Epilepsy Research 143 (2018) 70–74

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Predictive indicators for the development of epilepsy after acute encephalopathy with biphasic seizures and late reduced diffusion

Yuko Ichimiya[a,b], Noriyuki Kaku[a,b], Masafumi Sanefuji[a,c,*], Michiko Torio[a], Soichi Mizuguchi[a,b], Yoshitomo Motomura[a,b], Mamoru Muraoka[a,b], Sooyoung Lee[a,d], Haruhisa Baba[a,e], Yuri Sonoda[a,c], Yoshito Ishizaki[a], Momoko Sasazuki[a], Yasunari Sakai[a], Yoshihiko Maehara[b], Shouichi Ohga[a]

[a] Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[b] Emergency and Critical Care Center, Kyushu University Hospital, Fukuoka, Japan
[c] Research Center for Environment and Developmental Medical Sciences, Kyushu University, Fukuoka, Japan
[d] Department of Intensive Care, Fukuoka Children's Hospital, Fukuoka, Japan
[e] Department of Pediatrics, National Fukuoka-Higashi Medical Center, 1-1-1 Chidori, Koga, Fukuoka 811-3195, Japan

ARTICLE INFO

Keywords:
Acute encephalopathy
Child
Epilepsy
Magnetic resonance imaging

ABSTRACT

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is a newly defined clinicoradiologic syndrome characterized by biphasic seizures and altered consciousness followed by restricted diffusion in the white matter on magnetic resonance imaging in acute phase. Intractable epilepsy commonly occurs as the late complication. This study aimed to search predisposing factors to the development of epilepsy after AESD. Consecutively treated 22 patients with AESD in our institution from 2006 to 2016 were grouped into those with post-encephalopathic epilepsy (PEE, n = 10) or without PEE (n = 12). There was no difference between two groups in age at the onset of AESD, duration of the initial seizures, or the follow-up periods after discharge. PEE group patients more frequently showed coma or involuntary movements during the course of AESD than non-PEE group patients (36% *vs.* 8%, $p = 0.008$). The quantitative analysis of apparent diffusion coefficient (ADC) map revealed that PEE group showed broader areas with reduced diffusion in the posterior lobes at the onsets of AESD than non-PEE group (0.113 *vs.* 0.013, $p = 0.035$). On the other hand, the atrophy on day 30-ADC map did not correlate with the development or control of epilepsy. These results suggest that the clinical severity and ADC profiles in acute phase, rather than the brain atrophy in convalescent phase, may predict the development of post-AESD epilepsy.

1. Introduction

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is the most common form of childhood-onset encephalopathy in Japan (Takanashi et al., 2006; Mizuguchi et al., 2007; Takanashi, 2009). The first phase of AESD typically starts with a prolonged febrile seizure, followed by variable levels of recovery in consciousness from normal to coma. Over the first 2 days, magnetic resonance imaging (MRI) does not detect abnormal signals. However, during the period of day 4–6, patients present with a cluster of seizures and deterioration of consciousness, as the second-phase symptoms. In this second stage of the acute phase, diffusion-weighted images (DWI) reveal the distinct brain lesions with reduced diffusion that predominantly affect the subcortical white matter. The biphasic symptom and abnormal imaging leads to the diagnosis of AESD. Neurological manifestations of paralysis, cognitive impairments and seizures often emerge in the convalescent phase and remain as the persistent neurological sequelae.

Post-encephalopathic epilepsy (PEE) denotes the status with recurrent seizures that develop after acute encephalitis or encephalopathy, including AESD (Ito et al., 2015). PEE is generally characterized by the incidence of 10–20% after acute encephalitis or encephalopathy, the latent period within 3 years, and intractable seizures (Annegers et al., 1988; Chen et al., 2006; Lee et al., 2007; Sellner and Trinka, 2013). However, there is no information about the clinical parameters in acute phase of AESD associated with the development of PEE. In

Abbrevations: ADC, apparent diffusion coefficient; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; DWI, diffusion-weighted image; EEG, electroencephalogram; JCS, Japan Coma Scale; MRI, magnetic resonance imaging; PEE, post-encephalopathic epilepsy; PCPC, pediatric cerebral performance category

* Corresponding author at: Research Center for Environment and Developmental Medical Sciences, and Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.
E-mail address: sane26@pediatr.med.kyushu-u.ac.jp (M. Sanefuji).

https://doi.org/10.1016/j.eplepsyres.2018.04.006
Received 12 March 2018; Received in revised form 2 April 2018; Accepted 9 April 2018
Available online 11 April 2018
0920-1211/

order to explore the predictive factors for post-AESD epilepsy, we analyzed the clinical findings and outcomes of children with AESD, and quantitatively assessed their serial imaging data from the onset through the convalescent period.

2. Methods

2.1. Study population

Twenty-three patients consecutively received the 'definite' or 'possible' diagnosis of AESD, and were treated and followed up for more than 1 year in Kyushu University Hospital during the period of 2006–2016. They included 20 patients in our previous report (Lee et al., 2016). One patient was excluded from this study because she had received the diagnosis of epilepsy before the onset of AESD. Thus, the remaining 22 patients were subjected to the analysis in this study. For 17 patients, the diagnosis of AESD was 'definite' according to the criteria: i) a febrile seizure as an initial neurological symptom on day 1, ii) biphasic clinical course and iii) the reduced diffusion in the subcortical white matter at day 3 or later (Lee et al., 2016). The biphasic neurological symptoms were not identified in five patients (Cases 1, 3, 6 and 7 for PEE in Table 1, and another for non-PEE), because therapeutic hypothermia was started before the onset of the second phase. These five patients were designated as 'possible' AESD. This observational study was approved by the institutional review board of Kyushu University (#28-466).

2.2. Collection of clinical information

Patient's demographics, and clinical findings including duration of the initial seizure, the presence of coma and involuntary movements during the acute phase were collected from the medical records. Coma was defined with triple digit scores (100, 200 and 300) of Japan Coma Scale (JCS) modified for infants and children (Shigematsu et al., 2013), corresponding to a score of 3–8 in Glasgow coma scale (Ono et al., 2007). In order to estimate the degree of the patients' eventual brain damage, the neurodevelopmental outcomes were assessed at their last visit with the pediatric cerebral performance category (PCPC) scale of 1: normal, 2: mild disability, 3: moderate disability, 4: severe disability, 5: coma or vegetative state, and 6: brain death (Fiser, 1992).

2.3. Definition of PEE and seizure profiles

PEE was defined as multiple seizures that occurred after 14 days of illness and required continuous use of anti-epileptic drugs because AESD patients usually show a cluster of seizures in the second phase. We investigated types of the seizures and epilepsy, the onsets, and the treatments and controls of PEE. The types were determined with medical records of detailed interview from parents and video-electroencephalogram (EEG) monitoring, according to the 2017 classification by the International League Against Epilepsy (Fisher et al., 2017; Scheffer et al., 2017). The anti-epileptic drugs were described with reference to their last prescription.

2.4. Volumetric analysis of the low ADC lesions

We analyzed digital data (DICOM) of apparent diffusion coefficient (ADC) maps derived from DWI with b values of 0 and 1000 s/mm^2, using 3D Slicer (Fedorov et al., 2012), ITK-SNAP (Yushkevich et al., 2006) and SPM8 software, as previous study described (Lee et al., 2016). Briefly, the extent of lesions with reduced diffusion were quantitatively measured in the second phase (range: 4–10 days of illness, median: 6 days). Brain parenchyma was defined as the areas showing the ADC value of 1–1400 mm^2/s, and the "low ADC" was set to 1–600 mm^2/s (Fig. 1A). The low ADC lesions conformed well to those with high-intensity lesions in DWI. The relative ratio of low-ADC to parenchyma volume was calculated for the whole brain and segmented regions: i) anterior cerebrum, ii) posterior cerebrum, iii) basal ganglia, iv) thalamus and v) cerebellum and brainstem (Fig. 1A).

2.5. Measurement of the brain atrophy

The follow-up ADC maps were scanned during the convalescent period from 21 to 50 days of illness (Fig. 1B). The appropriate timeframe was made on the fact that the brain could remain still swollen before the third week of illness. The qualified ADC maps were available for PEE (n = 12) and non-PEE group (n = 7). Estimated volume at day 30 of illness was derived for each patient. "Atrophy index" was defined as follows: (second-phase volume – convalescent-phase volume)/(second phase volume).

2.6. Statistical analysis

To examine the difference between PEE and non-PEE groups, Fisher's exact tests and Mann-Whitney *U* tests were used for categorical and numerical variables, providing effect sizes of *phi* and *r*, respectively. These significance levels were set at 0.05. Statistical analyses were performed using SPSS Statistics version 23 (IBM, Tokyo, Japan).

Table 1
Types of seizure and epilepsy, onset ages of AESD and PEE, treatments and outcomes in PEE group.

No.	Seizure type	Sex	Age at AESD onset	Age at PEE onset [developing time]	Epilepsy type or syndrome	Observation period	AED	Seizure frequency	PCPC
Generalized onset seizures									
1	Spasm[$#]	F	2y1m	2y3m [2m]	Infantile spasm	1y1m	ZNS	None	4
2	Atonic seizure	M	1y3m	1y5m [59d]	Generalized epilepsy	7y9m	CZP	None	3
3	Spasm, FIA	M	8m	11m [2m]	Combined Generalized and Focal Epilepsy	4y4m	PB, CZP, VPA, LEV	Daily	5
4	Atonic seizure[$], FIA	M	1y0m	1y2m [2m]	Combined Generalized and Focal Epilepsy	6y3m	PB, VPA	Daily	4
5	Spasm[$]	F	2y8m	2y10m [2m]	Generalized epilepsy	6y4m	VPA, CZP	None	4
6	Spasm[$#], Atypical absence	F	1y0m	1y8m [8m]	Generalized epilepsy	1y6m	VPA, CLB	None	4
7	Tonic seizure	M	9y6m	10y6m [12m]	Generalized epilepsy	3y0m	VPA, LEV	Daily	4
Focal onset seizures									
8	FIA	F	11m	1y0m [25d]	Focal epilepsy	2y4m	CBZ	None	2
9	FIA	M	2y2m	2y5m [3m]	Focal epilepsy	10y7m	VPA, LTG	Daily	4
10	FBTC	F	1y1m	1y7m [6m]	Focal epilepsy	10y1m	PB	None	4

AED: antiepileptic drug, CBZ: Carbamazepine, CLB: Clobazam, CZP: Clonazepam, FBTC: focal to bilateral tonic-clonic seizure, FIA: focal impaired awareness seizure, LEV: Levetiracetam, LTG: Lamotrigine, PB: Phenobarbital, VPA: Valproate, ZNS: Zonisamide, [$]startle-induced, [#]controlled with ACTH.