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Original article

A severity score for acute necrotizing encephalopathy

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Abstract

Objective: To develop a score that predicts the prognosis of children with acute necrotizing encephalopathy (ANE).

Method: We retrospectively evaluated clinical variables and neurological outcome in two cohorts of children with ANE. Firstly, we developed the ANE severity score (ANE-SS) according to the clinical variables that correlated with neurological outcome in 41 children who were included in our previous reports in 2009. We then applied the scoring system to a second cohort of 32 patients who were newly collected in 2011. We investigated the correlation between the ANE-SS and neurological outcome in all 73 patients.

Results: In the first cohort, brain stem lesions on MRI and state of shock at onset were significantly correlated with outcome. Age over 48 months, elevated CSF protein, and low platelet counts tended to be correlated with outcome. No types of treatment were correlated with outcome. The developed ANE-SS ranged from 0 to 9 points, with 3 points for existence of shock, 2 points for brain stem lesions, 2 points for age over 48 months, 1 point for platelet count below 100,000/μL, and 1 point for CSF protein above 60 mg/dl. Patients were classed as low risk (ANE-SS 0–1 points), medium risk (ANE-SS 2–4 points), or high risk (ANE-SS 5–9 points). ANE-SS was significantly correlated with outcome in the group of 73 patients.

Conclusion: ANE-SS can be used to predict outcome in patients with ANE. More effective treatments need to be developed for high-risk patients.

Keywords: Acute necrotizing encephalopathy; ANE; Severity score; Prognosis; Risk

1. Introduction

Acute necrotizing encephalopathy (ANE) is a serious subtype of acute encephalopathy in children, first described by Mizuguchi et al. [1–3] ANE is characterized by symmetric lesions in bilateral thalami, and is often associated with lesions in the cerebral white matter, internal capsule, putamen, brainstem and cerebellum [3]. The exact etiology is not understood, although some studies have reported increased levels of cytokines such as interleukin-6 and tumor necrosis factor-α in patients with ANE and have postulated that a "cytokine storm" may be involved in the pathogenesis of this disease [4–9]. Neurological outcome of ANE is very poor and the mortality and morbidity rates are high [5,10]. Some immunomodulation therapies and hypothermia have been tried for children with ANE [10–12].

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The occurrence of ANE is rare. Hoshino et al. reported that ANE accounted for only 39 (4.0%) of 983 children with acute encephalopathy during a 3-year period in Japan [13]. Therefore, a randomized clinical trial is difficult to perform. In addition, the poor prognosis of ANE makes randomization of patients difficult because of ethical problems, and the treatment for ANE is different among hospitals because there is no standard regimen. In order to determine the efficacy of treatment and to establish a standard regimen, prognostication of children with ANE is necessary. Some previous studies have reported that neurological symptoms, abnormal laboratory data, and neuroimaging findings indicate poor prognosis in children with ANE [3,10,14,15]. However, the method for prognostication of ANE has been unclear.

The aim of this study is to establish a severity score for ANE that can predict the prognosis of children with ANE at the onset of the illness. When we can establish a well-applicable score, it will be useful to determine the efficacy of the treatment for ANE and to establish efficacious treatment regimen. For this purpose, we explored items that can be measured at onset and that correlate with outcome in children with ANE. We then combined these items into a scoring system that can be used for prognostication of children with ANE.

2. Patients and methods

We retrospectively evaluated the clinical manifestation, laboratory data, neuroimaging findings, treatment, and outcome of two groups of children with ANE. The first group comprised 41 children with ANE who had been admitted to 17 hospitals. (Supplementary Table 1) This cohort was derived from our previous report examining the relation between outcome and treatment [5,10,16]. The data were collected from the hospitals all over Japan, where the two senior authors (AO and MM) are collaborating for clinical studies on acute encephalopathy. All of them are tertiary medical centers. Data were collected during the 2006/07 winter season. The second group consisted of 32 children with ANE who were newly recruited from 27 hospitals in December, 2010. (Supplementary Table 2) This cohort was derived from a nationwide survey on the epidemiology of acute encephalopathy in Japan [13]. Thirty-nine children with ANE was identified during the first survey and data for this study were available in 32 of them. In both cohort, clinical data were obtained using a structured research form anonymously. This study was approved by the Research Ethics Commitee of the University of Tokyo (No.2116). In both groups, the diagnosis of ANE was made by the attending pediatric neurologists on the basis of neuroradiological findings according to the criteria proposed by Mizuguchi et al. [2,3] (Fig. 1). We included patients with acute encephalopathy who had multiple focal lesions that were symmetrically distributed in the bilateral thalami and other brain regions such as the putamina, cerebral and cerebellar white matter, and brainstem tegmentum [2,3,17]. We excluded patients with marked metabolic derangement indicated by elevated lactate, pyruvate, amino acid or organic acid levels.

We investigated the following items: age, sex, existence of shock on admission, laboratory data on admission (platelet count, serum levels of aspartate transaminase, alanine aminotransferase, lactate dehydrogenase, and creatine kinase, and CSF protein level), existence of brainstem lesions on CT or MRI, treatment (methylprednisolone pulse therapy, intravenous immunoglobulin, plasma exchange, hypothermia and antithrombin III) and outcome (normal, mild sequelae,

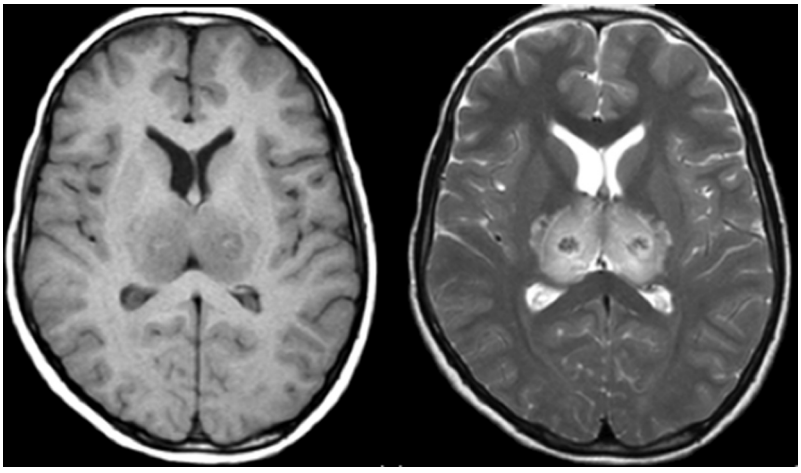

Fig. 1. MRI from a 12-year-old boy showing typical findings in ANE. The T1WI (left) and T2WI (right) show concentric lesions in the bilateral thalami and lentiform nuclei. The center and periphery of the thalamic and lenticular lesions show hyperintensity on T1WI (left) and hypointensity on T2WI (right), suggestive of hemorrhagic change.