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Original Articles

Acute Infantile Encephalopathy Predominantly Affecting the Frontal Lobes

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To establish a novel subtype of acute infantile encephalopathy, the clinical and radiologic features of nine infants with acute encephalopathy involving the bilateral frontal lobes were examined. These patients had convulsive status epilepticus with hyperpyrexia followed by a prolonged impairment of consciousness for 2-20 days. After the recovery of consciousness, all the patients manifested regression of verbal function and lack of spontaneity. Some of them also exhibited stereotypic movements, instability of mood, or catalepsy. Transient postictal edema in both frontal lobes was suggested by diffusion-weighted magnetic resonance imaging. Attenuated cerebral perfusion in the frontal lobes was demonstrated by single-photon emission computed tomography at the tenth day after onset or subsequently. Serial studies disclosed atrophic changes in the frontal lobes. All patients manifested regression or retardation of motor and verbal functions. The recovery of intellectual deficit was slower and less prominent than that of motor dysfunction. These unique features suggest that the frontal lobes are the focus of this novel subtype of acute encephalopathy, which we propose to call acute infantile encephalopathy predominantly affecting the frontal lobes.

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Introduction

Convulsive status epilepticus with hyperpyrexia and prolonged impairment of consciousness are common clinical features of acute encephalopathies and encephalitides in childhood. Several subtypes of acute encephalopathy have been established and classified based on their clinical, radiologic, and laboratory findings: Reye syndrome [1], hemiconvulsion-hemiplegia-epilepsy syndrome [2], acute necrotizing encephalopathy in childhood [3], and hemorrhagic shock and encephalopathy syndrome [4]. Among these, Reye syndrome and hemorrhagic shock and encephalopathy syndrome are presented with diffuse cerebral edema. By contrast, the other syndromes are characterized by the involvement of specific cerebral regions: unilateral cerebral hemispheric lesions in hemiconvulsion-hemiplegia-epilepsy syndrome, and bilateral symmetrical lesions in the thalamus, cerebral white matter, brainstem, and cerebellum in acute necrotizing encephalopathy. Focal cerebral lesions are also encountered in many types of acute encephalitis: e.g., orbital and medial temporal lesions in herpes simplex type 1 encephalitis, and disseminated multiple lesions in acute disseminated encephalomyelitis [5].

This study describes an acute encephalopathy of childhood characterized by unique clinical and radiologic features suggesting bilateral involvement of the frontal lobes. There are at least seven similar cases reported previously, but the nature of the syndrome has remained obscure [6,7]. We believe that this syndrome is a novel subtype of acute encephalopathy in childhood, and propose the term "acute infantile encephalopathy predominantly affecting the frontal lobes (AIEF)".

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Patients and Methods

This study focused on nine children (aged 7 months to 3 years at onset, four males and five females) who were admitted to our hospitals from 1999 through 2003 and had the following features: (1) convulsive status epilepticus with hyperpyrexia and prolonged impairment of consciousness, (2) regression of mental or motor function after the recovery of consciousness, (3) a cerebrospinal fluid leukocyte count of 8 cells/mm^3 or less at onset, (4) neuroradiologic evidence for selective involvement of both frontal lobes, and (5) no other reasonable explanation for the cerebral or metabolic abnormalities. Informed consent for this study was obtained from all parents.

Magnetic resonance imaging was performed with a 1.0 or 1.5 T clinical magnetic resonance system. Axial spin-echo T_1- and T_2-weighted images as well as fluid-attenuated inversion recovery images with 5 mm thickness were obtained in all patients. Diffusion-weighted imaging was performed in two patients. Apparent diffusion coefficient maps were not available for this study. Cerebral perfusion was evaluated by single-photon emission computed tomography using ^{99m}Tc-ethyl cysteinate dimer for seven patients, ^{99m}Tc-hexamethyl propylene amine oxime for one patient, and ^{123}I-*N*-isopropyl-*p*-iodoamphetamine for one patient. Single-photon emission computed tomography images were evaluated with reference to images of age-matched control cases reported in the literature [8-10]. Electroencephalograms were recorded every day until the recovery of consciousness. Subsequently, electroencephalograms were recorded monthly or bimonthly for the first half year and at 6-month intervals thereafter.

Results

Clinical Features of Patients

Prenatal and perinatal histories were uneventful in all patients. They had normal developmental milestones and no history of remarkable illness. Minor anomalies were not observed in any patient. None of the patients received immunization within several weeks before the onset of encephalopathy. The family history was also unremarkable except that two of the patients' parents had had febrile convulsions in childhood. There were neither similar encephalopathies, other neurologic and metabolic disorders, sudden infantile death syndrome, other forms of early unexplained death, nor consanguinity.

All patients had hyperpyrexia, and convulsions appeared within 24 hours after the onset of fever. The initial neurologic symptom was convulsions in seven patients and unconsciousness in two. The febrile illness was influenza type A in three patients, exanthema subitum in two, measles in one, and nonspecified upper respiratory viral illness in three. Acetaminophen was administered to Patients 1 and 3 before admission; the others received no antipyretic treatment. Although some patients were administered antibiotics or expectorants, or both, there was no history of exposure to drugs or chemical substances known to cause toxic encephalopathies. All patients had generalized tonic-clonic convulsions lasting for 30 minutes or longer. They were treated with antiepileptics, including diazepam, midazolam, phenytoin, and pentobarbiturate. All patients fell into a comatose state, reaching a score of 3 or 4 according to the Glasgow Coma Scale as modified for children [11]. Two patients were treated under mild hypothermia, with an eardrum temperature of

Table 1. Clinical features of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age at onset	1 yr 3 mo	11 mo	11 mo	2 yr	7 mo	2 yr 4 mo	2 yr 10 mo	3 yr 2 mo	1 yr 1 mo
Sex	male	female	female	female	male	female	female	male	male
Duration of convulsions	100 min	110 min	60 min	40 min	40 min	60 min	30 min	30 min	35 min
Initial feature	CSE	CSE	CSE	UC	UC	CSE	CSE	CSE	CSE
Recovery of consciousness after onset	7th day	20th day	15th day	5th day	14th day	2nd day	2nd day	14th day	2nd day
Clinical features after the recovery of consciousness									
Lack of spontaneity	yes	yes	yes	yes	yes	yes	yes	yes	yes
Regression of verbal function	yes	yes	yes	yes	yes	yes	yes	yes	yes
Instability of mood	no	no	no	yes	no	yes	yes	no	no
Catalepsy	no	no	no	no	no	yes	no	no	no
Stereotypic movements	yes	no	yes	no	no	yes	yes	no	no
Recovery or gain of function after onset									
Sitting	2nd mo	6th mo	4th mo	1st mo	3rd mo	1st mo	1st mo	1st mo	1st mo
Walking	3rd mo	8th mo	10th mo	2nd mo	10th mo	1st mo	1st mo	1st mo	2nd mo
Speaking words	22nd mo	14th mo	22nd mo	2nd mo	20th mo	3rd mo	no	no	no
Speaking sentences	no	19th mo	39th mo	2nd mo	no	8th mo	no	no	no
Period of observation	39 mo	43 mo	54 mo	24 mo	24 mo	44 mo	28 mo	26 mo	14 mo

Abbreviations
CSE = Convulsive status epilepticus
UC = Unconsciousness

34.5°C to 35.5°C. Consciousness recovered between the second day and the twentieth day from symptom onset.

Abnormal behavior was noticed after the recovery of consciousness. Regression of verbal function and lack of spontaneity (marked diminution of active and voluntary behavior) were observed in all patients, although they had no motor paralysis and could behave in response to the brief commands by parents or physicians. Loss of spoken words or sentences was evident in six patients, and disappearance of babbling in three. Instability of mood was observed in three patients. Patient 6 had catalepsy; once she had her arms lifted by the examiner, she maintained the fixed posture for several minutes. Four patients transiently manifested various types of stereotypic movements, including tapping on one hand, sucking the hands and then throwing the arms forward repeatedly, or jumping on the bed. Such movements appeared at the second or third week from onset, persisted through the waking hours, and lasted for 1 to 4 weeks (Table 1).

Clinical Features on Follow-up Study

Motor functions regressed in all patients. The patients could sit and walk without support by the sixth month and tenth month from onset, respectively. No patient had ataxia or paralysis. As compared with the recovery of motor function, regression and subsequent retardation of language development were generally striking. Seven patients could not speak words, even 12 months after symptom onset. Four patients (Patients 1, 3, 7, and 8) could not speak two-word sentences even at 3 years of age or after (Table 1).

Laboratory Findings

In most patients, laboratory tests indicated mildly to moderately increased levels of lactate dehydrogenase and creatine kinase, reaching peak levels on the third to the seventh day from symptom onset. In Patient 5, lactate dehydrogenase and creatine kinase rose strikingly to 4680 U/L and 63,400 U/L, respectively. No patient had hyperammonemia or hypoglycemia. The results of carnitine and amino acid analyses were normal. Cerebrospinal fluid samples obtained on the first or second day revealed normal protein levels in all patients but Patient 5, who had an elevated cerebrospinal fluid protein level of 52 mg/dL. Interleukin-6 was measured in three patients, and was elevated up to 157 pg/mL and 180 pg/mL in cerebrospinal

Table 2. Laboratory and radiologic findings

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Blood tests									
AST (U/L) (onset→peak)	11→13	39→104	21→19	12→22	6→58	14→14	13→32	16→22	13→63
LD (U/L) (onset→peak)	565→1046	834→1376	764→1502	636→917	702→4680	614→1164	335→622	576→969	375→529
CK (U/L) (onset→peak)	72→598	803→3345	285→458	58→101	319→63,400	68→121	84→153	96→132	112→765
ammonia (μg/dL)	32	1	11	5	22	51	53	113	5
glucose (mg/dL)	235	181	93	140	121	128	253	239	92
CSF									
Cell count (/μL)	7	8	7	2	1	1	3	2	1
Protein (mg/dL)	21	24	26	10	52	12	27	13	10
Glucose (mg/dL)	ND	ND	56	102	114	53	71	83	60
MRI									
Atrophy in FLs	yes	yes	yes	yes	yes	yes	yes	yes	yes
(the period of detection)	(29th day)	(23rd day)	(22nd day)	(40th day)	(20th day)	(21st day)	(23rd day)	(31st day)	(42nd day)
HI on FLAIR in FLs	no	yes	yes	no	yes	yes	yes	no	no
SPECT									
Decreased perfusion in FLs	yes	yes	yes	yes	yes	yes	yes	yes	yes
(the period of detection)	(10th day)	(23rd day)	(21st day)	(42nd day)	(19th day)	(19th day)	(13th day)	(40th day)	(30th day)
Follow-up studies (the period of the findings)	improved (21st mo)	normalized (20th mo)	normalized (38th mo)	normalized (7th mo)	normalized (16th mo)	normalized (7th mo)	unchanged (20th mo)	NA	improved (7th mo)

Abbreviations
AST = Aspartate aminotransferase
CK = Creatine kinase
CSF = Cerebrospinal fluid
FLAIR = Fluid-attenuated inversion recovery
FLs = Frontal lobes
HI = High intensity
LD = Lactate dehydrogenase
MRI = Magnetic resonance image
NA = Not available
ND = Not done
SPECT = Single-photon emission computed tomography

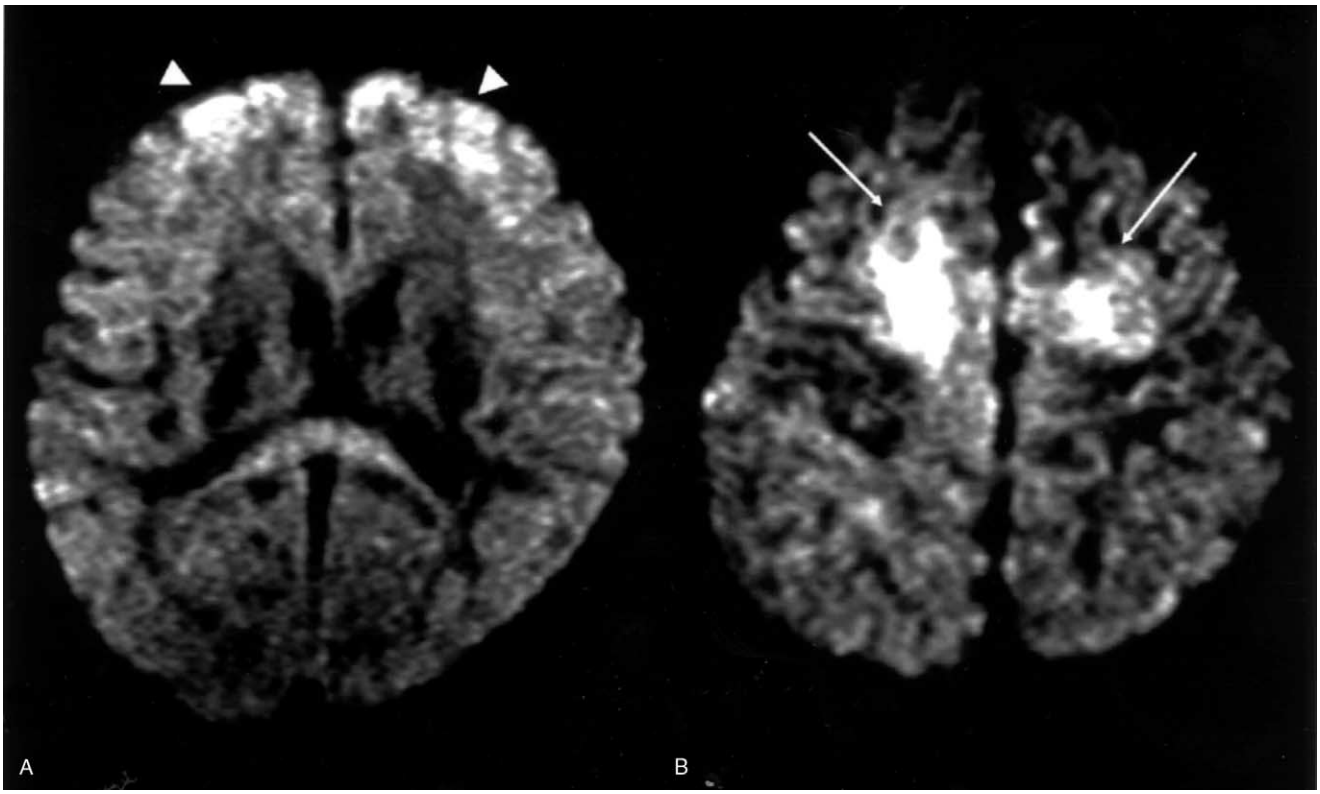

Figure 1. Diffusion-weighted magnetic resonance imaging (TR/TE = 3300 ms/123 ms, b = 1000 s/mm^2). (A) High signal intensity (arrowheads) in the cortex of both frontal lobes at the sixth day from onset in Patient 5. (B) High signal intensity (arrows) in the cortex and white matter of both frontal lobes at the sixth day from onset in Patient 9.

fluid of Patients 4 and 5, respectively. In these two patients, interleukin-6 in the serum was 3.1 and 16.9 pg/mL, respectively (Table 2).

Electroencephalography

Electroencephalograms were obtained at symptom onset in six patients and indicated slow background activity waves. Two patients presented with high-amplitude delta activity predominantly in both frontal areas. Follow-up electroencephalograms obtained 1 year after onset revealed focal spike or spike-and-wave discharge in three patients. Epilepsy developed in one patient (Patient 6), who had several episodes of staring with unconsciousness lasting for more than 5 minutes. This patient was given a diagnosis of localization-related epilepsy.

Neuroradiologic Findings

Initial magnetic resonance imaging was performed between the sixth and ninth days from symptom onset in six patients (Table 2). Two patients (Patients 5 and 9) who underwent diffusion-weighted magnetic resonance imaging on the sixth day had high signal intensity in the cortex and white matter of both frontal lobes on diffusion-weighted images, but not on spin echo T_2-weighted images (Figs 1A, 1B). One patient (Patient 7) had diffusely increased signal intensity in the cortex and subcortical white matter of both frontal lobes on T_2-weighted magnetic resonance imaging on the sixth day from symptom onset (Figs 2A, 2B). Diffusion-weighted images were not obtained in this patient. The other patients disclosed no abnormal findings on the initial T_1, T_2, and fluid-attenuated inversion recovery magnetic resonance imaging studies. On serial magnetic resonance imaging studies performed between the 20th day and 42nd day from onset, atrophic changes were observed in both frontal lobes of all patients; fluid-attenuated inversion recovery images documented mildly increased intensity in the white matter of both frontal lobes in five patients (Figs 3 and 4). Follow-up magnetic resonance imaging studies were performed in eight patients between the seventh month and fiftieth month from symptom onset. Atrophic changes had improved or resolved in seven patients, but progressive atrophic changes were present in the frontal cortex and insular cortex in one patient (Patient 7, Fig 2C).

On single-photon emission computed tomography studies, decreased perfusion in both frontal lobes was detected in all patients between the tenth day and the 42nd day after onset (Figs 2D, 3D-3F, 4E, 4F). Follow-up single-photon emission computed tomography studies were performed in eight patients. In five patients, normalized cerebral perfusion was observed between the seventh month and the 38th month after symptom onset (Figs 4G, 4H). Two patients demonstrated improved perfusion between the seventh month

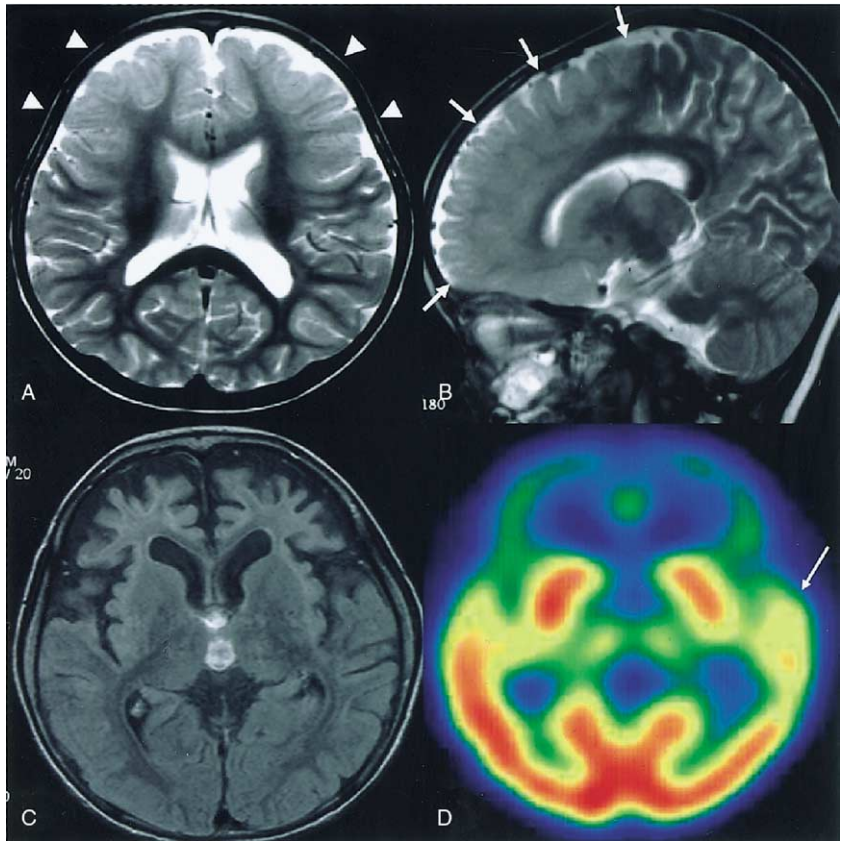

Figure 2. Axial (A) and sagittal (B) views of T_2-weighted magnetic resonance imaging (TR/TE = 4600 ms/110 ms) at the sixth day from onset in Patient 7, depicting high intensity in the cortex and subcortical white matter of both frontal lobes (arrowheads in (A) and small arrows in (B)). (C) Fluid-attenuated inversion recovery image (TR/TE/TI = 6744 ms/110 ms/1588 ms) at the 20th month after onset in Patient 7, revealing atrophic cortical changes and high intensity of both frontal lobes and insulae. (D) Single-photon emission computed tomography study (^{99m}Tc-ethyl cysteinate dimer) at the 20th month in the same patient, revealing decreased perfusion in the bilateral frontal lobes and left temporal lobe (arrow).

and the 21st month from onset. In one patient (Patient 7), decreased perfusion in the frontal lobes was observed even at the twentieth month after symptom onset. In this patient, decreased perfusion was also observed in the left temporal lobe (Fig 2D).

Discussion

All patients in our series manifested convulsive status epilepticus within 24 hours after the onset of hyperpyrexia. Although initially suspected, the diagnosis of prolonged febrile seizures was eventually ruled out based on their subsequent neurologic and imaging findings. They had prolonged impairment of consciousness after the prolonged convulsions, and lack of spontaneity and regression of verbal function were observed after the recovery of consciousness. As compared with the relatively good recovery of motor functions, acquisition or restoration of verbal function was delayed in most patients. In addition, some of the patients subsequently exhibited abnormal behaviors: stereotypic movements and catalepsy. Magnetic resonance imaging suggested postictal edematous changes in the white matter and cortex of both frontal lobes. Single-photon emission computed tomography studies revealed decreased perfusion predominantly in the frontal lobes, which improved or normalized over the course of months or years in most patients. Rarely, decreased perfusion persisted and was associated with progressive bilateral atrophic changes with sustained high signal intensity on T_2-weighted image in the frontal lobes.

These unique features differ distinctly from those observed in previously established types of acute encephalopathy in childhood. None of the patients in the present study had the metabolic abnormalities typically observed in Reye syndrome, such as hyperammonemia, hypoglycemia, or abnormal amino acid analyses [1]. Other congenital metabolic disorders, such as aminoaciduria, urea cycle disorders, or disorders of β-oxidation of fatty acids, are also ruled out on the same grounds [12]. The biochemical abnormalities of our patients' serum were mostly mild and nonspecific. The high serum level of creatine kinase is ascribed to the prolonged convulsions, whereas that of lactate dehydrogenase may have resulted from the underlying viral infections, or from the effect of cytokines, such as interleukin-6, as discussed later.

In our patients, the clinical picture consisted of multiple focal neurologic signs, and the radiologic picture was characterized by multiple localized lesions in the cerebral cortex. These features are reminiscent of acute disseminated encephalomyelitis. This encephalitis is caused by an autoimmune response, and is usually observed several days or more after the viral illness. Imaging studies in acute disseminated encephalomyelitis commonly reveal multiple areas of T_2 prolongation in the white matter, and to a lesser extent in the cortical and deep gray matter. They are moderate to large in size, and disseminated randomly

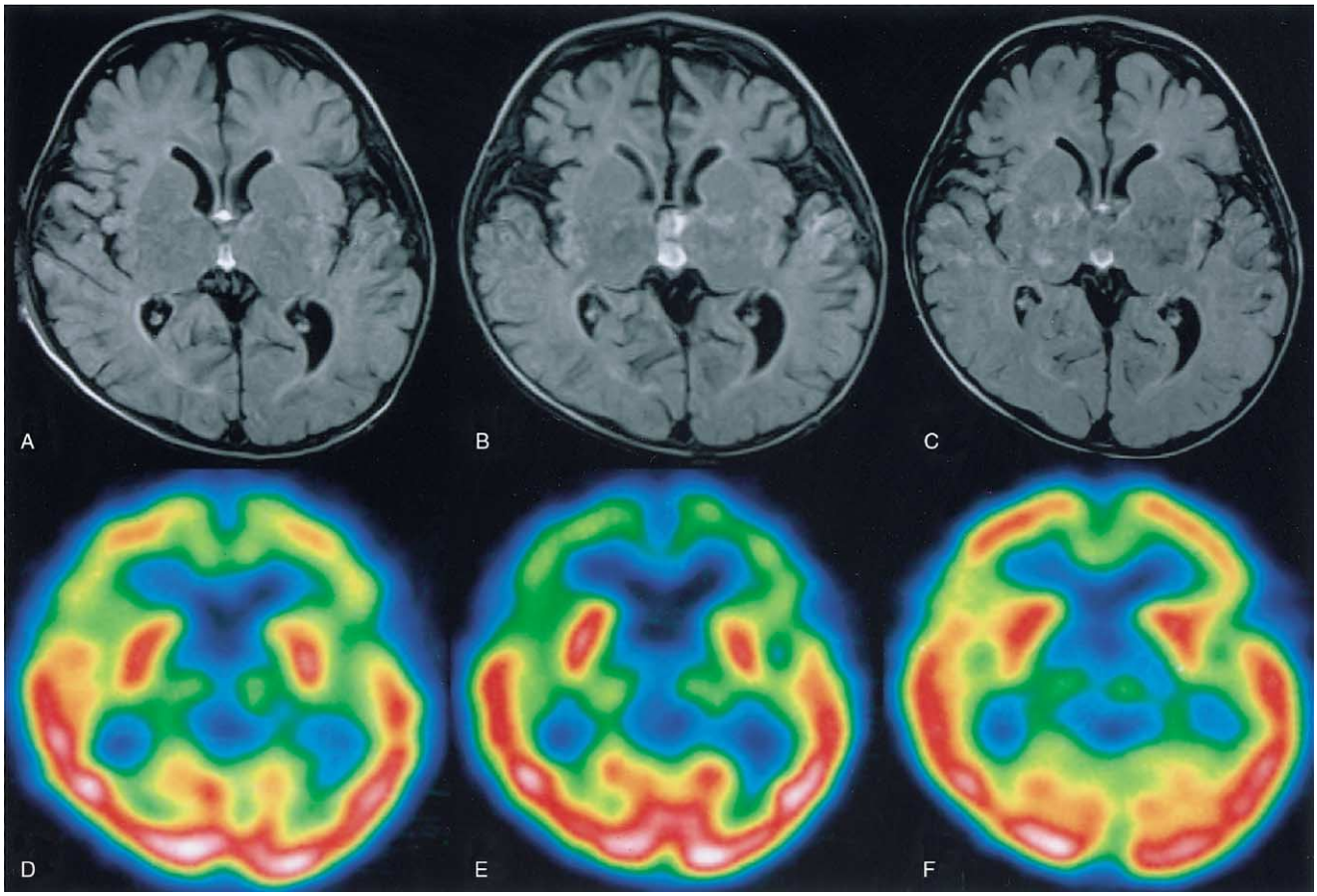

Figure 3. Serial magnetic resonance imaging (A, B, C: fluid-attenuated inversion recovery images, TR/TE/TI = 6744 ms/110 ms/1588 ms and single-photon emission computed tomography (D, E, F: ^{99m}Tc-ethyl cysteinate dimer) studies in Patient 1, which were performed at the tenth day (A, D), the seventh month (B, E), and the 21st month (C, F) from onset. Decreased cerebral perfusion in the frontal lobes was evident at the tenth day (D). Progressively decreased perfusion as well as atrophic change in the frontal lobes was observed at the seventh month. Improvement of perfusion and atrophy in the frontal lobes appeared at the 21st month.

in various regions of the brain [5,13]. However, neurologic symptoms in the patients in the present study developed within 24 hours after the development of viral infection. Lesions detected by magnetic resonance imaging studies were symmetric and localized exclusively in the frontal lobes. These findings differentiate our patients' condition from acute disseminated encephalomyelitis.

On diffusion-weighted or T_2-weighted magnetic resonance imaging, increased intensity in both frontal lobes was found in three of the six patients who underwent magnetic resonance imaging between the sixth day and the ninth day from onset. Transient signal changes on magnetic resonance imaging in patients with status epilepticus have been reported, suggesting focal episodes of transient cerebral cytotoxic or vasogenic edema caused by epileptic seizures [14,15]. Diffusion-weighted magnetic resonance imaging is useful for detecting periictal edematous lesions of the cerebrum after seizures, as demonstrated by studies in which initial magnetic resonance was generally done within 3 days from symptom onset [14,15]. Earlier diffusion-weighted images might consistently reveal postictal edematous changes in the white matter and cortex of the frontal lobes.

One of the cardinal features of our patients was decreased perfusion predominantly in the frontal lobes on single-photon emission computed tomography, appearing on the tenth day or subsequently. Decreased perfusion normalized or improved between the seventh month and the 38th month from onset in seven patients, but persisted in one patient who had progressive atrophy of both frontal lobes found on magnetic resonance imaging. These characteristics of cerebral perfusion, including the distribution and chronologic changes of suspected lesions, are not observed in other subtypes of acute encephalopathy. Evidence of restoration of cerebral perfusion in the frontal lobes suggests that this syndrome is associated with neural dysfunction or hypofunction in the cortex of the frontal lobes, which gradually resolves with the passage of time in most cases.

The frontal lobe is thought to have crucial roles in initiation, planning, designing, and sequencing [16,17]. Dysfunction of the frontal lobe and its connections produces a wide array of signs and symptoms, such as cognitive impairment, disturbance of behavioral planning, and loss of working memory, i.e., temporary storing of information used to guide future actions [16,17]. Func-

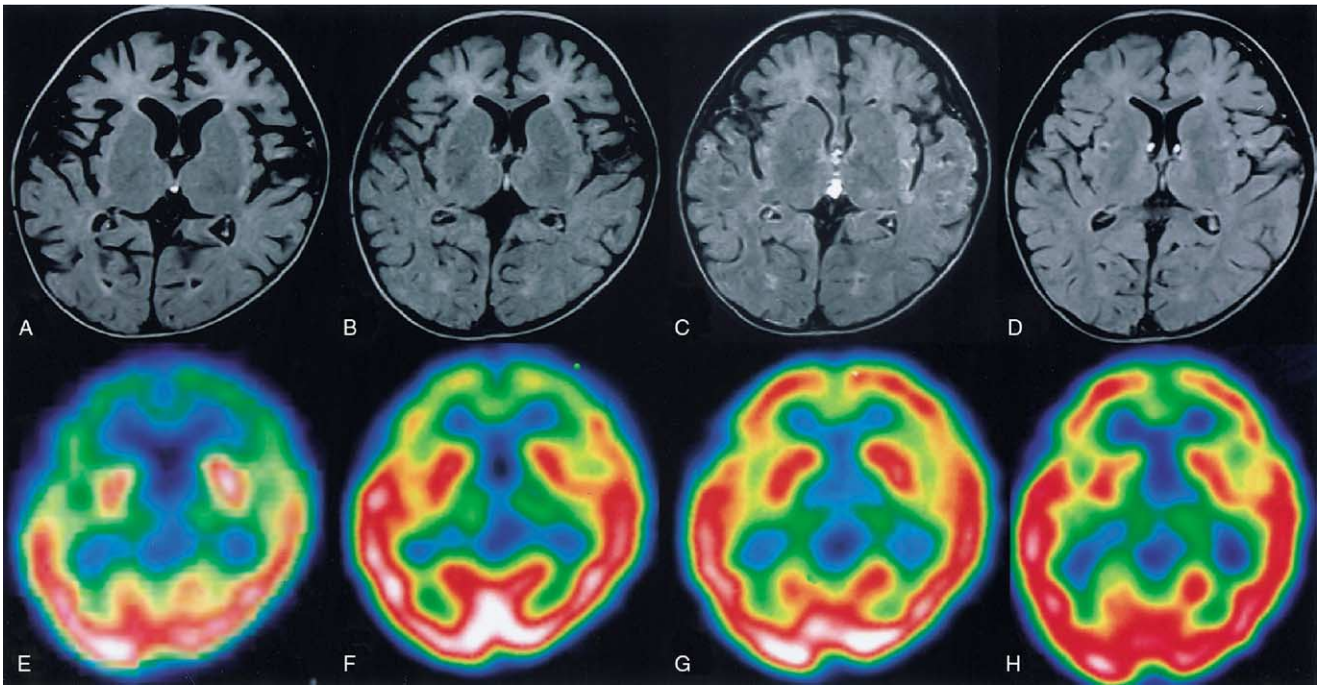

Figure 4. Serial magnetic resonance imaging (A, B, C, D: fluid-attenuated inversion recovery image, 6744 ms/110 ms/1588 ms) and single-photon emission computed tomography (E, F, G, H: ^{99m}Tc-ethyl cysteinate dimer) studies in Patient 3, which were performed at the 21st day (A, E), the twelfth month (B, F), the 38th month (C, G), and the 52nd month (D, H) from the onset. Markedly decreased perfusion and atrophic changes were observed in the frontal lobes at the 21st day (A, E). The decreased perfusion was improved at the 12th month, and then normalized at the 38th month or subsequently. High signal intensities in the white matter of the frontal lobes were observed between the 21st day and the 38th month, and disappeared at the 52nd month.

tional magnetic resonance imaging studies have demonstrated activation of the dorsolateral prefrontal cortex in awake infants processing normal speech, suggesting that precursors of adult cortical language areas are already active in infants, well before the onset of speech production [18]. Psychologic testing, using the A not B task, has documented the emergence of working memory from 7 to 12 months of age [19]. Frontal lobe dysfunction may occur even during infancy, during which bursts of functional development emerge in the premotor and prefrontal cortex. The regression of verbal function and lack of spontaneity as well as the various stereotypic movements in our patients are considered signs of dysfunction of the frontal lobes and related areas [20]. Defective social and moral behaviors are suspected to occur in adults with a history of prefrontal cortex lesions developing before the age of 16 months [21]. Children with AIEF should therefore be carefully observed for the potential development of psychopathy.

The etiology and pathogenesis of AIEF are unknown. In an attempt to explore the possible involvement of immunologic mechanisms, we assayed cytokines in the blood and cerebrospinal fluid of three patients, and found that the concentration of interleukin-6 in cerebrospinal fluid was much higher than that in serum in two of them. Although the number of patients examined was limited, this evidence suggests that interleukin-6 was, at least in part, actively produced in the central nervous system in this illness. A high cerebrospinal fluid level of interleukin-6 is also present in other types of acute encephalopathy in childhood, but not in prolonged febrile seizure [22].

The mechanisms and contributions of overexpressed interleukin-6 in patients with acute encephalopathy remain controversial: both destructive and protective roles of interleukin-6 in the central nervous system have been suggested. Transgenic mice in which interleukin-6 is expressed under the control of the glial fibrillary acidic protein promoter manifest neurodegeneration and disruption of the blood–brain barrier [23]. Phenotypically, these mice exhibit impaired learning as well as tremor, ataxia, and seizures [24]. In contrast, increased levels of interleukin-6 might have a neuroprotective role, acting against insults such as against excitotoxic brain injury [25]. Prolonged convulsions could provoke oxidative stress and accumulation of calcium in neurons, resulting in the release of cytochrome c from mitochondria, activating caspase-3 and caspase-7. These series of events could lead to apoptotic neuronal cell death. Apoptotic processes have been demonstrated in status epilepticus [26] as well as in acute encephalopathy in childhood [27]. Interleukin-6 is produced in neurons in response to excitatory receptor activation and protects against excitotoxic effects potentially leading to apoptosis [28]. Measurement of cytochrome c and cytokines including interleukin-6 in cerebrospinal fluid may be helpful when evaluating brain insults in AIEF and other acute encephalopathies in children.

In conclusion, this study describes a unique subtype of acute encephalopathy in infancy, characterized by pro-

longed impairment of consciousness after convulsive status epilepticus with hyperpyrexia, regression and subsequent retardation of language development, lack of spontaneity, periictal edematous changes, and subsequent decreased perfusion in the frontal lobes. We believe that this syndrome is a novel subtype of acute encephalopathy in infancy, and we propose to call it acute infantile encephalopathy predominantly affecting the frontal lobes (AIEF).

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