Journal of the Neurological Sciences 370 (2016) 39–43

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Involuntary movements and coma as the prognostic marker for acute encephalopathy with biphasic seizures and late reduced diffusion

Sooyoung Lee, MD [a,b,c,1], Masafumi Sanefuji, MD, PhD [a,d,*,1], Michiko Torio, MD [a], Noriyuki Kaku, MD [a,b], Yuko Ichimiya, MD [a,b], Soichi Mizuguchi, MD [a,b], Haruhisa Baba, MD [a,b,e], Yasunari Sakai, MD, PhD [a], Yoshito Ishizaki, MD, PhD [a], Hiroyuki Torisu, MD, PhD [a,f], Ryutaro Kira, MD, PhD [c], Toshiro Hara, MD, PhD [a,c], Shouichi Ohga, MD, PhD [a]

[a] Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
[b] Emergency and Critical Care Center, Kyushu University Hospital, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
[c] Fukuoka Children's Hospital, 50101 Kashiiteriha, Higashi-ku, Fukuoka 813-0017, Japan
[d] Research Center for Environment and Developmental Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
[e] Department of Pediatrics, National Fukuoka-Higashi Medical Center, 1-1-1 Chidori, Koga, Fukuoka 811-3195, Japan
[f] Section of Pediatrics, Department of Medicine, Fukuoka Dental College, 2-15-1 Tamura, Sawara-ku, Fukuoka 814-0193, Japan

ARTICLE INFO

Article history:
Received 29 July 2016
Received in revised form 7 September 2016
Accepted 9 September 2016
Available online 10 September 2016

Keywords:
Acute encephalopathy
Coma
Involuntary movement
Magnetic resonance imaging
Prognosis

ABSTRACT

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) occurs in children associated with infection. It is characterized by a prolonged febrile seizure in the first phase, and a cluster of seizures, deterioration of consciousness and the white matter lesions with reduced diffusion in the second phase. The patients often have severe neurological sequelae, but the prognostic indicators remain unknown. The present study aimed to clarify the characteristics of AESD patients who subsequently exhibited severe neurological sequelae. We retrospectively analyzed the clinical and laboratory findings along with the brain imaging in patients who had severe ($n = 8$) and non-severe neurodevelopmental outcomes ($n = 12$). Severe group more frequently showed coma ($p = 0.014$) or involuntary movements including dystonia and oral dyskinesia ($p = 0.018$) before the second phase than non-severe group. Severe group exhibited higher levels of serum alanine aminotransferase than non-severe group ($p = 0.001$). Quantitatively assessed MRI in the second phase revealed that severe group had more extensive lesions than non-severe group, in the anterior ($p = 0.015$) and posterior parts ($p = 0.011$) of the cerebrum and basal ganglia ($p = 0.020$). Early appearing involuntary movements or coma might account for the extension of acute brain lesions and the poor neurological outcomes in AESD patients.

1. Introduction

Acute encephalopathy develops in association with common infectious diseases, as represented by Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and acute necrotizing encephalopathy [1]. As a subtype of acute encephalopathy in childhood, Takanashi et al. proposed acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [2,3]. The initial symptom of AESD is a prolonged febrile seizure on day 1 (the first phase). After the phase, patients have variable levels of consciousness from normal to coma. Irrespective of the consciousness levels, magnetic resonance imaging (MRI) during the first 2 days shows no abnormality, which makes it difficult to differentiate AESD from febrile seizure status. During the period between day 4 and day 6 (the second phase), patients show a cluster of seizures and deterioration of consciousness. Diffusion-weighted images (DWI) then (day 3–9) reveal the brain lesions with reduced diffusion predominantly in the subcortical white matter, that confirms the diagnosis of AESD. After the acute stage, consciousness levels come to improve with the emerging focal neurological signs.

The neurological outcomes of AESD are varied from normal to mild or severe sequelae including mental retardation, paralysis and epilepsy [2,3]. Only a few studies reported coma, hepatic enzyme, creatinine kinase, creatinine, platelet counts and widespread MRI lesions as the prognostic indicators for acute encephalopathy with reduced diffusion (AED) [4–6]. The entity of AED includes not only AESD but also any encephalopathies with reduced diffusion in MRI. AED patients exhibit no seizures, a monophasic clinical course, or the reduced diffusion during

Abbreviations: ADC, apparent diffusion coefficient; AED, acute encephalopathy with reduced diffusion; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; DWI, diffusion-weighted image; JCS, Japan Coma Scale; PCPC, pediatric category scale.

* Corresponding author at: Research Center for Environment and Developmental Medical Sciences, Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.
E-mail address: sanefuji39@gmail.com (M. Sanefuji).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.jns.2016.09.018
0022-510X/

day 1—2, constituting more heterogeneous presentations than AESD. On the other hand, the prognostic indicators remain unknown for AESD.

A mild form of AESD has been proposed in cases with a brief seizure as an initial symptom and no neurological sequelae [3,7]. However, it is hard to discriminate it from the severe disease at diagnosis. The present study aimed to characterize the AESD patients who subsequently exhibited severe neurological sequelae. We retrospectively reviewed clinical symptoms, laboratory data and the extent of brain lesions, which were assessed by quantitative MRI analyses, and compared them between patients who had 'severe' and 'non-severe' prognoses. An early identification of severe AESD may change the treatment strategy. The present study focused especially on the findings until the onset of second phase in which the diagnosis is confirmed.

2. Methods

2.1. Study population

This study was approved by the institutional review board of Kyushu University. We enrolled a total of 20 patients with 'definite' or 'possible' AESD. They were all admitted to Kyushu University Hospital during the period of 2006–2015 and followed up over 1 year. The diagnosis of AESD was made based on clinical course and radiological findings. Inclusion criteria of definite AESD were 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. In 17 patients with definite AESD, the biphasic clinical course was identified with seizures and/or consciousness deterioration in the second phase. For three patients, however, the biphasic course could not be identified because their second phase symptoms would be masked by therapeutic hypothermia with muscle relaxants and barbiturates. The hypothermia was started before the identification of the second phase, because of the emerging brain lesions in DWI on day 5 (no. 4 in Table 1) and the prolonged coma (no. 19 and 20). For the latter two patients, the lesions were validated after the hypothermia (day 10 and day 5, respectively). All the three patients had no neurological lesions in DWI on day 1—2 of illness. Although, strictly, they should be regarded as AED, they could develop AESD if untreated with hypothermia and therefore were designated as 'possible' AESD.

2.2. Data collection

We retrospectively reviewed medical records of the patients. We collected the data of the demographics, infectious agents, duration of the initial seizure, anticonvulsant drugs, neurological manifestations, specific treatments for acute encephalopathy, and neurological outcomes. Neurological manifestations (consciousness levels and neurological symptoms) were recruited during the period between the first and second phases. Consciousness levels were assessed with Japan Coma Scale (JCS) modified for infants and children, which is widely used in Japan to measure impaired consciousness [8] and well correlated with Glasgow Coma Scale [9]. A higher JCS score represents more severe impairments. A JCS score of 0 indicates alert consciousness. Single digit scores (1, 2 and 3) denote patients who are awake without any stimuli. Double-digit scores (10, 20 and 30) indicate patients who can be aroused by some stimuli. Triple-digit scores (100, 200 and 300) mean coma, in which patients cannot be aroused by maximal painful stimuli, corresponding to a score of 3–8 in Glasgow Coma Scale. Because the consciousness levels could fluctuate during the period, we selected the best levels for each patient. The levels were all assessed before the initiation of hypothermia. We also collected data of blood examinations (Table 2) that have often been assessed to predict neurological outcome for AED, a more heterogeneous entity than AESD [4–6]. The worst values until the onset of the second phase were collected for analysis.

2.3. Classification of neurological prognoses

Neurodevelopmental outcomes were assessed by the pediatric cerebral performance category scale (PCPC) because most of the patients were infants and toddlers. PCPC has 6 categories of 1: normal, 2: mild disability, 3: moderate disability, 4: severe disability, 5: coma or vegetative state, 6: brain death [10]. The patients were classified into 'non-severe' group with PCPC score of 1—3 and 'severe' group with the score of 4–6.

Table 1
Clinical expressions and treatments.

No.	PCPC	Onset age	Sex	1st seizure		Neurological manifestations between 1st and 2nd phases		2nd phase (onset day)	Specific therapies (initiation day[b])
				Duration (min)	Drugs	JCS (time[a])	Neurological symptoms (onset day[b])		
Non-severe group ($n = 12$)									
1	1	1 y 2 m	F	40	D	0(3 d)		5	
2	1	1 y 3 m	M	5		0(1 h)		5	S(5), I(5), H(5)
3	1	1 y 11 m	M	20	D	0(15 h)	Left hemiplegia (1)	6	
4	1	2 y 9m	M	5	D	1(1 h)	Right hemiplegia (1)	ND	S(2), H(5)
5	2	11 m	F	40	D	0(11 h)	Inability to sit (1)	5	S(5), I(5), H(6)
6	2	1 y 0 m	F	35		1(3 d)	Inability to sit (1)	5	S(5), I(5), H(5)
7	2	1 y 1 m	F	10	D	0(3 h)	Inability to sit (1)	5	S(5), H(5)
8	2	1 y 4 m	M	49	D	20(18 h)		4	S(4), I(1), H(4)
9	2	1 y 6 m	M	5	D	2(19 h)	Inability to stand (1)	6	S(6), I(6), H(6)
10	3	1 y 3 m	M	60	D, M	1(22 h)		4	S(4), I(4), H(4)
11	3	1 y 5 m	F	90	D, M	20(10 h)	Right hemiplegia, oral dyskinesia & purposeless mov.[c] (1)	4	S(3), H(5)
12	3	1 y 7 m	M	85	D, M	2(22 h)		4	S(4), I(4), H(4)
Severe group ($n = 8$)									
13	4	11 m	F	180	D, M, T, P	3(3 h)	Oral dyskinesia (2)	4	S(3), I(4), H(4)
14	4	1 y 0 m	M	58	D, M	2(6 h)	Dystonia[c] (4)	5	S(2), I(2), H(6)
15	4	1 y 1 m	F	3		2(12 h)	Dystonia, oral dyskinesia & choreic mov.[c] (3)	6	S(6), H(6)
16	4	2 y 2 m	M	60	D	200(1 h)	Dystonia (3)	4	S(1), I(1), H(4)
17	4	2 y 6 m	F	47	D, M	100(4 d)		4	
18	4	2 y 8 m	F	40	D, M	3(21 h)	Dystonia[c] (2)	6	S(6), I(6), H(6)
19	4	9 y 6 m	M	150	D, M, T	200(9 h)		ND	S(1), I(2), H(2)
20	5	8 m	M	73	D, M, T	300(1 h)		ND	S(1), I(1), H(1)

D: diazepam, M: midazolam, T: thiamylal, P: phenytoin, mov.: movements, ND: not determined, S: steroid, I: intravenous immunoglobulin, H: hypothermia.
[a] The earliest hours (h) or day (d; if over 24 h) after the first seizure
[b] Day 1 denotes 'within 24 h'.
[c] Seizures were ruled out electrophysiologically.