

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/ μ L, 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.

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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 Committee 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 anti-thrombin III) and outcome (normal, mild sequelae,

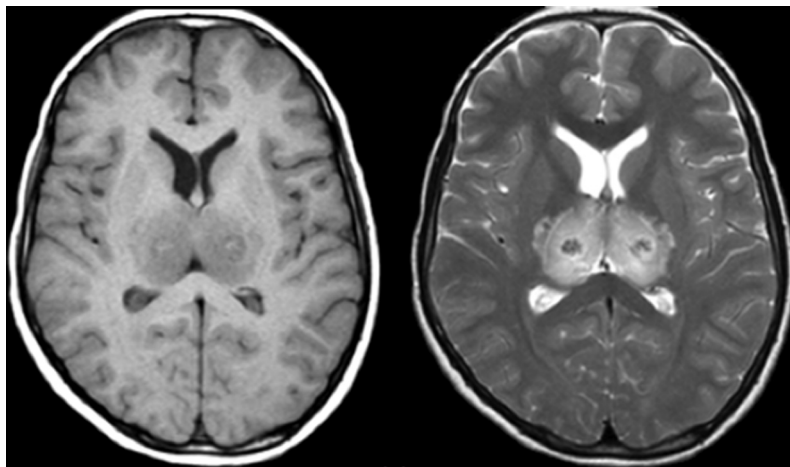


Fig. 1. MRI from a 12-year-old boy showing typical findings in ANE. The T1WI (left) and T2WI (right) show concentric lesions in the bilateral thalami and lentiform nuclei. The center and periphery of the thalamic and lenticular lesions show hyperintensity on T1WI (left) and hypointensity on T2WI (right),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

moderate sequelae, severe sequelae, or death). These data were obtained using a structured research form that was completed by the attending pediatric neurologist in each hospital. Outcome of surviving children was determined according to both motor and cognitive impairments. Motor impairment was categorized as none, mild (walking with or without support), moderate (sitting with or without support), or severe (required support to sit). Cognitive impairment was categorized according to a developmental (DQ) or intelligence quotient (IQ) as none ($DQ/IQ \geq 70$), mild ($50 \leq DQ/IQ < 70$), moderate ($30 \leq DQ/IQ < 50$), or severe ($DQ/IQ < 30$). The severest of the motor and cognitive impairment categories was used as the grade of neurological outcome. For example, neurological outcome was severe in a child with mild motor impairment and severe cognitive impairment. Neurological outcome was determined one year or longer after the onset of ANE, whereas the duration of follow-up was not collected for this study.

To select items for inclusion in the ANE severity score (ANE-SS), we analyzed the correlation between each item and neurological outcome in the first cohort. For the purpose of statistical analyses, neurological outcome was expressed as 1 for normal, 2 for mild, 3 for moderate, 4 for severe, and 5 for death. Numerical and categorical variables were analyzed using Pearson's correlation test

and Spearman's rank correlation test, respectively, and the correlation coefficient was calculated for each variable. The Mann–Whitney U test was performed to determine the degree of contribution for some candidate items. The ANE-SS was constructed by adopting the items that had a significant correlation with neurological outcome. Each item was weighted according to the degree of correlation. The adequacy of this score was evaluated in the first cohort and in a combined group of the first and second cohorts by Spearman's rank correlation test. In all statistical analyses, a p value < 0.05 was determined as statistically significant.

3. Results

3.1. Correlation between each item and outcome in the first cohort

Among the 41 patients in the first cohort, 10 of 11 patients over 48 months of age had severe sequelae or death (Fig. 2A) and patients with elevated CSF protein or low platelet count tended to have severe sequelae (Fig. 2B and C). Age, CSF protein level, existence of shock on admission, and brain stem lesions on CT or MRI were significantly correlated with outcome, but sex, serum levels of aspartate transaminase aspartate

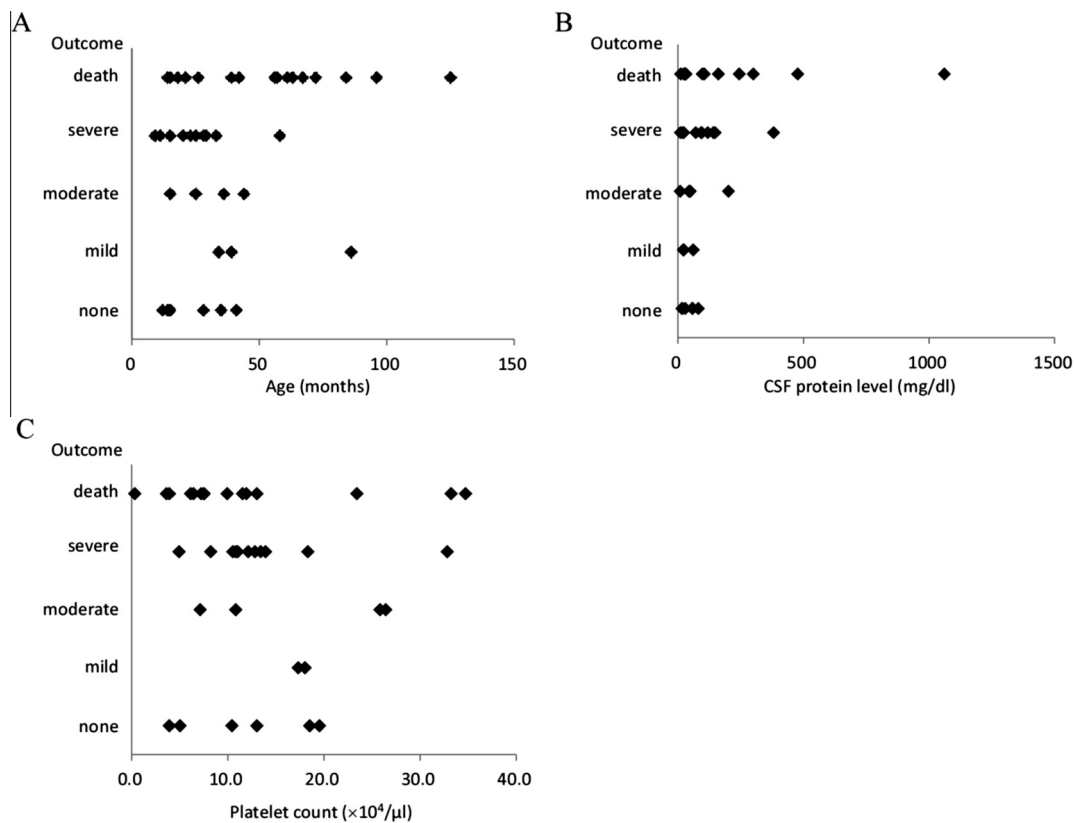


Fig. 2. Scatter diagram of outcome and age (A), CSF protein level (B) and platelet count (C). Ten of 11 patients over 48 months of age had severe sequelae or death, and patients with elevated CSF protein or low platelet count tended to have severer sequelae.

transaminase, alanine aminotransferase, lactase dehydrogenase, and creatine kinase, platelet count, and treatment types were not significantly correlated with outcome (Table 1). Comparison analyses also showed that shock, brainstem lesions, and age > 48 months were significantly correlated with poor outcome, whereas CSF protein > 60 mg/dL showed a marginal result. (Table 2) Although platelet count did not have a significant correlation with outcome, we included this in the ANE-SS because of clinical importance.

3.2. Ane-ss

The weight of each item in the ANE-SS was determined according to the strength of correlation with

Table 1
Correlations between clinical information and prognosis (continuous variable).

	p Value	Correlation coefficient
<i>Patient characteristics</i>		
Age*	0.043	0.318
Sex**	0.253	0.183
Shock on admission**	<0.001	0.627
Brainstem lesions**	0.004	0.441
<i>Laboratory data</i>		
AST (IU/L)*	0.183	0.212
ALT (IU/L)*	0.333	0.155
LDH (IU/L)*	0.114	0.254
CK (IU/L)*	0.152	0.237
Platelet count* (×10 ⁴ /μL)	0.211	0.208
CSF protein* (mg/dL)	0.041	0.347
<i>Treatment</i>		
mPSL pulse**	0.138	0.236
Intravenous immunoglobulin**	0.769	0.047
Plasma exchange**	0.633	0.077
Hypothermia**	0.951	0.010
Anti-thrombin III**	0.951	0.010

AST: aspartate transaminase, ALT: alanine aminotransferase, LDH: lactase dehydrogenase, CK: creatine kinase, CSF: cerebrospinal fluid, mPSL: methylprednisolone.

* Analyzed by Pearson's correlation test.

** Analyzed by Spearman's rank correlation test.

Table 2
Correlations between clinical information and prognosis (categorical variables).

	Mean neurological outcome class (range)		p Value
	Yes	No	
Age > 48 months	5 (2–5)	4 (1–5)	0.007
Shock at onset	5 (3–5)	3.5 (1–5)	<0.001
Brainstem lesions	5 (2–5)	4 (1–5)	0.006
Platelet count < 10 × 10 ⁴ /μL	5 (1–5)	4 (1–5)	0.059
CSF protein > 60 mg/dL	4 (1–5)	3 (1–5)	0.071

Analyzed by Mann–Whitney U test.

outcome. Because shock on admission was most closely related to outcome, it accounted for 3 points in the ANE-SS. Age > 48 months and existence of brainstem lesions were also closely correlated with outcome and accounted for 2 points each. Platelet count <100,000/μL and CSF protein > 60 mg/dl were weakly correlated with outcome and accounted for 1 point each. Among 41 patients in the first cohort, 30 had sufficient information to determine ANE-SS. In these 30 patients there was a significant correlation between ANE-SS and outcome (Spearman's $r = 0.781$, $p < 0.001$; Table 3). Sixteen of 32 patients in the second cohort had sufficient information to determine ANE-SS. In the combined group of 46 patients from the first and second cohorts there was a significant correlation between ANE-SS and outcome (Spearman's $r = 0.627$, $p < 0.001$; Table 4).

We divided patients into three groups according to ANE-SS: low risk (0–1 points, $n = 11$), medium risk (2–4 points, $n = 18$), and high risk (5–9 points, $n = 17$). There was a significant correlation between risk classification and outcome (Spearman's $r = 0.518$,

Table 3
Acute necrotizing encephalopathy severity score (ANE-SS) and outcome in the first cohort ($n = 30$).

ANE-SS	Outcome				
	No sequelae	Mild sequelae	Moderate sequelae	Severe sequelae	Death
0	3	0	0	1	0
1	3	0	0	2	0
2	0	1	3	1	1
3	0	0	0	3	0
4	0	0	0	1	1
5	0	0	1	1	2
6	0	0	0	0	2
7	0	0	0	0	1
8	0	0	0	0	0
9	0	0	0	0	3

Spearman's rank test: correlation coefficient 0.781 ($p < 0.001$).

Table 4
Acute necrotizing encephalopathy severity score (ANE-SS) and outcome in the first and second cohorts combined ($n = 46$).

ANE-SS	Outcome				
	No sequelae	Mild sequelae	Moderate sequelae	Severe sequelae	Death
0	3	1	0	1	0
1	4	0	0	2	0
2	0	1	3	2	1
3	0	0	1	6	0
4	0	1	0	1	2
5	0	0	1	1	2
6	0	0	0	2	4
7	0	0	0	1	1
8	0	0	0	0	0
9	1	0	0	1	3

Spearman's rank test: correlation coefficient 0.627 ($p < 0.001$).

Table 5
Risk classification and outcome in the first and second cohorts combined ($n = 46$).

	No or mild sequelae	Moderate sequelae	Severe sequelae or death
Low risk (ANE-SS 0–1)	8	0	3
Medium risk (ANE-SS 2–4)	2	4	12
High risk (ANE-SS 5–9)	1	1	15

Spearman's rank test: correlation coefficient 0.518 ($p < 0.001$).

ANE-SS: Acute necrotizing encephalopathy severity score.

$p < 0.001$; Table 5). Of the 11 patients classified as low risk, eight had no or mild sequelae. Of the 18 patients classified as medium risk, two had no or mild sequelae, four had moderate sequelae, and 12 had severe sequelae or death. Of the 17 patients classified as high risk, 15 had severe sequelae or death.

4. Discussion

In this study we developed the ANE-SS, which will be useful for presuming the prognosis of children with ANE. We verified that there was a significant correlation between the ANE-SS and outcome in a combined cohort of patients. There are no previous reports of a score that indicates the severity of ANE. This is attributable to several factors including low incidence of ANE and wide differences in treatment across different hospitals. We addressed these problems by accumulating patients from many hospitals in Japan.

The items used in the ANE-SS were closely related to pathogenesis and clinical features of ANE. Shock and reduced platelet count are signs of multiorgan failure and/or disseminated intravascular coagulation resulting from systemic hypercytokinemia which is considered to be the main pathomechanism of ANE [4,18]. Elevated CSF protein level is ascribed to an increased permeability of blood–brain barrier and destruction of brain parenchyma [19]. For these reasons, a decrease in platelet count and an increase in CSF protein were included in the ANE-SS despite relatively weak correlations with outcome. On the other hand, the existence of brainstem lesions and age > 48 months were also selected as the component of ANE-SS, primarily because of their robust statistical correlation with outcome. Brainstem lesions were shown to be a strong indicator of poor outcome probably due to the functional importance. [14] The reason why the older patients had worse outcome is unclear, and requires further analysis.

An important feature of the ANE-SS is its simplicity. The score consists of only five items, which can all be determined within a few hours after presentation. None of the five items is difficult to judge or necessitates

additional load to patients or physicians. Thus, we expect the ANE-SS to be widely used for clinical as well as research purposes. Another important feature of the ANE-SS is the weighting of items according to the strength of their relation with outcome. This will increase the accuracy of ANE-SS in prognostication and result in a greater accuracy compared to a simple summation of items. Because of these advantages, ANE-SS can be used for prognostication of children with new-onset ANE and can contribute to the evaluation of treatment efficacy. In Japan, an increasing number of patients with ANE have recently been treated with early application of hypothermia, which is expected to be effective for ANE [11]. ANE-SS will be useful in evaluating the efficacy of hypothermia or other novel treatments for ANE.

There are several limitations in this study. Prognostication of the medium risk group was insufficient compared with that of low and high risk groups. The majority of patients in the medium risk group had severe sequelae or death. Further revision will be necessary to differentiate between medium- and high-risk groups. The timing of the laboratory examination may influence the result, because symptoms of ANE often show rapid deterioration. Thus, a few hours' difference in the timing of neuroimaging, blood sampling, or spinal tap may have a large effect on the results. For precise prognostication, it may be necessary to consider the timing of examination. The patients included in this study received different treatments over different time scales, according to the hospital at which they were treated. (Supplementary Tables 1 and 2) There is a possibility that some treatments affected the outcome, even though statistical analyses did not show a significant difference in the outcome according to treatment. It is also problematic that some patients were omitted from the study because of insufficient data to calculate ANE-SS. CSF protein levels were often unavailable because lumbar tap is not always necessary for diagnosis of ANE and may not be performed due to impending brain herniation. We tried to modify the ANE-SS by eliminating CSF protein levels, but the accuracy of the modified score was clearly reduced (data not shown).

In conclusion, we developed the ANE-SS for prognostication of children with ANE. This score is simple and easy to apply. The correlation between ANE-SS and outcome was significant in the cohort studied. We consider that the ANE-SS will be useful for evaluation of novel treatments for new-onset ANE and will contribute to evaluation of the optimal treatment.

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Hiroyuki Yamamoto designed the study and drafted the initial manuscript, and approved the final manuscript as submitted. Akihisa Okumura originated the

idea for this study, supervised data collection and interpretation, critically reviewed and revised manuscript, and approved the final manuscript as submitted. Jun Natsume and Seiji Kojima interpreted the data and reviewed and revised manuscript, and approved the final manuscript as submitted. Masashi Mizuguchi critically supervised data collection and interpretation, reviewed and revised manuscript, and approved the final manuscript as submitted.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.braindev.2014.05.007>.

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