Brain & Development 36 (2014) 608–612

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Serum and cerebrospinal fluid levels of visinin-like protein-1 in acute encephalopathy with biphasic seizures and late reduced diffusion

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Received 3 December 2012; received in revised form 22 August 2013; accepted 28 August 2013

Abstract

Background: Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) has recently been recognized as an encephalopathy subtype. Typical clinical symptoms of AESD are biphasic seizures, and MRI findings show reduced subcortical diffusion during clustering seizures with unconsciousness after the acute phase. Visinin-like protein-1 (VILIP-1) is a recently discovered protein that is abundant in the central nervous system, and some reports have shown that VILIP-1 may be a prognostic biomarker of conditions such as Alzheimer's disease, stroke, and brain injury. *Methods:* However, there have been no reports regarding serum and cerebrospinal fluid (CSF) levels of VILIP-1 in patients with AESD. We measured the serum and CSF levels of VILIP-1 in patients with AESD, and compared the levels to those in patients with prolonged febrile seizures (FS). *Results:* Both serum and CSF levels of VILIP-1 were significantly higher in patients with AESD than in patients with prolonged FS. Serum and CSF VILIP-1 levels were normal on day 1 of AESD. *Conclusions:* Our results suggest that both serum and CSF levels of VILIP-1 may be one of predictive markers of AESD.

Keywords: Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD); VILIP-1; Febrile seizure

1. Introduction

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) has recently been recognized as a type of acute encephalopathy [1]. Typical clinical symptoms of AESD present biphasic seizures, and MRI findings show reduced subcortical diffusion during clustering seizures with unconsciousness after the acute phase [1,2]. The first seizures show febrile seizure for more than 30 min, and the secondary seizures occur on several days after initial seizures. The pathogenesis of AESD remains unclear. Between the biphasic seizures of AESD, some patients have normal consciousness with no neurological symptoms. These patients commonly have normal diffusion-weighted MR images, which may lead to an initial misdiagnosis of prolonged febrile seizure (FS). Therefore, a biomarker for the early diagnosis of AESD between the initial seizure and the 1–3 days prior to the secondary seizures is important.

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http://dx.doi.org/10.1016/j.braindev.2013.08.010

Visinin-like protein-1 (VILIP-1) is a recently discovered protein that is abundant in the central nervous system, and some reports have shown that VILIP-1 may be a prognostic biomarker for a number of conditions such as Alzheimer's disease, stroke, and brain injury [3–5]. It has been reported that VILIP-1 penetrates into the cerebrospinal fluid (CSF) after the destruction of brain cells [4]. However, there have been no reports regarding serum VILIP-1 levels in patients with AESD.

In this study, we determined serum and CSF levels of VILIP-1 during the acute phase of AESD to investigate the pathogenesis of AESD, and compared the levels of VILIP-1 in patients with AESD with levels of VILIP-1 in patients with prolonged FS.

2. Patients and methods

2.1. Patients with AESD

Informed consent was obtained from the parents of all the patients enrolled in this study. Serum and CSF samples were obtained from 15 patients with AESD (median age, 1.6 years; age range, 8 months to 4.4 years; male:female, 3:12) admitted to our hospital and 4 collaborating hospitals between January 1998 and March 2012 (Table 1). All the patients were diagnosed with clinical symptoms that included not only typical biphasic seizures, but also an atypical monophasic course, and characteristic MRI findings that showed reduced subcortical diffusion during clustering seizures with unconsciousness after the acute phase.

The day of onset of the febrile seizure was considered to be the first day of illness due to AESD. The serum samples were obtained on day 2 of illness (median value; range, 1–5 days) and the CSF samples were obtained on day 4 of illness (median value; range, 1–9 days). Samples were stored at −80 °C after collection. The VILIP-1 levels in all the samples were measured at the same time without freezing/thawing the samples.

We evaluated developmental quotient (DQ) of patients with AESD using the Enjoji developmental test as one of the neurological sequelae of AESD at the last visit to the hospital after the acute phase in patients with AESD during follow-up duration for more than 5 years.

2.2. Patients with prolonged FS

Prolonged FS was defined as seizures lasting for more than 30 min or recurrent seizures lasting a total of more than 30 min without the child fully regaining consciousness. In addition, FS was defined as impaired consciousness lasting less than 24 h without neurological sequelae [6]. Serum samples from patients with prolonged FS were obtained from 39 patients (median age, 3.0 years; age range, 8 months to 14.2 years; male:female, 16:23) and CSF samples from patients with prolonged FS were also collected from 21 patients (median age, 3.0 years; age range, 8 months to 14.2 years; male:female, 13:8). The day of onset of the febrile seizure was considered the first day of illness due to prolonged FS. The serum and CSF samples were obtained on day 2 (median value; range, 1–9 days) and day 1 (median value; range, 1–2 days) of illness, respectively. Samples were stored at −80 °C after collection.

2.3. Determination of serum and CSF VILIP-1 levels

Levels of VILIP-1 were determined using a human VILIP-1 enzyme-linked immunosorbent assay kit (BioVendor, Brno, Czech Republic) with a detection limit of 100 pg/mL, according to the manufacturer's instructions.

Table 1
Clinical features of patients with AESD.

Patient no.	Age	Gender	Causative agents	Neurological symptoms after initial seizure	Outcome
1	1 year	M	Unknown	Somnolence	MeR (DQ 54), Epi
2	9 months	F	H3N2	Semicoma	Epi
3	1 year	F	FluA	Somnolence, right hemiparesis	MoP & MeR (DQ 43)
4	2 years	F	H3N2	Somnolence	MeR (DQ 50)
5	4 years	F	FluA	Coma	MeR (DQ 70)
6	3 years	F	Unknown	Coma	MoP & MeR (DQ 20), Epi
7	10 months	F	Unknown	Coma	MoP & MeR (DQ <10)
8	8 months	F	Unknown	Left hemiparesis	MoP & MeR (DQ <10)
9	1 year	F	Rota	Coma	death
10	2 years	M	Unknown	Disorientation	MeR (DQ 79)
11	2 years	M	FluA	Right hemiparesis	MeR (unknown)
12	1 year	F	Rota	Coma	MoP & MeR (DQ <20), Epi
13	1 year	F	Rota	Coma	MoP & MeR (DQ <20), Epi
14	1 year	F	*Escherichia coli*	Somnolence	MoP & MeR (DQ <10), Epi
15	1 year	F	HHV6	Left hemiparesis	MoP (DQ <20)

Abbreviations: FluA: influenza A, HHV6: human herpes virus 6, MeR: mental retardation, Epi: epilepsy, MoP: motor paralysis.