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Original article

Early prognostic factors for acute encephalopathy with reduced subcortical diffusion

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Abstract

Objective: The aim of this study was to determine the prognostic factors for acute encephalopathy with reduced diffusion (AED) during the acute phase through retrospective case evaluation.

Methods: The participants included 23 patients with AED. The diagnosis of AED was based on their clinical course and radiological findings. We divided the patients into severe and non-severe groups based on the neurodevelopmental outcome. The severe group included seven patients (median age, 21 months; range, 6–87 months) and the non-severe group included 16 patients (19 months, 9–58 months). Clinical symptoms, laboratory data and electroencephalogram (EEG) findings within 48 h from the initial seizure onset were compared between the two groups to identify neurological outcome predictors.

Results: The incidence of coma 12–24 h after onset, serum creatinine (Cr) levels within 2 h after onset, maximum aspartate aminotransferase (AST) levels within 24 h after onset, and the rate of electrographic seizures in EEG were significantly higher in the severe group (Coma, 80%; Cr, 0.40 mg/dl, 0.37–0.73; AST, 363 IU/L, 104–662; electrographic seizures, 80%) than the non-severe group (Coma, 0%; Cr, 0.29 mg/dL, 0.19–0.45; AST, 58.5 IU/L, 30–386; electrographic seizures, 0%).

Conclusions: Coma 12–24 h after onset, elevation of Cr levels within 2 h after onset, elevation of AST levels within 24 h after onset, and non-convulsive status epileptics (NCSE) in comatose patients were early predictors of severe AED. Patients in a coma after a febrile seizure should be checked for NCSE signs in EEG to terminate NCSE without delay.
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Keywords: Acute encephalopathy with reduced subcortical diffusion; Prognostic factor; Coma; Creatinine; Aspartate aminotransferase; Non-convulsive status epilepticus

Abbreviations: AED, acute encephalopathy with reduced subcortical diffusion; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; ANE, acute necrotizing encephalopathy; AST, aspartate aminotransferase; BBB, blood-brain barrier; BTA, bright-tree appearance; Cr, creatinine; EEG, electroencephalogram; GCS, Glasgow Coma Scale; HHV, human herpes virus; HSES, hemorrhagic shock and encephalopathy syndrome; NCSE, non-convulsive status epilepticus; NSE, neuron-specific enolase; MDL, midazolam; MRI, magnetic resonance imaging; PC, platelet count; PCPC, Pediatric Cerebral Performance Category; SE, status epilepticus; TTM, target temperature management

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1. Introduction

Acute encephalopathy is a severe brain dysfunction caused by various factors such as infection, metabolic disease, and systemic disorders. Recently, several subtypes of acute encephalopathies have been established on the basis of magnetic resonance imaging (MRI) findings and clinical manifestations. Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is the most frequent subtype of acute encephalopathy and amounts to about 30% of all acute encephalopathy cases in Japan (120–200 per year) [1]. It begins with a prolonged febrile seizure and altered consciousness, followed by improvement while still in a state of altered consciousness [2]. Biphasic seizures often occur on days 3–9, concurrent with diffusion-weighted brain MRI showing a reduced signal in the subcortical white matter. Reduced subcortical diffusion is a neuroradiological hallmark of AESD, essential for the diagnosis. However, recent reports have shown that reduced subcortical diffusion may be present in patients who may not completely manifest features of AESD [3–6]. Bilateral reduced subcortical diffusion can be seen in patients with a monophasic clinical course or reduced diffusion on the first or second day of illness [3]. A mild form of AESD has been proposed in cases with an initial brief seizure and no neurological sequelae [4]. Hayashi et al. proposed the entity of acute encephalopathy with reduced subcortical diffusion (AED) which covers a spectrum including not only typical AESD but also encephalopathy with no prolonged febrile seizures, a monophasic clinical course, or reduced diffusion on days 1–2 [7]. AED can be divided into two distinct groups according to the distribution of brain lesions: patients with diffuse lesions appear to represent a severe phenotype of AED, and those with central-sparing lesions a milder phenotype. These authors also showed that a prolonged seizure at the onset, a decreased consciousness level during the first 24 h, mechanical ventilation, and high levels of serum aspartate aminotransferase (AST), alanine aminotransferase, and creatine kinase were associated with poor neurological outcomes. Other investigators reported the serum creatinine (Cr) level, peripheral platelet counts (PC), and involuntary movement as prognostic factors for AED or similarly classified acute encephalopathies [3,8,9]. However, prognostic factors in the acute phase of AED have not been revealed in previous reports. The only reliable prognostic factor in AED is the presence of diffuse lesion in diffusion-weighted brain MRI, starting 3 days after the onset. The lack of prognosis information at onset can lead to underestimation of severity and a delay in therapy initiation in the acute phase of AED. If we could distinguish between severe AED and mild AED in the acute phase, we might be able to better select appropriate therapeutic strategies including more aggressive treatments for severe patients.

The present study aimed to characterize AED patients who exhibited severe neurological sequelae in the acute phase. We retrospectively reviewed clinical symptoms, laboratory data, and electroencephalograms (EEGs) and compared them between patients who had ‘severe’ and ‘non-severe’ outcomes. Early identification of severe AED may be critical for treatment strategy selection.

2. Patients and methods

The participants were 23 patients with AED admitted to Nagano Children’s Hospital from 2004 to 2016 and followed-up for over 1 year after onset. Their ages ranged from 6 months to 87 months (median, 20 months). Five of the 23 patients presented with some underlying conditions (two with mild intellectual disability of unknown cause, and one each with autism, tuberous sclerosis and brain tumor). The diagnosis of AED was made based on the clinical course and radiological findings. The inclusion criteria of AED were (i) a febrile seizure as an initial neurological symptom, and (ii) reduced diffusion in the subcortical white matter involving one or both hemispheres, a pattern known as “bright tree appearance” (BTA). Children fulfilling both criteria were diagnosed with AED, with or without a biphasic clinical course, although a biphasic clinical course is typical in children with AESD. The study protocol was approved by the Ethics Committee of Nagano Children’s Hospital, and written informed consent was obtained from the parents of the patients enrolled in the study.

We divided the patients into severe and non-severe groups based on the neurodevelopmental outcomes beyond 1 year after the onset of encephalopathy. Neurodevelopmental outcomes were assessed on the Pediatric Cerebral Performance Category scale (PCPC). The PCPC scale has six categories: normal, mild disability, moderate disability, severe disability, coma or vegetative state, brain death [10]. The patients with PCPC scores of 1–3 were classified as non-severe and those with scores of 4–6 as severe.

The following clinical parameters, obtained from medical records were evaluated as potential prognostic factors for AED: age of onset, prodromal illness, duration of first seizure, presence of prolonged seizure, presence of biphasic clinical course, consciousness level 12–24 h after onset, findings of diffusion-weighted images in MRI, commencing day of steroid pulse therapy and target temperature management (TTM). Seizure duration was defined as the time elapsed from the earliest signs of seizure until cessation of all seizure symptoms, and was determined clinically by the doctor

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