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Case Report

Familial acute necrotizing encephalopathy with *RANBP2* mutation: The first report in Northeast Asia

Yun-Jeong Lee [a], Su-Kyeong Hwang [a], So Mi Lee [b], Soonhak Kwon [a,*]

[a] *Department of Pediatrics, Kyungpook National University Children's Hospital, Daegu, South Korea*
[b] *Department of Radiology, Kyungpook National University College of Medicine, Kyungpook National University Hospital, Daegu, South Korea*

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Abstract

Background: Acute necrotizing encephalopathy (ANE) is a rare but rapidly progressing encephalopathy following a febrile illness, commonly a viral infection. It is characterized by the features of acute encephalopathy such as seizure, alteration of consciousness, and symmetric involvement of the bilateral thalamus on neuroimaging tests. Although most ANE cases have occurred sporadically, familial or recurrent ANE has been reported in Caucasian patients, with genetic susceptibility to ANE noted in some patients due to a *RANBP2* mutation. We report the cases of two Korean siblings with typical ANE and *RANBP2* mutation.

Case report: A 2 year-old Korean girl presented with prolonged seizures and encephalopathy after two days of febrile illness. Brain computed tomography (CT) showed diffuse brain swelling and low attenuation in the bilateral thalamus. Two months later, her younger sister presented with lethargy and flurries of seizures after a *Mycoplasma pneumoniae* infection. Brain magnetic resonance imaging scan (MRI) showed a characteristic involvement of the bilateral thalamus, suggesting ANE. Although they received intravenous steroids and immunoglobulin, the older child died; her sister remained in a coma. Both were diagnosed with familial ANE after identifying a common missense mutation in *RANBP2* (c.1754C > T: p.Thr585Met) in the younger sister and their father.

Conclusions: This report is the first case of familial ANE in Northeast Asia identifying a *RANBP2* mutation with poor outcome. Due to rapidly deterioration and recurrent nature of familial ANE, genetic test of *RANBP2* mutation should be considered for early diagnosis. Further studies are needed to elucidate the nature of ANE.

Keywords: Acute necrotizing encephalopathy; *RANBP2*; Familial

1. Introduction

Acute necrotizing encephalopathy (ANE) is a rare but rapidly progressing encephalopathy, characterized by seizures and rapid alteration of consciousness, which may progress to coma within days after the onset of febrile infection such as influenza A or parainfluenza, without direct invasion of the central nervous system [1]. Neuroimaging typically shows multiple symmetric brain lesions affecting the thalamus and the brainstem, periventricular white matter, and cerebellum [1]. Most cases are sporadic; however, several cases of familial or recurrent ANE were reported recently in North America and Europe [2–4]. Patients with mutations in the *RANBP2* gene (OMIM601181) have been identified; the gene encodes the nuclear pore component of Ran binding protein 2, causing genetic susceptibility to

* Corresponding author at: Department of Pediatrics, Kyungpook National University Children's Hospital & School of Medicine, Hogook-Ro 807, Book-Gu, Daegu 702-210, South Korea. Fax: +82 53 200 2029.
E-mail address: shkwon@knu.ac.kr (S. Kwon).

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ANE [2–4]. Herein, we report the first case of siblings with familial ANE due to *RANBP2* mutation from Northeast Asia.

2. Case reports

2.1. Case 1

A previously healthy 2-year-old girl was transferred to our emergency room due to recurrent vomiting and a generalized tonic–clonic seizure after 2 days of cough and fever. She was born at term with uneventful ante- and perinatal periods. Her immunizations were up to date according to the Korean immunization schedule. Seven hours after the first seizure, she developed repetitive seizures and unresponsiveness and became comatose. She was admitted to the intensive care unit with hypotension and respiratory compromise. Laboratory findings, including liver function tests and ammonia levels, were normal. Cerebrospinal fluid (CSF) analysis was normal except for an elevated protein level (protein: 523 mg/dl, glucose: 93 mg/dl). The patient was empirically started on vancomycin, cefotaxime, and acyclovir to treat possible meningoencephalitis. Computed tomography (CT) revealed low attenuation in the bilateral thalamus and diffuse effacement of the sulci and lateral ventricles, indicating diffuse cerebral edema (Fig. 1). Despite treatment in intensive care and immunosuppressive therapy including intravenous methylprednisolone (30 mg/kg/day for 2 days) and immunoglobulin (1 g/kg/day for 2 days), the patient died 2 days after the onset of initial neurological symptoms. Results of polymerase chain reaction (PCR) for respiratory viruses (parainfluenza, influenza, corona virus, rhinovirus, respiratory syncytial virus, bocavirus, and enterovirus) and herpes simplex viruses in the CSF as well as the results from cultures for bacteria in the CSF, serum, and urine were all negative.

2.2. Case 2

Two months after the death of the patient in case 1, her sibling, a 12-month-old girl, presented with 2 days of fever, vomiting, and a seizure. Initial examination revealed that the child was alert without focal neurologic signs. Laboratory findings were within normal ranges except for positive test for *Mycoplasma pneumoniae* IgM antibody (14 AU/ml, negative test <10 AU/ml). Chest X-ray revealed perihilar infiltration indicating pneumonia. In the next 4 h, she became lethargic and unresponsive. CSF analysis did not show pleocytosis but an elevated protein level (protein: 264 mg/dl, glucose: 63 mg/dl). Brain magnetic resonance imaging (MRI) revealed T2 hyperintensities in the bilateral thalamus, external/extreme capsule, brainstem, and cerebral and cerebellar white matter (Fig. 2). Antibiotics and antiviral agents were administered, followed by intravenous methylprednisolone (30 mg/kg/day for 5 days) and immunoglobulin (1 g/kg/day for 2 days). Despite the aggressive immunotherapy, she remained in deep coma with continuous respiratory support.

The characteristic MRI findings and family history of encephalopathy indicated familial ANE. We performed next generation sequencing followed by direct sequencing of entire coding regions of the *RANBP2* gene for the younger sister. She was diagnosed as ANE1 after identifying a heterozygous missense mutation in the *RANBP2* gene (c.1754C > T: p.Thr585Met) (Fig. 3). The genetic testing result were negative for her mother but the father showed the same mutation, but was asymptomatic. We diagnosed familial ANE based on clinical features and the family mutations.

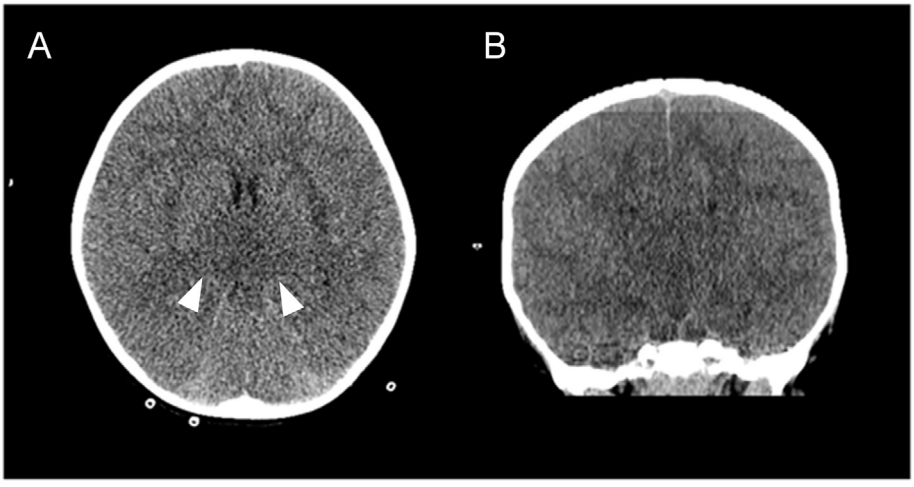

Fig. 1. Brain CT of Case 1. Axial (A) and coronal (B) non-contrast CT shows low attenuation in the bilateral thalamus (arrowhead) and diffuse effacement of the sulci and lateral ventricles, indicating diffuse cerebral edema.

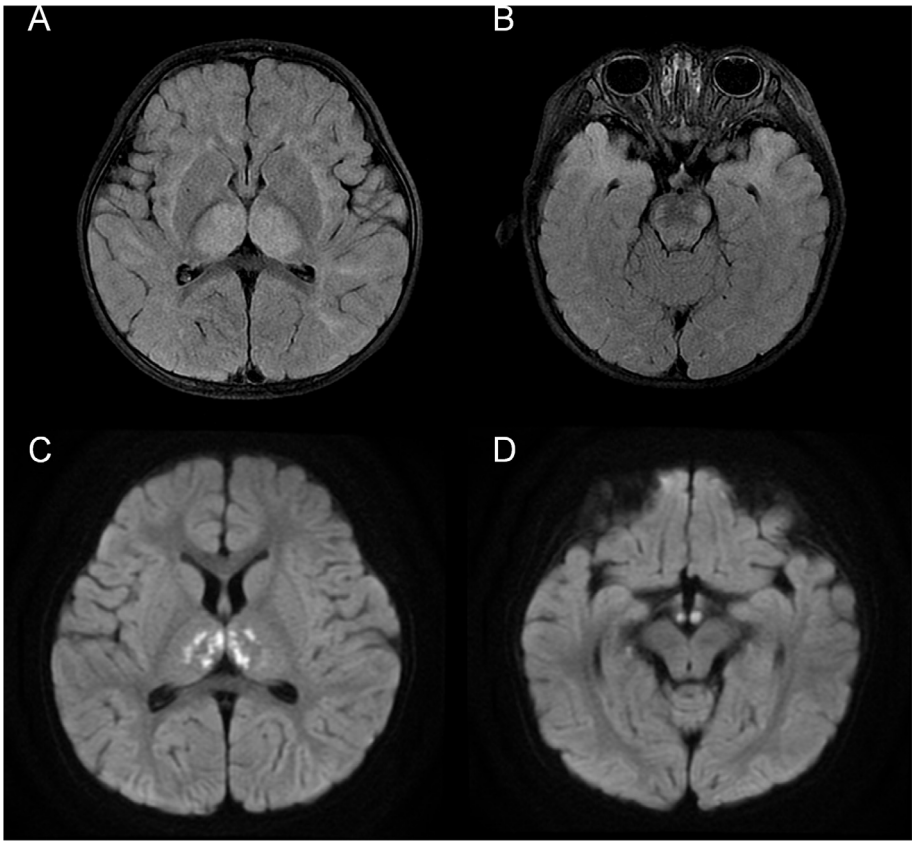

Fig. 2. Brain MRI of Case 2. Fluid attenuated inversion recovery images (A, B) reveal hyperintense signal changes in the bilateral thalamus, external/extreme capsule, brainstem tegmentum, and mammillary bodies as well as multifocal foci in cerebral and cerebellar white matter. Diffusion-weighted images (C, D) show diffusion restrictions in the bilateral thalamus and mammillary bodies.

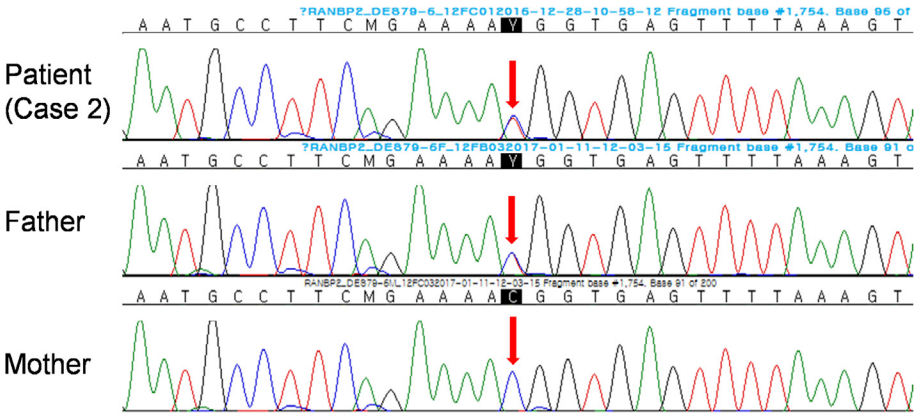

Fig. 3. Sequencing electropherograms of *RANBP2*-specific cDNA reveals a c.1754C > T mutation in the patient from case 2 and the father, but not in the mother. We could not perform genetic analysis on the patient from case 1 (deceased).

3. Discussion

Although we understand ANE from a wider perspective [5], here we report the first familial case of two Korean siblings with ANE with a mutation in *RANBP2* (c.1754C > T: p.Thr585Met). Since the first description of ANE in 1995 [1], numerous cases of sporadic ANE have been reported. In 2009, Neilson et al. reported multiple affected family members with acute necrotizing encephalopathy [2]. They identified a recurrent missense mutation (c.1754C > T: p.Thr585Met, c.1958C > T: p.Thr653Ile, c.1966A > G: p.Ile656Val) in the *RANBP2* gene in a large multigenerational family with autosomal-dominant ANE and concluded this gene mutation predisposes patients to increased susceptibility to familial ANE with an estimated 40% penetrance [2].

Hence, the sporadic form is referred to as ANE, and the familial/recurrent form with *RANBP2* mutation is referred to as ANE1 with various clinico-radiological presentations [4]. However, the pathogenic mechanism of *RANBP2* mutation for ANE1 remains unclear. Several authors believe that *RANBP2* may be a critical modulator of neuronal activity, glucose catabolism, and energy homeostasis [2,6]. However, there are case reports of familial and recurrent ANE without *RANBP2* mutation, suggesting a heterogeneous genetic contribution to ANE [7]. Till date, 61 patients with *RANBP2* mutation-positive ANE have been reported in American and European populations [4,8] but only one case of recurrent ANE with *RANBP2* mutation has been reported from Asia (an Indian child) [9].

Previous reports suggested that patients with ANE1 presented MRI changes of ANE with additional regions in any of the following structures: medial temporal lobe, insular cortex, claustrum, external capsule, amygdala, hippocampus, mammillary bodies, and spinal cord [2,4]. Similarly, our case 2 patient presented neuroimaging findings with bilateral thalamus and the external capsule and mammillary bodies. These findings may also suggest ANE1.

Although our patients received intravenous steroids and immunoglobulin within 24 h after onset, the outcomes were poor. According to previous outcome data of 30 patients with ANE1, 4(13%) died, 17(57%) had neurological or cognitive sequelae, and 9(30%) made full recovery [4]. Immunomodulation therapy has been suggested for the management of ANE1 in children, in which a fetal course has been frequently reported [10].

We report the first Northeast Asian case of siblings with familial ANE diagnosed by characteristic MRI results and *RANBP2* mutation. Typically poor outcome of ANE1 in cases of familial childhood encephalopathy shows that early diagnosis of ANE1 is important for prompt treatment and to prevent rapid deterioration of neurological health. Further studies with a larger group is necessary to identify the nature and the proper management of ANE1.

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