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Original article

Serial outcomes in acute necrotising encephalopathy of childhood: A medium and long term study

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Abstract

Objective: Acute necrotising encephalopathy (ANEC) is a severe, debilitating childhood disorder. We used the ANEC scoring system (ANE-ss) and standardised neurodevelopmental scores to objectively characterise medium and long term outcomes.

Methods: Retrospective review of children with ANEC at KK Women's and Children's Hospital, Singapore, from 2005 to 2012. ANE-ss was determined from clinical features and neuroimaging, and neurodevelopmental scores (Pediatric Glasgow Outcome Scale Extended, Pediatric Cerebral Performance Category scale and Pediatric Overall Performance Category scale) were applied at 1, 6, 12 and 24 months post diagnosis.

Results: Seven patients with ANEC were studied. All had a viral prodrome with fever, and encephalopathy at presentation, and received immunotherapy (steroids or immunoglobulin). ANE-ss scores were medium risk in 4 patients and high risk in 3 patients. One died (high risk ANE-ss) and outcome was determined in the 6 survivors. At 1 month post diagnosis, 3 patients (50%) were mildly affected and 3 (50%) were severely affected. Morbidity rates improved by 12 months, with 67% and 33.3% scoring in the mildly affected and severely affected ranges, respectively. Medium risk patients did well with majority having little or no neurological deficits and good outcome scores.

Conclusion: Mortality and severe morbidity correlated well with high risk ANE-ss. However, our patients with medium risk ANE-ss had good neurodevelopmental sequelae. Serial disability scoring is useful in evaluating the progress of ANEC patients on follow up. Assessment at 1 month post diagnosis can aid prognostication of long term outcome.

Keywords: Acute necrotising encephalopathy; ANE; ANEC; Outcomes; ANE-ss

1. Introduction

Acute necrotising encephalopathy of childhood (ANEC) is well recognised as an important disease entity since its first description by Mizuguchi et al. [1–3]. Afflicted patients develop an acute encephalopathy with a characteristic rapidly deteriorating neurological course. Neurodevelopmental outcomes are described to be poor; with high mortality and morbidity rates [3]. The disease is usually preceded by a non-descript viral illness [4–7] but exact etiologies are not well understood. Kansagra et al. has postulated the involvement of proinflammatory cytokines and soluble

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cytokine receptors in the pathogenesis of this disease [8,9].

Diagnosis is made on a basis of a non-inflammatory encephalopathy (CSF leucocyte count 8/mm^3 or less) and demonstration of multifocal lesions symmetrically distributed in brain regions including the thalamus, in absence of any other reasonable explanation for the cerebral abnormalities [2,3].

Treatment strategies such as immunomodulators and hypothermia have been employed [10–12]. Yamamoto et al. developed a severity score (ANE-ss) comprising 5 components: shock on admission; age >48 months; existence of brainstem lesions; platelet count <100,000 and CSF protein >60 mg/dl. This has provided a means of risk stratification in children afflicted with ANEC [13].

Despite its clinical significance, the disease remains under-researched as it is a rare entity [14]. Medium and long term mortality and morbidity is not well described in the current body of literature. Okumura et al. [10] described poor neurological outcomes in 25 out of 34 patients with ANEC (73.5%), however, there was no specification regarding the time point from onset of disease at which they were evaluated [10]. In 2010, Hye-Eun Seo et al. described mortality of 16.7% in a cohort of 6 Korean children studied from 1999 to 2007. 66.7% had moderate to severe neurological sequelae at 6 months. No further data was described for longer term morbidity and mortality [15]. Within Singapore, apart from an abstract from the present group [16], a single case has been reported as part of a series of patients with neurological sequelae related to H1N1 virus [17].

Our team aims to add to existing literature by systematically scoring outcomes using established neurodevelopmental scores over standardised time periods, hence hoping to better describe medium and long term morbidity and mortality. ANE-ss was also applied to our patient cohort to define its relationship to both initial and long term outcomes.

2. Patients and methods

We reviewed a retrospective cohort of patients diagnosed with ANEC at our centre over an 8 year period. Case identification was done by reviewing data of patients with the diagnosis of "Acute Necrotising Encephalopathy of Childhood" or "Acute Necrotising Encephalitis" from Paediatric Neurology and Radiology databases at KK Women and Children's Hospital, Singapore, from 2005 to 2012.

Records of all identified cases were reviewed by our team of investigators to exclude other causes of altered mentation: inborn errors of metabolism, central nervous system (CNS) thrombosis/haemorrhages, proven invasive CNS infection by known pathogen, neoplastic CNS disease, or acute disseminated encephalomyelitis (ADEM). Eighteen patients were identified and included into the study.

Clinical manifestations, laboratory data, neuroimaging findings, treatment modalities, discharge and follow up outcomes were evaluated. Scans of all eighteen patients were reviewed by two paediatric neurologists and two neuro-radiologists and scored in a single blinded fashion using a radiological checklist derived from Mizuguchi et al's radiological criteria for diagnosis of ANEC (Appendix 1). Cases were classified into 3 categories based on the scores: "unlikely ANEC" (no thalamic involvement/striking features suggestive of other diagnoses), "possible ANEC" (bilateral thalamic involvement, with or without other typical features) and "definite ANEC" (bilateral symmetrical thalamic involvement with necrosis seen, with or without other typical features).

We reviewed records of all cases classified as "definite" or "possible" ANEC and recorded demographic details, clinical presentation, laboratory and imaging findings, causative organisms and treatment modalities on a structured anonymous research form. Neurological outcomes in cognition, motor, speech and swallowing, visual deficit, presence of epilepsy and developmental milestones were determined at several time points: discharge, 1, 6, 12, 24 months and last follow up. Neurodevelopmental scores (Pediatric Glasgow Outcome Scale Extended [18,19], Pediatric Cerebral Performance Category scale and Pediatric Overall Performance Category scale [20,21] were applied for each time point. Patients were divided into two age groups; children less than 4 years of age and children more than 4 years of age. Outcome assessments recorded in children less than 4 years of age were focused mainly on cognition, swallowing and motor function/ambulation. In addition, in children more than 4 years of age, we included assessments of bathing, dressing, bladder and bowel continence, as well as schooling. Motor impairment was divided into none, mild (requiring some assistance), or severe (wheelchair or bed bound). We recorded dichotomous outcomes (present/absent) for impairments in cognition, swallowing, vision and presence of epilepsy. The team also took note of each child's ability to attain age-appropriate developmental milestones and any requirement for special schooling.

The study was approved by the Singhealth Centralised Institutional Review Board (CIRB Ref 2012/709/E).

3. Results

3.1. Description of patient population and outcomes

Eighteen patients were identified with a diagnosis of ANEC. Of these, 7 cases were classified as "definite"