡例7例（13.7%），後遺症例13例（25.5%）であった。しかし入院時検査値については検討されておらず，またインフルエンザ脳症の流行前の検討であり，インフルエンザ脳症の症例は含まれていなかった。今回は，前回の検討で施行されなかった入院時検査値と予後との関係について検討した。

今回の検討の結果，肝機能障害，播種性血管内凝固症，横紋筋融解症，腎不全いずれの合併も予後と相関がみられ，入院時検査値ではCre，血小板数，FDP値が予後不良に関連する因子であった。また今回の検討で原因が明らかになった症例ではインフルエンザが多く，インフルエンザ脳症の流行および死亡例の多さも今回の結果に影響を及ぼしたと考えられた。予後不良因子として肝機能障害の合併が認められたが，急性脳症では非特異的にGOT，NH_3上昇がみられ，Reye症候群様の症状を呈することも多い。Reye症候群との鑑別が問題になることもあるが，Reye症候群の診断にはCDC診断基準（GOT，GPT，NH_3の上昇，意識障害，脂肪肝，他の疾患の除外）は用いるべきではないと考えられており，また重症の急性脳症とReye症候群とは類似の病態と思われ，特にReye症候群が他の急性脳症と比べ特殊な病態ではないと考えられている[8]。

川崎ら[9]は1986年から2000年までの15年間に福島県内における急性脳炎・脳症105例について検討し報告した。病因が判明した症例は46例（43.4%）と低率であり，その内訳はインフルエンザ11例，HHV6　5例，水痘5例，風疹5例，麻疹4例，マイコプラズマ4例であった。6歳未満が81.9%で，12月から3月の冬期に64.8%が発症していた。後遺症38例（36.1%），死亡15例（14.2%）であった。予後不良因子は，遷延する意識障害，肝・腎機能障害やDICなどの多臓器不全を有すること，病初期から頭部画像および脳波上異常所見を有することなどであった。これらは当院でのデータとほぼ一致していると思われた。

インフルエンザ脳症流行前の報告では，1984年から1987年に愛知県下におけるアンケート調査[10]がある。160例の脳炎・脳症が確認され，原因は麻疹（25%），単純ヘルペス（16%），風疹（11%），水痘（10%），原因不明（32%）であった。死亡率は6.8%で1/3に後遺症がみられた。意識障害の重い例と，頭部CTで異常がある例で予後が悪い傾向が認められた。Ishikawaら[11]の愛知県下のアンケート調査では，1990～1992年に小児脳炎は256例が確認された。発病率は小児10万人あたり3.3人で，0～4歳で6.6人，5～15歳で2.0人であった。原因が明らかになったものは105例で，麻疹24例，単純ヘルペス21例，風疹24例などであり，予後は死亡7.8%（20例），後遺症24%（58例）であった。これらの報告における原因はインフルエンザ脳症流行後の報告とは異なり，1994年の予防接種法改正との関係も推察される。また国によって脳炎の原因も異なる。フィンランドでは，1993～1994年の2年間にサーベイランス調査[12]をし，15歳までの小児人口791,712人中175例の急性脳炎が確認され，発病率は10.5人/10万であった。原因は，水痘，RS，エンテロウイルスが主体であり，日本での報告と明らかに異なっていた。

小児期急性脳炎・脳症の予後に関しては，Ishikawaら[11]は死亡7.8%，後遺症24%，渡辺ら[2]は死亡13.7%，後遺症25.5%　川崎ら[9]は死亡14.3%，後遺症36.1%，因田ら[10]は死亡6.8%と報告している。また，米国ではウイルス性脳炎の死亡率は3.8～12%と報

告[13][14]されている。今回の結果は，死亡16.2%，後遺症26.0%であり，これらの報告とほぼ一致する数字であると思われた。

治療に関しては，急性脳炎，脳症の根本治療はなく，抗脳浮腫療法や全身管理などの対症療法のみである。エビデンスレベルの高い治療法はほとんどないが，デキサメサゾン，パルス療法などのステロイド剤，グリセロールをはじめとする高浸透圧療法が高頻度に施行されていた。また，原因不明のウイルス性脳炎ということで，アシクロビルが病初期より高率に使用されていたのは，やむをえないと思われた。今後，前方視的研究を含めた検討を行い治療ガイドラインを作成していく必要があると思われた。

本研究の一部は，平成15年度厚生労働省精神・神経疾患研究委託費　発達期に発症する外因性脳障害の診断・治療ガイドラインに関する臨床的実証的研究（15指-4）によって行われた。

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原　著

小児けいれん重積症に対するミダゾラム静注療法の検討

A Study of Intravenous Midazolam for Status Epilepticus in Children

吉川秀人[1,2]　山崎佐和子[1]

要旨：1997年から2002年までの6年間に小児けいれん重積症に対してミダゾラム静注療法を施行した71例89機会の治療効果につき検討した。けいれんの原因はてんかん43機会、急性脳炎・脳症17機会、テオフィリンけいれん12機会、熱性けいれん重積11機会等であった。第1選択42機会、第2選択34機会、第3選択12機会、第4選択1機会で施行し75/89機会(84.2%)でけいれんは消失した。持続静注時間は1～240時間(平均51.2時間)で、使用量はbolus dose 0.05～0.4 mg/kg、持続量0.06～0.6 mg/kg/hrであった。副作用として1例で呼吸抑制が認められたが挿管は不要であった。同時期にジアゼパム静注を施行した159機会中有効であったのは106機会(66.7%)で、14機会で呼吸抑制を来たし挿管または人工呼吸管理を必要とした。小児けいれん重積症に対するミダゾラム治療は、安全かつ有効であると思われた。

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Key Words：midazolam, status epilepticus, children, diazepam, adverse effect

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はじめに

小児けいれん重積症は、最も緊急を要する救急疾患の一つであり、その初期治療は重要である。近年、小児けいれん重積症に対するミダゾラム静注療法の有用性および安全性が報告され注目されている[1,2]。

新潟市民病院は、新潟市周辺および新潟県北部の人口約120万人をカバーする3次救急病院であり、この地区では最も多くの小児救急疾患を診ている施設である。当院におけるけいれん重積症に対する初期治療の概要については既に報告した[3]。今回1997年から2002年までの6年間に当院小児科にけいれんを主訴に入院しミダゾラム静注を施行した症例について検討したので報告する。

対象と方法

当院小児科において、1997年から2002年までの6年間にミダゾラム静注療法を施行した71例

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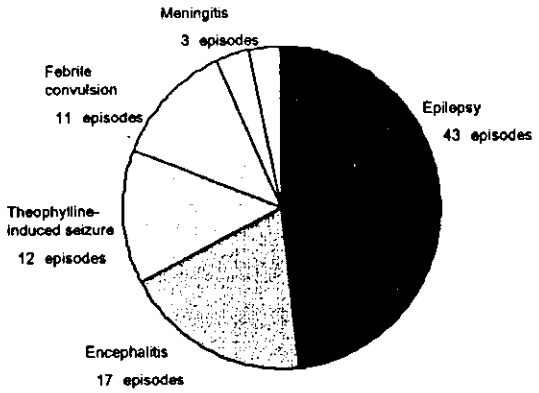

Fig. 1　Itemized etiologies of 89 episodes of status elilepticus treated with midazolam

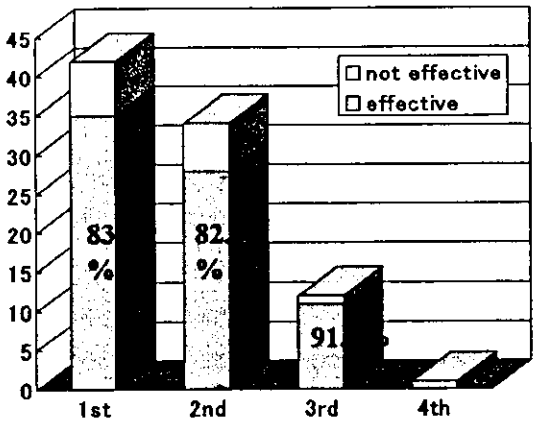

Fig. 2　Results of midazolam infusion in each line
1st：first-line, 2nd：second-line, 3rd：third-line, 4th：fourth-line

89機会のけいれん重積症を対象とした。既に1997年から1999年までの第一選択で使用した10例16機会については報告済み[4]である。けいれん重積症は、けいれんが30分間以上持続するか(持続型)、意識障害が続いたままでけいれんは反復する状態が30分以上続いた状態(群発型)と定義した。年齢は1カ月から16歳(平均3.31歳)で、男児39例、女児33例であった。けいれんの原疾患は、てんかん31例（症候性局在関連性てんかん24例、特発性全般てんかん5例、Doose症候群2例）43機会、急性脳炎・脳症14例17機会、テオフィリンけいれん11例12機会、熱性けいれん重積9例11機会、髄膜炎3例3機会、その他3例3機会であった(Fig. 1)。けいれん重積は持続型55機会、群発型34機会であった。

ミダゾラムは0.05～0.4 mg/kgを静注した後0.06～0.6 mg/kg/hrで持続静注し、有効であれば6～24時間後より漸減開始した。30分以内にけいれんが停止し、ミダゾラム中止後48時間以上発作が抑制された場合を有効とした。また同時期に痙攣を主訴として入院した症例のうちジアゼパム静注療法を施行した159機会(前医での治療を含む)の有効性と比較検討した。ジアゼパム座薬の使用はけいれんを止めるための治療ではないので統計には含んでいない。その他の治療にはフェノバルビタール筋注、フルニトラゼパム静注、抱水クロラール注腸などが施行された。統計学的な検定はχ^2-テストを施行し、$p<0.05$を有意とした。ミダゾラム使用例は、人工呼吸器施行中の症例、バルビタール麻酔を前提とした麻酔前投薬として使用したもの以外は家族の同意を得た上で施行した。

結　果

第1選択薬として42機会、第2選択薬として34機会、第3選択薬として12機会、第4選択薬として1機会で施行した。第1選択として35/42機会(83.3%)、第2選択として28/34機会(82.3%)、第3選択として11/12機会(91.7%)、第4選択として1/1機会(100%)、計75/89機会(84.2%)でけいれんは消失し有効であった(Fig. 2)。持続型での有効率は49/55機会(89.1%)、群発型での有効率は26/34機会(76.4%)であった。原因別の有効率はてんかん37/43機会(86.0%)、急性脳炎・脳症14/17機会(82.4%)、テオフィリンけいれん8/12機会(66.7%)、熱性けいれん11/11機会(100%)、髄膜炎3/3機会(100%)、その他2/3機会(66.7%)であった。有効であった75機会中71機会は1分間以内にけいれんは消失した。ミダゾラム使用法は静注のみが8機会、静注後持続静注が81機会で、持続時間は1～240時間(平均51.2時間)であった。使用量はbolus dose 0.05～0.4 mg/kg(平均0.154 mg/kg)、持続量が0.06～0.6 mg/kg/hr(平均0.178 mg/kg/hr)であったが、有

Table 1 Bolus dose and infusion rates of intravenous midazolam infusion

	Bolus dose (mg/kg)	Infusion rate (mg/kg/hr)
Total 89 episodes	0.05–0.4 (mean 0.154)	0.06–0.6 (mean 0.178)
Effective 75 episodes	0.06–0.3 (mean 0.151)	0.06–0.32 (mean 0.145)

Table 2 Comparison of effectiveness between midazolam and diazepam

DZP (first-line) : 106/159 (66.7%) MDL (first-line) : 35/ 43 (83.3%)	$p < 0.05$
MDL (total) : 75/ 89 (84.2%)	

DZP : diazepam, MDL : midazolam

効例75機会だけでみてみると、bolus dose 0.06～0.3 mg/kg (平均0.151 mg/kg)、持続量0.06～0.32 mg/kg/hr (平均0.145 mg/kg/hr) であった (Table 1)。有効例のほとんどは、0.3 mg/kg以下の静注でけいれんは消失した。副作用として1例で興奮状態が認められ、1例で呼吸抑制が認められたが気管内挿管は不要であった。

当院小児科で同6年間にけいれんを主訴として入院した症例でジアゼパム静注を施行したのは145例159機会であった (前医での治療を含む)。けいれんに対する初期治療法は主治医の判断で選択され、症例、疾患によって選択されたものではなかった。けいれんが消失したのは106機会 (66.7%) であり、ミダゾラムの有効率と比較すると有意に低かった (Table 2)。ジアゼパム静注159機会のうち14機会で呼吸抑制を来たし気管内挿管または人工呼吸管理を要した。そのうち10機会は他院でジアゼパム静注施行後、呼吸抑制をきたし挿管後、搬送された症例であった。この14機会の原疾患は急性脳炎・脳症6機会、てんかん4機会、熱性けいれん2機会、テオフィリンけいれん2機会であったが、明確に分類できない症例もあった。

Table 3 Domestic reports of midazolam infusion for status epilepticus in children

Author	Region	episodes	Effectiveness (%)	First-line	Mean bolus dose (mg/Kg)	Mean infusion rates (mg/Kg/hr)	Mean infusion time (hr)
Minagawa et al[6]	Hokkaido	82	85.4%	35/82	0.173	0.191	132.7
Hamano et al[7]	Saitama	53	79.2%	n.d.	0.35	0.30	49.0
Present report	Niigata	89	84.2%	42/89	0.154	0.178	51.2

n.d. : no description