

# Only a Touch of the Flu? The Simultaneous Manifestation of Acute Necrotizing Encephalopathy in Two Consanguineous Patients

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**This case report describes the simultaneous manifestation of acute necrotizing encephalopathy in 2 consanguineous patients after infection with influenza B based on the autosomal dominant missense mutation of the RANBP2-gene. Differential diagnosis of acute encephalopathy, clinical and radiological clues, and treatment strategies are outlined.**

**Keywords.** ANE; encephalopathy; genetic; influenza; RANBP2-gene.

## CASE REPORT

In January 2013, a 40-year-old woman and her 10-year-old nephew were referred simultaneously to the medical intensive care units (ICUs) for adults and children at our hospital with an altered mental status and fever.

Five days earlier, both attended a family dinner. The same day, the female patient's daughter fell ill with fever and myalgia. Subsequently, 3 more family members suffered from flu-like symptoms including fever, headache, and vomiting. Whereas the others recovered, 1 female patient developed generalized tonic-clonic seizures and impaired consciousness with a Glasgow Coma Scale (GCS) of 9 two days after disease onset. The nephew showed agitation on the first day after development

of fever, and the following day he became comatose (GCS 6). Both were febrile without a clinical focus of infection besides the brain. Laboratory results on admission are shown in Table 1. Cerebral magnetic resonance imaging in both patients surprisingly showed almost identical symmetric T2 hyperintense lesions of thalamus, hippocampus, and pons (Figure 1).

After thorough discussion of the 2 involved ICUs, both patients were isolated due to the rapidly evolving encephalopathic picture with unknown and potentially infectious cause. The differential-diagnostic evaluation included toxic, autoimmune, parainfectious, mitochondrial, and infectious causes. Extensive investigations were initiated, and treatment with ceftriaxone, acyclovir, oseltamivir (150 mg twice daily in the adult patient), and anticonvulsants (750 mg of levetiracetam twice daily) was started. Electroencephalography under anticonvulsant treatment showed moderate background slowing compatible with an encephalopathic pattern but no epileptiform activity in both patients. Case history and laboratory results regarding toxic exposure and autoimmune and mitochondrial diseases displayed no abnormalities. Although cultures of blood and cerebrospinal fluid (CSF) as well as polymerase chain reaction (PCR) for herpes simplex virus type 1 and 2 and varicella zoster virus were negative, PCR from a nasopharyngeal swab detected influenza B in both patients. Therefore, acute parainfectious encephalopathy was suggested. Therapy with 1 g of methylprednisolone twice daily for 10 days (adult patient) and immunoglobulins was started, whereas ceftriaxone and acyclovir could be stopped.

**Table 1. Results From Laboratory Tests at Admission**

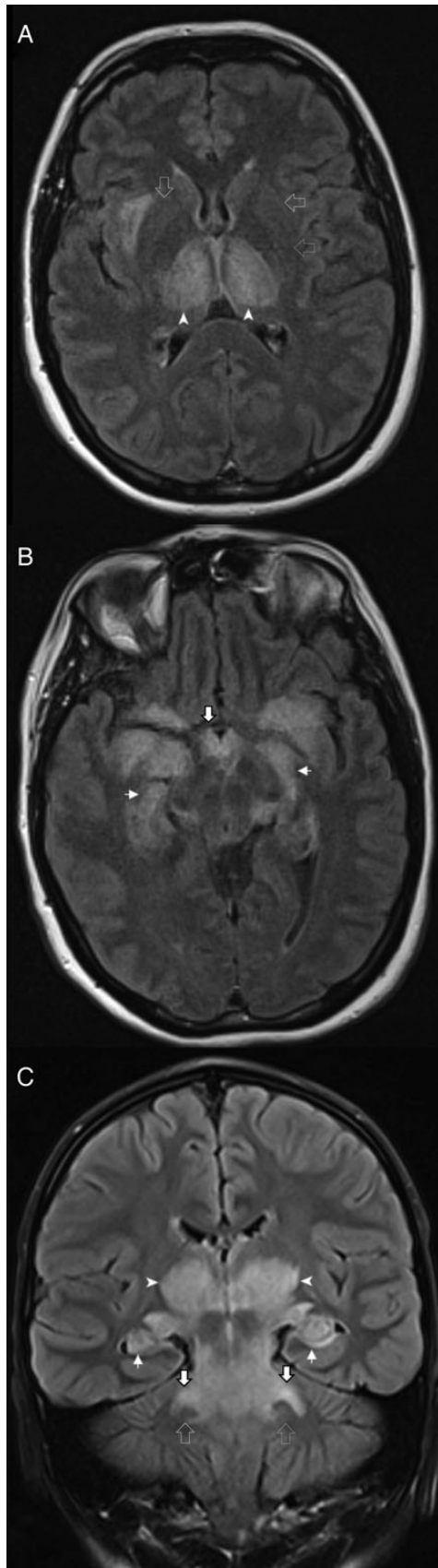
	40-Year-Old Female Patient	10-Year-Old Nephew	Normal Range
<b>Blood tests</b>			
White blood cell count	$9.4 \times 10^9/\text{mm}^3$	$2.04 \times 10^9/\text{mm}^3$	$3.5\text{--}10.0 \times 10^9/\text{mm}^3$
Lymphocytes	$0.63 \times 10^9/\text{mm}^3$	$0.55 \times 10^9/\text{mm}^3$	$0.9\text{--}3.3 \times 10^9/\text{mm}^3$
C-reactive protein	122 mg/L	0.5 mg/L	<10 mg/L
Aspartate transaminase	87 U/L	35 U/L	11–34 U/L
Alanine transaminase	88 U/L	20 U/L	8–41 U/L
<b>Cerebrospinal fluid</b>			
Aspect	Clear	Clear	Clear
White blood cell count	1.7 Lc/ $\mu\text{L}$	12 Lc/ $\mu\text{L}$	<4 Lc/ $\mu\text{L}$
Protein	2680 mg/L	1263 mg/L	150–500 mg/L
Glucose	4.8 mmol/L	3.7 mmol/L	3.8–6.1 mmol/L
Lactate	2.4 mmol/L	2.1 mmol/L	1.1–1.9 mmol/L

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**Figure 1.** T2-weighted images with fluid attenuation of the brain of both the adult patient (a and b) and her nephew (c) display symmetric

The strikingly simultaneous onset of encephalopathy in 2 consanguineous patients infected with influenza B raised suspicion of a genetic component of the disease. After literature research on the topic of encephalopathy after viral infection, a mutation of the RANBP2-gene was hypothesized. Thereupon, a missense mutation in the RANBP2-gene (c. 1754 C>T) was identified in both patients leading to the diagnosis of autosomal dominant familial acute necrotizing encephalopathy (ANE1).

Within the next days, the adult patient almost completely recovered. Steroids were tapered and oseltamivir was stopped after 10 days. Levetiracetam was increased in dosage and combined with lacosamid and lamotrigin due to epileptic potentials on EEG on day 5. Nine months after disease onset, she suffered from mild cognitive deficits. Her nephew remained mute with spastic tetraparesis for several weeks and recovered slowly during the following months. By 9 months, he had essentially returned to normal activity and was able to attend regular classes, but he was still emotionally instable.

Postulating the presence of ANE1, a thorough family history was conducted. However, no additional family members ever suffered from seizures or unexplained encephalopathic symptoms. After genetic counselling, the other family members decided against genetic testing.

## DISCUSSION

Acute necrotizing encephalopathy is a rare disease characterized by a rapidly evolving encephalopathy shortly after viral infection. The majority of cases occur sporadically. If familial clustering was seen, an autosomal dominant missense mutation of the RANBP2-gene was detected in 75% of cases, designated as ANE1 [1]. Acute necrotizing encephalopathy shows incomplete penetrance, with half of the individuals affected suffering from 1 or recurrent episodes of ANE1. The other half does not show symptoms, but they are asymptomatic carriers.

The RANBP2-gene encodes the RAN-binding protein 2. This protein is localized on the cytoplasmic surface of the nuclear membrane in the region of the nuclear pores. It has vital regulatory functions controlling the transport of proteins between the cytoplasmic and nuclear compartments of the cell. To date, it is not yet understood how a missense mutation of the RANBP2-gene provokes ANE1.

Recent acute viral infection preceded ANE as well as ANE1 in more than 90% of patients. Influenza is the virus most

*Figure 1 continued.* involvement of the thalamus (arrowheads), the limbic system including hippocampus (small arrows), and the mammillary bodies (arrows in b) as well as the pons and cerebellar peduncles (arrows in c). The basal ganglia and the nucleus olivarius are relatively spared (open arrows in a and c) with only minor involvement of the claustrum and external capsule on the right in the adult patient (a). Involvement of the basal and mesiotemporal structures is common in viral infections.

commonly detected [2], but other pathogens, such as Coxsackie virus, parainfluenza viruses, human herpesvirus 6, and *Mycoplasma* spp have been associated with ANE. The assumption is that an infectious trigger is needed to induce ANE, with the type of infection being of minor importance.

Patients with ANE showed increased levels of interleukin (IL)-6 and tumor necrosis factor (TNF)- $\alpha$  in CSF and blood [3]. Therefore, this cytokine storm is suspected to be involved in the pathogenesis of ANE and ANE1 as well, and it may contribute to the high frequency of seizures because IL-6 and TNF- $\alpha$  are highly icthogenic [4]. In our patient, IL-6 and TNF- $\alpha$  were not measured. Furthermore, the clinical and radiological findings of ANE and ANE1 resemble diseases with disruption of cerebral energy metabolism such as Wernicke encephalopathy. Accordingly, similar pathways might be involved in the pathogenesis of ANE and ANE1.

The first episode of ANE1 usually occurs in early childhood, rarely in adolescents or in adults. Although the boy described in this case report matches very well the features of a first episode of ANE1, the female patient with first manifestation of ANE1 at the age of 40 is the oldest patient published so far. The simultaneous manifestation in 2 consanguineous family members is an outstanding feature of these 2 cases, which has not been described yet. It must be presumed that the sister of the female patient and mother of the boy who developed symptoms is an asymptomatic carrier of the identified missense mutation. Because the family relatives refused genetic testing, we could not ascertain the distribution of the mutation in this family.

The 2 hallmarks of ANE1 diagnosis remain the suggestive history and cerebral imaging. The clinical picture typically shows rapid neurological deterioration with altered mental status, epileptic seizures, and coma 1 to 3 days after a preceding viral infection. Cerebral imaging reveals bilateral multifocal lesions in the thalamus. In addition, changes in brainstem, cerebellum, periventricular white matter, and other regions can be present [5]. Laboratory analyses usually show marked elevation

of protein levels in CSF, but, apart from that, findings are unspecific and probably due to the triggering infection.

The outcome of ANE1 varies from lethal courses to full recovery. Poor prognostic signs are involvement of the brainstem, delayed diagnosis, and recurrent episodes. High-dose steroids are effective in cases without brainstem involvement but otherwise lack efficacy [6]. Immunoglobulins, antiviral therapy, plasmapheresis, hypothermia, and different drugs supporting mitochondrial function have been tested, and to date there is no proof of effectiveness for any of those. Although routine influenza vaccination may protect susceptible individuals from ANE1 [2], safety and efficacy of vaccination of patients after a first episode of ANE1 is unclear, and vaccination is not routinely recommended. Immediate prophylactic use of oseltamivir after contact with influenza may be a rational therapeutic strategy for these patients.

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**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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