



## Clinical Observations

## Hypoxic-Ischemic Encephalopathy Mimicking Acute Necrotizing Encephalopathy



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### ABSTRACT

**BACKGROUND:** Acute necrotizing encephalopathy is a rare childhood syndrome associated with distinct and unifying neuroimaging features that are often used for the diagnosis of this entity. **PATIENT:** We describe a previously healthy 9-month-old girl who presented with upper respiratory symptoms, suspected seizures, and positive nasopharyngeal rapid antigen test for influenza A virus. Magnetic resonance imaging revealed signal abnormality in both thalami, bilateral caudate nuclei, brainstem tegmentum, subcortical white matter, and cerebellar hemispheres, suggestive of acute necrotizing encephalopathy. She subsequently had a cardiac arrest, was placed on extracorporeal membrane oxygenation, and treated with methylprednisone, intravenous immunoglobulin, and plasmapheresis without apparent clinical response. On autopsy, neuropathology showed evidence of hypoxic-ischemic injury but lacked evidence of hemorrhagic necrosis, which is typically associated with acute necrotizing encephalopathy. **CONCLUSION:** Combined clinical and neuroimaging features may be suggestive but not sufficient for the diagnosis of acute necrotizing encephalopathy.

**Keywords:** acute necrotizing encephalopathy, pediatric, influenza, hypoxic-ischemic encephalopathy

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### Introduction

Acute necrotizing encephalopathy (ANE) is a rare childhood disease preceded by an acute febrile illness and characterized by the rapid onset of progressive symptoms including convulsions, vomiting, deteriorating consciousness, hepatic dysfunction, and ultimately resulting in coma. First reported in Japan in 1995, it has subsequently been recognized worldwide.<sup>1</sup> Proposed diagnostic criteria for ANE specify an acute encephalopathy after a febrile illness,

deterioration of consciousness and convulsions, the absence of cerebrospinal fluid pleocytosis, a normal serum ammonia level, and imaging evidence for symmetric multifocal brain lesions of the thalami (Table 1).<sup>2</sup> Although there are no specific diagnostic markers, one of the most characteristic neuroimaging features include symmetric lesions affecting the bilateral thalami.<sup>2</sup> Additional lesions may also be found in the putamen, brainstem tegmentum, cerebellum, and deep periventricular white matter. Neuropathologically, vasogenic edema and hemorrhagic necrosis are typically located within the center of gray matter lesions.

Here we describe a child diagnosed with ANE based on a classic clinical presentation and neuroimaging findings who on postmortem lacked the neuropathologic features typically seen with this disorder. Neurohistopathology instead revealed global hypoxic-ischemic injury.

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**TABLE 1.**  
Diagnostic Criteria for ANE (modified from Mizuguchi<sup>2</sup>)

1. Acute encephalopathy following a febrile disease.
2. No CSF pleocytosis.
3. CT or MRI evidence of symmetric, multifocal brain lesions involving the thalami. Lesions also common in cerebral periventricular white matter, internal capsule, putamen, upper brainstem tegmentum, and cerebellar medulla.
4. Elevation of serum aminotransferases of variable degrees.
5. No increase in blood ammonia.
6. Exclusion of resembling diseases.

Abbreviations:  
 ANE = Acute necrotizing encephalopathy  
 CSF = Cerebrospinal fluid  
 CT = Computed tomography  
 MRI = Magnetic resonance imaging

### Patient Description

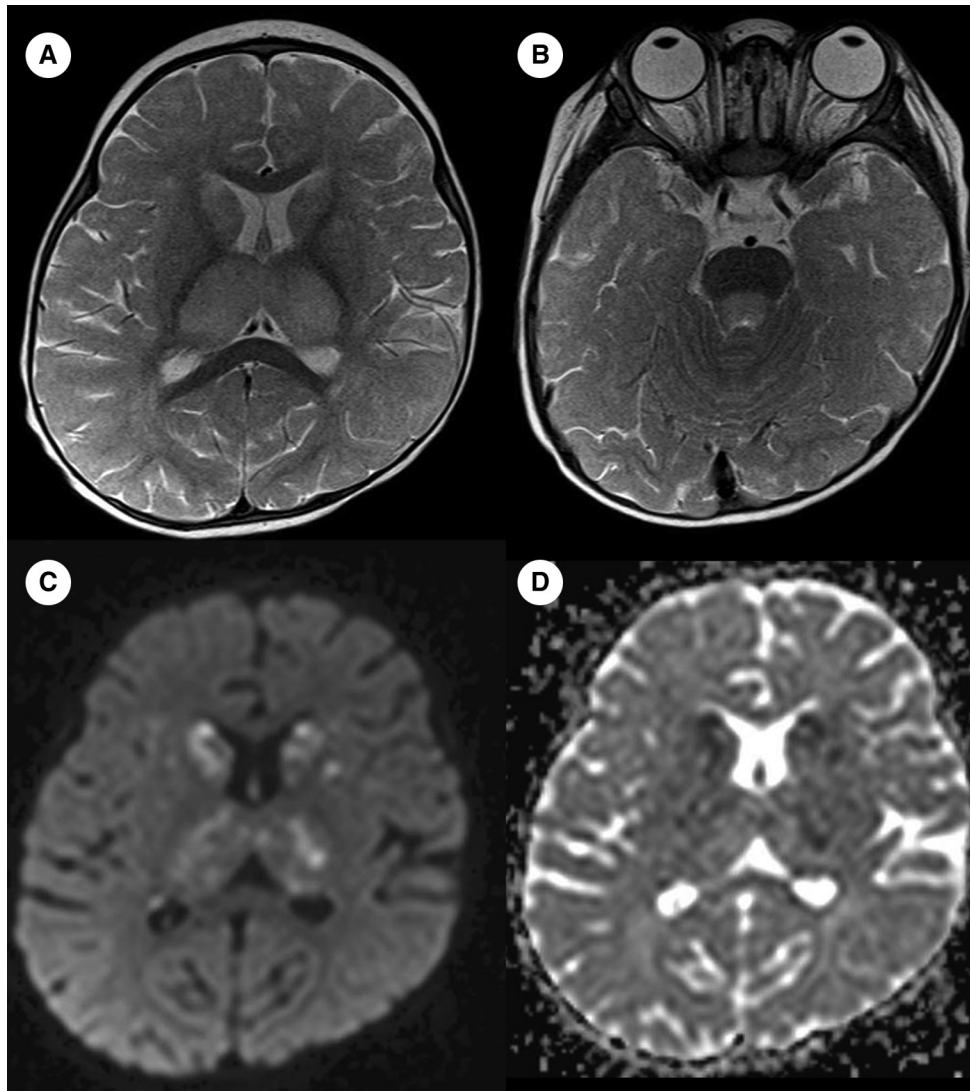
This 9-month-old African-American girl presented to the emergency department with suspected seizures after a 4-day prodromal illness with cough, rhinorrhea, and fever and a 1-day history of emesis. Two family

members also had upper respiratory symptoms. Her immunizations were up to date, and she had received the seasonal influenza vaccine.

In the emergency department, a chest computed tomography (CT) suggested pneumonia, and initial studies including a urinalysis were unremarkable. She was admitted to the general pediatric floor and given intravenous ampicillin. A respiratory rapid antigen test from a nasopharyngeal swab confirmed the presence of an influenza A infection, and oseltamivir was started.

The following morning, she developed focal seizures that included right facial droop, became unarousable, and her examination revealed miosis and decorticate posturing. She remained hemodynamically stable with no evidence of cardiac or respiratory decompensation. A head CT was unremarkable (not illustrated). Laboratory investigation showed elevated transaminase levels (aspartate aminotransferase level, 330 U/L; alanine aminotransferase level, 123 U/L), azotemia (blood urea nitrogen level, 38 mg/dL; creatinine, 0.6 mg/dL), elevated C-reactive protein (1.0 mg/dL), and thrombocytopenia (17,000 U/L). Normal studies included serum glucose, electrolytes on metabolic panel, lactate, urinalysis, and blood cultures.

Magnetic resonance imaging (MRI) performed 5 hours after head CT demonstrated numerous foci of restricted diffusion in the thalami and caudate nuclei bilaterally with associated swelling and mass effect on surrounding parenchyma (Fig 1). Additional restricted diffusion was



**FIGURE 1.**

T<sub>2</sub>-weighted magnetic resonance imaging demonstrates increased signal intensity in the thalami, bilateral caudate nuclei, left anterior putamen (A), and brainstem tegmentum (B). Diffusion-weighted imaging (C) and apparent diffusion coefficient map (D) suggest associated regions of restricted diffusion.

observed along the subcortical white matter bilaterally in the frontal lobe, cerebellar hemispheres, medial right midbrain, and left posterior pons. There was no contrast enhancement. Susceptibility-weighted imaging did not reveal any evidence of hemorrhages. Magnetic resonance angiography demonstrated no stenosis. Perfusion-weighted imaging (PWI) was unremarkable.

Supportive care in the intensive care unit included intubation and treatment with levetiracetam, methylprednisone, vancomycin, and cefepime. In spite of the aforementioned, her clinical condition further decompensated. While in the intensive care unit about 3 hours after completion of the MRI, she rapidly deteriorated and suffered cardiac arrest, including two episodes of pulseless electrical activity. She received cardiopulmonary resuscitation and was ultimately placed on extracorporeal membrane oxygenation. Echocardiography revealed severe biventricular dysfunction and an extremely limited aortic valve opening.

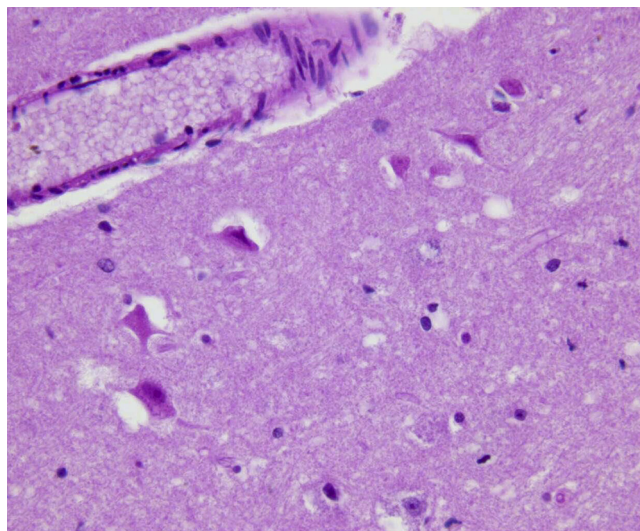
On hospital Day 3, she developed disseminated intravascular coagulation, her urine output ceased, and she was placed on continuous veno-venous hemofiltration. Additional complications included gastrointestinal bleeding, ascites, and pulmonary hemorrhage. Plasmapheresis followed by intravenous immunoglobulin was started on hospital Day 4 without apparent improvement. A follow-up head CT performed on Day 5 revealed extensive areas of low attenuation involving the cerebral hemispheres, thalami, caudate nuclei, upper brainstem, and cerebellum bilaterally. Diffuse effacement of basal cisterns sulcus and cerebellar tonsillar herniation was also evident. Supportive measures were withdrawn the following day.

On postmortem examination, multiple organs including the intestines, pancreas, and adrenal glands demonstrated ischemic injury. Microscopic examination of the heart showed normal coronary arteries and necrosis without inflammation within the ventricles circumferentially. Microscopic findings of the brain showed extensive global hypoxic-ischemic injury characterized by hypereosinophilic neurons in the cortex, putamen, thalami (Fig 2), deep nuclei of the cerebellum, and nuclei within the midbrain, pons, and medulla. No areas of hemorrhage or necrosis were identified. There were no inflammatory cells or microglial nodules. In the brain regions that initially demonstrated MRI abnormality, key findings of ANE, including hemorrhagic necrosis and small vessel vasculopathy, were absent.

## Discussion

This report describes a patient with a clinical presentation and neuroimaging findings strongly suggestive of influenza A-associated ANE. On postmortem examination, however, histological findings showed no evidence to support this diagnosis, but instead demonstrated changes consistent with hypoxic-ischemic injury. Although this child ultimately suffered from a severe hypoxic-ischemic injury as confirmed on autopsy, her ANE-typical MRI findings were present before her cardiac arrest and not in the setting of any severe hypoxia or hypotension. Furthermore, the perfusion weighted imaging on the initial MRI revealed no evidence of significant hypoperfusion, suggesting that areas of restricted diffusion were not because of impairment of vascular flow. Hence, it is difficult to ascribe the clinical course and neuroimaging findings within the early phase of the child's illness to a hypoxic-ischemic insult.

The clinical course of ANE is rapidly progressive. Within typically 72 hours of an antecedent febrile illness, patients experience rapid deterioration in consciousness and invariably generalized or simple partial seizures. As in this case, it is not uncommon in the early phase of encephalopathy to demonstrate vomiting, upper brainstem dysfunction such as miosis or decorticate posturing, and systemic abnormalities such as thrombocytopenia and elevated transaminase levels.<sup>2</sup> Although elevated



**FIGURE 2.**

Lesion in thalamus demonstrating hypereosinophilic neurons (hematoxylin-eosin stain, 400 $\times$ ). (The color version of this figure is available in the online edition.)

transaminase levels may also be seen in myocardial necrosis, the concomitant findings of encephalopathy and serum transaminase abnormality before the onset of cardiac arrest in the current case was thought to be supportive of hepatic dysfunction typically seen in ANE. Ultimately, coma ensues within 24 hours of onset of altered consciousness. Although none of the aforementioned signs and symptoms are specific for ANE, the intercase variability among cases of ANE is remarkably small.<sup>2</sup>

In this case, symmetrical lesions involving the thalami, caudate nuclei, subcortical white matter in the bilateral frontal lobes, cerebellar hemispheres, medial right midbrain, and posterior pons were strongly suggestive of ANE. In hypoxic-ischemic brain injury, involvement is most commonly seen bilaterally and symmetrically in the cortex (particularly perirolandic) and deep gray including the basal ganglia and thalami; however, basal ganglia involvement is typically more pronounced than the thalami.<sup>3</sup> In contrast, ANE almost invariably involves bilateral thalami, with occasional reports of involvement of the putamen or caudate. Abnormalities of the subcortical white matter, pons, and midbrain are also commonly seen in ANE, which represent less likely features in hypoxic-ischemic injury. Severe hypoxic-ischemic brain injury would also likely involve the hippocampi, perirolandic regions, and occipital cortex, which were spared in this case. Ultimately, although the patient experienced a cardiac arrest likely resulting in severe hypoxic-ischemic injury, a hypoxic-ischemic picture would not readily explain the clinical course and neuroimaging findings within the early phase of the illness. The MRI changes were apparent before her cardiac arrest and not in the setting of any reported or observed hypoxia or hypotension; thereby, hypoxic-ischemic injury was not considered as a likely diagnosis or differential diagnosis initially.

In ANE, neuropathology typically reveals necrosis, petechial hemorrhage, and absence of inflammatory infiltrate within the involved deep gray matter and tegmental

**TABLE 2.**  
Summary of Neuroimaging and Neuropathology in Cases of ANE

Study	Year	Country	Age	Gender	Initial Presentation	Symmetric Thalamic Lesions	Additional Lesion Involvement	Histopathology
Lyon et al. <sup>9</sup>	2010	USA	12	Female	S, DC	+	WM, PT, CB	Hemorrhagic necrosis
Ng et al. <sup>10</sup>	2010	China	6	Male	S, DC, P	+	CB, BG, PT, MT	Hemorrhagic necrosis
San Millan et al. <sup>7</sup>	2007	Spain	1	Female	DC, P, V	–	CB, WM	Hemorrhagic necrosis
Mastroianni et al. <sup>11</sup>	2006	Greek	2	Female	DC, C, ET	+		Hemorrhagic necrosis
Kirton et al. <sup>1</sup>	2005	Canada	1	Female	S, DC, P, V, ET	+	PT, MT, WM	Hemorrhagic necrosis
Kirton et al. <sup>1</sup>	2005	Canada	2	Female	DC, P, V	+		Hemorrhagic necrosis
Sazgar et al. <sup>12</sup>	2003	Canada	9	Female	S, DC, C, H, ET	+	BG, MT, PT	Hemorrhagic necrosis
Ravid et al. <sup>8</sup>	2001	USA	12	Female	DC, H, ET	+	BG, MT, WM	Chronic inflammatory cells and microglia
Mizuguchi et al. <sup>13</sup>	2002	Japan	1	Male	DC, V, ET	+	BG, WM, PT, CB	Hemorrhagic necrosis
Mizuguchi et al. <sup>13</sup>	2002	Japan	1	Male	S, DC	+	BG, WM, PT, CB	Hemorrhagic necrosis
Mizuguchi et al. <sup>13</sup>	2002	Japan	3	Male	DC, C, ET	+	BG	Hemorrhagic necrosis
Yagishita et al. <sup>14</sup>	1995	Japan	1	Male	S, DC, V, ET	+	WM, PT, CB	Hemorrhagic necrosis
Nakano et al. <sup>15</sup>	1993	Japan	1	Male	S, DC, V	+	CB, PT, MT	Hemorrhagic necrosis

Abbreviations:

BG	= Basal ganglia
C	= Coagulopathy
CB	= Cerebellum
DC	= Decreased consciousness
ET	= Elevated transaminases
H	= Hyper-reflexia
MT	= Midbrain tegmentum
P	= Posturing
PT	= Pontine tegmentum
S	= Seizure
V	= Vomiting
WM	= Subcortical or periventricular white matter

structures.<sup>2</sup> A search of the literature revealed 13 case reports from 10 publications with histologic findings of the brain in the acute stage of ANE (Table 2). All histologic findings were from autopsy examination with the exception of one case, which was derived from a stereotactic biopsy of a surviving patient. Twelve of the 13 cases reported consistent neuropathologic features of hemorrhagic necrosis. In contrast, no evidence of hemorrhagic necrosis was present histopathologically in this case. Neurohistopathology instead revealed global hypoxic-ischemic injury. Hypoxic-ischemic injuries are known to induce an inflammatory response and play a role in disruption of the blood-brain barrier.<sup>4</sup> Similarly, although the pathophysiologic mechanism of ANE remains unclear, reports of consistently elevated tumor necrosis factor- $\alpha$  and interleukin-6 in serum and in the cerebrospinal fluid suggest that an exaggerated immune response to a viral or bacterial agent may play a role.<sup>5</sup> An overproduction of cytokines is thought to alter blood-brain barrier permeability and cause endothelial damage, leading to vasogenic edema and necrotic lesions.<sup>5</sup> The cytokine-mediated systemic inflammatory response is also thought to contribute to the cases of multi-organ failure, shock, and disseminated intravascular coagulation commonly seen in ANE. *RANBP2* gene has also been implicated in the pathophysiologic mechanism of ANE. A heterozygous mutation in the *RANBP2* gene predisposes to the development of recurrent ANE during early childhood.<sup>6</sup> This familial form is thought to be autosomal dominant and demonstrates a 40% penetrance, suggesting other genetic or environmental factors are involved in manifesting ANE. Familial ANE differs from the sporadic form in that it may present at later years, demonstrate normal transaminase levels, and involve brain regions atypical for the sporadic form.<sup>6</sup>

Ultimately, in this case, whether global hypoxic-ischemic injury could have arrested the ongoing changes associated with ANE sufficiently early such that evidence of the characteristic hemorrhagic necrosis was not appreciated is unclear. The variability of appreciable necrotic changes may ultimately depend on the severity of ANE and timing of histologic examination.

This case demonstrates that the combined clinical radiological findings may at most be suggestive but is not often sufficient for diagnosis of ANE, and that pathology is necessary for definitive diagnosis. Several other reports had similar dilemmas, San Millan et al.<sup>7</sup> described a case of ANE without characteristic thalamic involvement on imaging, but confirmed to have hemorrhagic necrosis on histopathology. Conversely, a report describing a brain biopsy performed on a surviving child with characteristic imaging features failed to reveal necrosis but rather nonspecific inflammation.<sup>8</sup> It is plausible that those with less severe disease who progress to clinical recovery may demonstrate only inflammation without necrotic changes. ANE may also be more heterogeneous than previously thought, with a spectrum including less obvious pathologic and neuro-radiological, obfuscating the diagnosis of ANE in certain cases.

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