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Original article

Early risk factors for mortality in children with seizure and/or impaired consciousness accompanied by fever without known etiology

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Abstract

Background: Children who present with seizure and/or impaired consciousness accompanied by fever without known etiology (SICF) may be diagnosed with either acute encephalopathy (AE) or febrile seizure (FS). Although approximately 5% of AE cases are fatal, it is difficult to identify fatal cases among children with SICF, which are often critical by the time of diagnosis. Thus, early prediction of outcomes for children with SICF, prior to diagnosis, may help to reduce mortality associated with AE. The aim of the present study was to identify clinical and laboratory risk factors for mortality acquired within 6 h of onset among children with SICF.

Methods: We retrospectively reviewed the medical records of children who had been admitted to Kobe Children's Hospital (Kobe, Japan) with SICF between October 2002 and September 2015. We compared clinical and laboratory characteristics acquired within 6 h of onset and outcomes between survivors and non-survivors using univariate and multivariate analyses.

Results: The survivor and non-survivor groups included 659 and nine patients, respectively. All patients in the non-survivor group received a final diagnosis of AE. Univariate analysis revealed significant differences between the groups with regard to seizure duration and the following laboratory parameters: aspartate transaminase (AST), alanine aminotransferase, lactate dehydrogenase, sodium, and lactate. The multivariate analysis identified AST as a significant independent factor associated with mortality.

Conclusions: Elevation of AST within 6 h of onset is independently correlated with mortality in children with SICF. Our result may elucidate earlier intervention for patients with high risk of mortality.

Keywords: Acute encephalopathy; Febrile seizure; Mortality; Risk factors

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1. Introduction

Children with either febrile seizure (FS) or acute encephalopathy (AE) exhibit seizures and/or impaired consciousness accompanied by fever without known etiology (SICF). Whereas FS is a transient condition in which children do not experience sequelae [1], AE is defined as impaired consciousness lasting longer than 24 h and is often associated with neurological sequelae. Previous studies have indicated that the mortality rate among patients with AE is 5.6% [2]. Although FS and AE differ greatly in severity and outcome, it is often difficult to distinguish AE from FS in the early stages of the disease. Furthermore, children with a certain subtype of AE—hemorrhagic shock and encephalopathy syndrome (HSES) [3]—are almost always in critical condition and exhibit multiple organ failure (MOF) by the time of diagnosis [4]. Thus, early prediction of outcomes for children with SICF, prior to diagnosis, may help to reduce mortality associated with AE.

Although some previous studies have investigated risk factors associated with the morbidity or specific syndromic diagnosis of AE [5–8], to the best of our knowledge, no studies have aimed to identify acute-phase risk factors associated with mortality in children with SICF. In previous studies, we revealed that risk factors for morbidity could be obtained within 6 h of onset in patients with SICF [5,8]. Therefore, the aim of the present study was to identify risk factors for mortality acquired within 6 h of onset among children with SICF.

2. Patients and methods

The present retrospective study was conducted following approval from the Ethics Committee of Hyogo Prefectural Kobe Children's Hospital (KCH) (Kobe, Japan), who waived the requirement for informed consent due to the retrospective nature of the study. We retrospectively reviewed the medical records of consecutive patients (age range: 1 month to 15 years) admitted to the pediatric intensive care unit (PICU) in KCH with SICF between October 2002 and September 2015. KCH provides tertiary pediatric services for the Hyogo prefecture (population: 5.6 million), with a PICU that can provide treatment for patients who require advanced respiratory and/or circulatory support, and for those exhibiting impaired consciousness. We defined SICF as the presence of seizures and/or impaired consciousness accompanied by fever without known etiology such as epilepsy, known metabolic disorders, structural anomalies in the central nervous system (CNS), or CNS infection with pleocytosis (cerebrospinal fluid cells >8 cells/μl). Onset time was defined as the time at which seizure or altered mental state was first observed in conjunction with a temperature >38 °C.

2.1. Methods

We retrospectively reviewed the medical records, patient characteristics, and the following clinical data obtained within 6 h of onset: clinical presentation, laboratory data, existence of abnormalities on brain computed tomography (CT) images and therapeutic data. The laboratory data evaluated included white blood cells (WBC), hemoglobin (Hb), platelets (PLT), prothrombin time (PT), aspartate transaminase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine kinase (CK), sodium (Na^+), calcium (Ca^{2+}), glucose (Glu), C-reactive protein (CRP), and lactate (Lac). Although magnetic resonance imaging (MRI) may provide more informative findings [9], only a few patients had undergone MRI. Furthermore, it is impossible to obtain MRI data for critically ill patients. Therefore, MRI findings were not included in our analyses of clinical data. We also evaluated the frequency of intubation, steroid treatment, targeted temperature management (TTM), and the number of anti-epileptic drugs (AEDs) administered within the first 24 h of disease onset.

Onset was defined as the time at which the patient's neurological symptoms were first observed. Neurological outcomes were defined based on Pediatric Cerebral Performance Category (PCPC) [10] scale scores at the time of discharge. We divided the patients into survivor (PCPC score = 1–5) and non-survivor (PCPC score = 6) groups, following which we compared the data between the two groups. When multiple laboratory values were available due to repeated testing, we chose the first value obtained. Patients who had been diagnosed with AE were further classified based on the specific syndrome, such as acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [11]; acute necrotizing encephalopathy (ANE) [12]; acute encephalitis with refractory, repetitive partial seizures (AERRPS) [13]; HSES [3]; and Reye-like syndrome [14].

2.2. Statistical analysis

All statistical analyses were performed using EZR (Saitama Medical Center, Jichii Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R Commander designed to add statistical functions frequently used in biostatistics [15]. Univariate analysis was performed in the survivor and non-survivor groups using Fisher's exact tests and Mann-Whitney U-tests. Variables for which significant differences were observed in univariate analyses were subjected to multiple regression analysis, followed by an analysis of Pearson's correlation coefficients. For all statistical analyses, the level of statistical significance was set a $p < 0.05$.

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