A Rare Case of Acute Necrotizing Encephalopathy in A Young Adult: Correlation between Neuroradiological Imaging and Clinical Outcome

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CONFLICT OF INTEREST

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CONSENT

Written informed consent was obtained from the patient for the publication of this case report, including all clinical details and any accompanying images. The patient was informed about the purpose of the report and agreed to the anonymous use of their medical data for scientific and educational purposes.

ETHICAL STATEMENT

This case report was conducted in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki Declaration and its later amendments.

ABSTRACT

Acute necrotizing encephalopathy (ANE) is a rare, potentially fatal neurological disorder predominantly affecting pediatric patients, with a poor prognosis and high mortality rate. Here, we report a case of a 22-year-old woman diagnosed with ANE, analyzing neuroimaging features correlated with clinical outcomes. Brain magnetic resonance imaging demonstrated characteristic extensive bilateral symmetric lesions involving the thalamus, external capsule, optic tracts, and mammillary bodies. Following corticosteroid therapy, a follow-up MRI at three months revealed complete remission.

CASE REPORT

BACKGROUND

Acute necrotizing encephalopathy (ANE) is a rare, rapidly progressive encephalopathy typically triggered by viral infections, most commonly affecting children but increasingly recognized in adults. Although classically associated with mutations in the **RANBP2 gene**, sporadic cases without a genetic predisposition have also been described. The pathogenesis is believed to involve a **cytokine storm**, leading to **blood-brain barrier breakdown**, cytotoxic edema, and neuronal injury, rather than direct viral invasion. Diagnosis is often challenging due to non-specific early symptoms and inconclusive laboratory findings, necessitating a high index of clinical suspicion and prompt neuroimaging. **Acute necrotizing encephalopathy** is characterized by **multifocal, symmetric lesions** predominantly involving the **thalami**, **brainstem** visible on magnetic resonance imaging (MRI) as hyperintensities on FLAIR and restricted diffusion on DWI. Early immunomodulatory treatment with high-dose corticosteroids and intravenous immunoglobulin may improve outcomes, although residual neurological deficits are common.

CASE REPORT

A 22-year-old woman presented to the emergency department with sudden-onset paresthesia of the right upper limb, bilateral visual impairment, frontal-temporal headache, mental confusion, and difficulty concentrating. She reported an upper respiratory tract infection with fever, productive cough with yellowish sputum, and pharyngodynia in the preceding days.

Neurological examination revealed a conscious and cooperative patient with mild finger drop on the right hand, tingling paresthesia in the right upper limb and ipsilateral lip, with preserved superficial and deep sensation. Severe bilateral visual impairment, more pronounced in the right eye, was noted in the bitemporal region, although the photomotor reflex was preserved.

ECG showed a normal sinus rhythm at 95 bpm. EEG revealed diffuse "epileptiform" dysfunction. Blood tests demonstrated iron-deficiency anemia and mildly elevated aminotransferases. Autoimmune screening, HIV serology, Borrelia, and syphilis tests were negative, with normal ESR levels.

A cerebrospinal fluid (CSF) analysis was negative for viral antigens, including Zika, West Nile, and JC virus, with normal biochemical parameters (protein 34.7 mg/dL, glucose within normal limits, K-index of 6.3, and negative isoelectric focusing for IgG bands). Due to clinical suspicion, genetic testing for RANBP2 mutation was performed but returned negative.

An emergency three-phase CT angiography was unremarkable, showing no supra- or infratentorial tissue abnormalities or vascular anomalies in the circle of Willis (Figure 1). After 72 hours, brain MRI on a 1.5T scanner with gadolinium contrast was performed, revealing bilateral, symmetric hyperintense signal abnormalities on FLAIR sequences, involving the thalami, external capsules, optic tracts, and mammillary bodies (Figure 2). DWI sequences demonstrated restricted diffusion with corresponding ADC reduction, indicative of cytotoxic edema (Figure 3a,3b). SWI sequences showed no hemorrhagic component, and no pathological contrast enhancement was observed.

Despite negative laboratory and cerebrospinal fluid findings, the clinical progression, neuroradiological features, and remote family history (a brother who died following a similar neurological event) raised suspicion of ANE. Consequently, treatment was initiated with intravenous Methylprednisolone at a dose of 1 g per day for 5 days, followed by intravenous immunoglobulin therapy at 0.4 g/kg per day for 5 days.

After three months, the patient showed symptomatic improvement, except for persistent visual impairment. A follow-up MRI revealed complete resolution of the previously reported neuroradiological abnormalities (Figure 4a-4c).

DISCUSSION

Acute necrotizing encephalopathy (ANE) is a severe neurological condition affecting both pediatric and young adult patients, with variable gender distribution and mortality rates [1]. In pediatric cases, the incidence is equal between sexes, whereas in adults, females are more frequently affected, with a female-to-male ratio of 2.25. The mortality rate in pediatric ANE is approximately 25%, while in adults, despite the limited number of reported cases, it reaches nearly 40% [1].

The etiology of ANE remains unclear, though genetic and environmental factors, particularly viral infections, are considered predominant triggers. Sporadic cases secondary to viral infections such as Influenza A and B, Varicella, HHV6, HHV7, Enterovirus, and H1N1 are more frequent [2], while familial hereditary cases with RANBP2 gene mutations are less common [3].

The neurological symptoms result from a cytokine storm leading to systemic immune dysregulation, increased vascular permeability, and subsequent brain lesions affecting both white and gray matter. This process can extend to multiorgan failure, including hepatic-renal insufficiency and disseminated intravascular coagulation (DIC) [4]. Initial symptoms typically include focal neurological deficits with a rapidly progressive decline. Clinical manifestations range from severe forms with high mortality to milder presentations with an initial prodromal phase, evolving into an acute stage and recovery period [5]. Less than 10% of patients achieve complete neurological recovery [6].

Neuroimaging studies, particularly MRI, play a fundamental role in diagnosing acute necrotizing encephalopathy [7]. The hallmark radiological feature is the presence of bilateral, symmetric, and multifocal lesions primarily affecting the thalami, with involvement of both white and gray matter. These findings, confirmed by MRI and histopathological autopsy studies, are essential for differentiating ANE from other encephalopathies [7, 8]. MRI is superior to CT in diagnosing ANE, with T2-weighted and FLAIR sequences revealing hyperintense bilateral thalamic lesions as a distinguishing feature [8]. The radiological pattern of ANE is dynamic, evolving with disease progression. In the acute phase, parenchymal edema caused by vascular congestion and neuronal swelling leads to restricted diffusion on DWI/ADC sequences. In later stages, some cases exhibit partial regression of edema with the emergence of necrotic-hemorrhagic components, particularly in severe cases associated with poor prognosis [9].

Patients with ANE showing diffusion restriction may develop a characteristic "ring-like" pattern with high ADC values in the perilesional region, reflecting vasogenic edema, low ADC in the pericore indicative of cytotoxic edema, and high ADC in the core suggesting hemorrhage and/or necrosis [10]. Wong et al. proposed an MRI-based prognostic scoring system, assigning points based on lesion location and signal intensity on FLAIR sequences. A score of 1 indicated a favorable prognosis, while higher scores correlated with worse outcomes. Based on this system, our patient was assigned a score of 1 due to the absence of necrotic or hemorrhagic areas, suggesting a positive prognosis [9].

The role of gadolinium contrast in MRI for ANE is debated. While contrast enhancement can aid in early diagnosis when CT, standard MRI, and even DWI/ADC appear normal, not all ANE patients exhibit enhancement. This variability may be related to disease severity and timing of imaging relative to disease onset [10]. Additionally, MR spectroscopy can assess metabolic alterations, particularly the lipid-lactate complex and glutamate/glutamine peaks, which may provide insight into neuronal membrane damage mediated by excessive glutamate release. However, the absence of these spectral changes in some patients, including our case, suggests that such findings may be disease severity-dependent [12].

Some diseases, such as Reye's syndrome, vascular occlusion, tumor, hemorrhage of the thalamus, metabolic disorders such as Sandhoff disease, Leigh and Wernicke encephalopathies, methyl l malonic acidemia, glutaric aciduria, carbon monoxide poisoning, acute disseminated encephalomyelitis (ADEM), and acute hemorrhagic leukoencephalitis may have similar clinical, radiological, or pathological findings and have to be considered in differential diagnosis.

Of these, the metabolic disorders are differentiated based on clinical and biochemical investigations. However, it is difficult to differentiate from Reye's syndrome and ADEM. Reye's syndrome is associated with metabolic alterations such as hypoglycemia and hyperammonemia, and ANE is usually associated with antecedent diarrhea and increased CSF protein compared to Reye's syndrome. Radiologically, the lesions in ADEM are asymmetric in distribution, and usually not associated with necrosis and hemorrhage compared to ANE. Acute hemorrhagic leukoencephalitis is asymmetric in distribution, has perivascular distribution, and is associated with meningeal inflammation compared to acute necrotizing encephalopathy [11].

Despite these clinical insights, no specific treatment or preventive measures have been identified [7].

TEACHING POINT

Despite the rarity of ANE and the presence of a family history suggestive of genetic predisposition, the neuroradiological findings in this case evolved favorably. This highlights the potential for a positive outcome even in cases with extensive but reversible neurological involvement.

QUESTIONS

1. Which of the following statements is correct regarding age-related mortality in Acute Necrotizing Encephalopathy (ANE)?

A. Mortality rates are higher in pediatric cases compared to adults

B. Adult cases have a lower mortality rate due to more robust immune responses

C. Pediatric ANE has a mortality rate of around 25%, while adult ANE mortality can approach 40% (applies)

D. ANE affects only pediatric patients, with negligible adult mortality

E. Mortality in ANE is not influenced by age

Explanation: [In pediatric cases, the incidence is equal between sexes, whereas in adults, females are more frequently affected, with a female-to-male ratio of 2.25. The mortality rate in pediatric ANE is approximately 25%, while in adults, despite the limited number of reported cases, it reaches nearly 40%.]

Applies to article: Yi-Ying Lin, Kuang-Yung Lee, Long-Sun Ro, Yen-Shi Lo, Chin-Chang Huang, Kuo-Hsuan Chang; Clinical and cytokine profile of adult acute necrotizing encephalopathy; Biomedical journal, June 2019, Pages 178-186.

2. What is the distinctive radiological feature of ANE?

A. Asymmetric lesions in the brainstem

B. Hypointense lesions on FLAIR sequences

C. Bilateral symmetric lesions involving the thalami and external capsules (applies)

D. Lesions localized to the corpus callosum

E. Gray-white matter lesions in both cortical areas

Explanation: [The hallmark radiological feature is the presence of bilateral, symmetric, and multifocal lesions primarily affecting the thalami, with involvement of both white and gray matter. These findings, confirmed by MRI and histopathological autopsy studies, are essential for differentiating ANE from other encephalopathies]

Applies to article: Mizuguchi, Masashi; Acute necrotizing encephalopathy of childhood: a novel form of acute encephalopathy prevalent in Japan and Taiwan; Brain and Development, Volume 19, Issue 2, 81 – 92.

3. Which of the following statements best reflects the current understanding of gadolinium contrast use in MRI for Acute Necrotizing Encephalopathy (ANE)?

A. Gadolinium contrast is essential for diagnosing all ANE cases

B. Contrast enhancement is consistently present in ANE and confirms the diagnosis

C. Gadolinium is avoided in ANE due to risk of worsening edema

D. Contrast enhancement may be helpful in early diagnosis, but not all ANE patients show enhancement (applies)

E. Gadolinium contrast is only useful in pediatric patients with ANE

Explanation: [The role of gadolinium contrast in MRI for ANE is debated. While contrast enhancement can aid in early diagnosis when CT, standard MRI, and even DWI/ADC appear normal, not all ANE patients exhibit enhancement. This variability may be related to disease severity and timing of imaging relative to disease onset]

Applies to article: Yoshida, Takeshi et al.; MRI gadolinium enhancement precedes neuroradiological findings in acute necrotizing encephalopathy; Brain and Development, Volume 35, Issue 10, 921 – 924.

4. What MRI features differentiate acute necrotizing encephalopathy (ANE) from Acute Disseminated Encephalomyelitis (ADEM)?

A. Presence of bilateral necrosis and symmetric lesions in the brainstem

B. Asymmetric lesions and absence of necrosis in ADEM (applies)

C. Hypointense lesions in the corpus callosum in ANE

D. Contrast enhancement in ADEM compared to ANE

E. Absence of periventricular lesions in ADEM

Explanation: [Radiologically, the lesions in ADEM are asymmetric in distribution, and usually not associated with necrosis and hemorrhage compared to ANE]

Applies to article: Narra R, Mandapalli A, Kamaraju SK. Acute necrotizing encephalopathy in an adult. J Clin Imaging Sci. 2015 Apr 30;5:20.

5. Based on the neuroradiological evaluation and the scoring system proposed by Wong et al., what could be the prognosis for patience, who showed a symmetric pattern without necrotic or hemorrhagic components?

A. Favorable prognosis, with possible complete recovery (applies)

B. Poor prognosis, with irreversible brain damage

C. Uncertain prognosis, with progressively worsening lesions

D. Severe prognosis, with a high likelihood of death within 72 hours

E. Stable prognosis, with no long-term improvements

Explanation: [Wong et al. proposed an MRI-based prognostic scoring system, assigning points based on lesion location and signal intensity on FLAIR sequences. A score of 1 indicated a favorable prognosis, while higher scores correlated with worse outcomes. Based on this system, our patient was assigned a score of 1 due to the absence of necrotic or hemorrhagic areas, suggesting a positive prognosis]

Applies to article: Wong AM, Simon EM, Zimmerman RA, Wang HS, Toh CH, Ng SH; Acute necrotizing encephalopathy of childhood: correlation of MR findings and clinical outcome; AJNR Am J Neuroradiol. 2006 Oct;27(9):1919-23.

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FIGURES

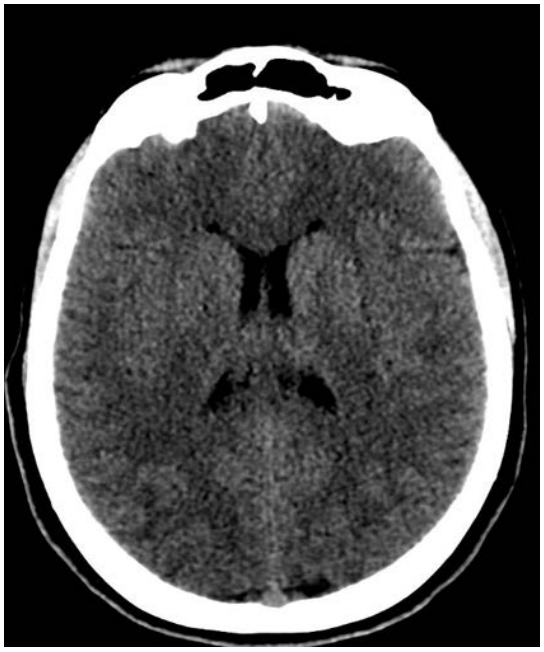

Figure 1: The non-contrast CT scan did not reveal any evident focal lesions in the brain tissue.

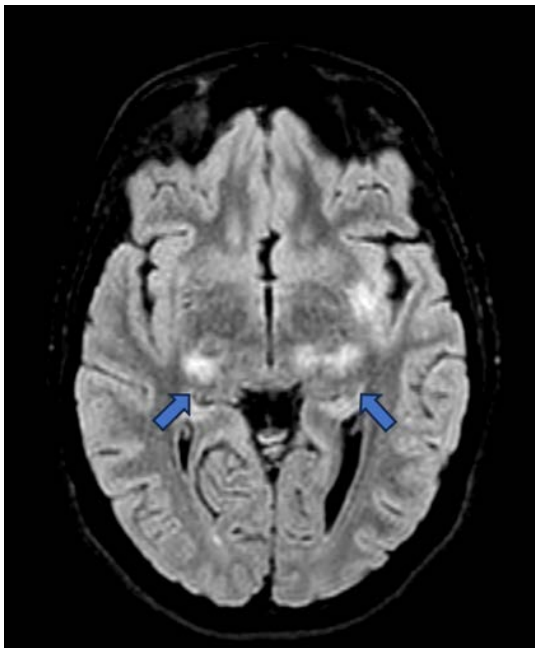

Figure 2: Axial FLAIR image acquired 72 hours after symptom onset. Bilateral and symmetric hyperintense signal areas are observed in the thalami, external capsules, optic tracts, and mammillary bodies. The blue arrows indicate the pathological areas in the bilateral thalamic region, which are pathognomonic for ANE.

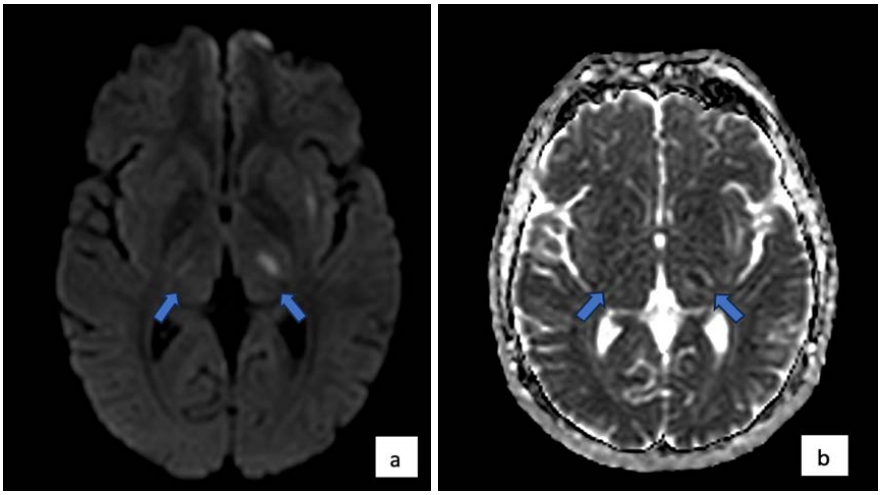

Figure 3 (a,b): Diffusion-weighted image (a) and corresponding ADC map (b). The blue arrows indicate areas of restricted diffusion in the thalami.

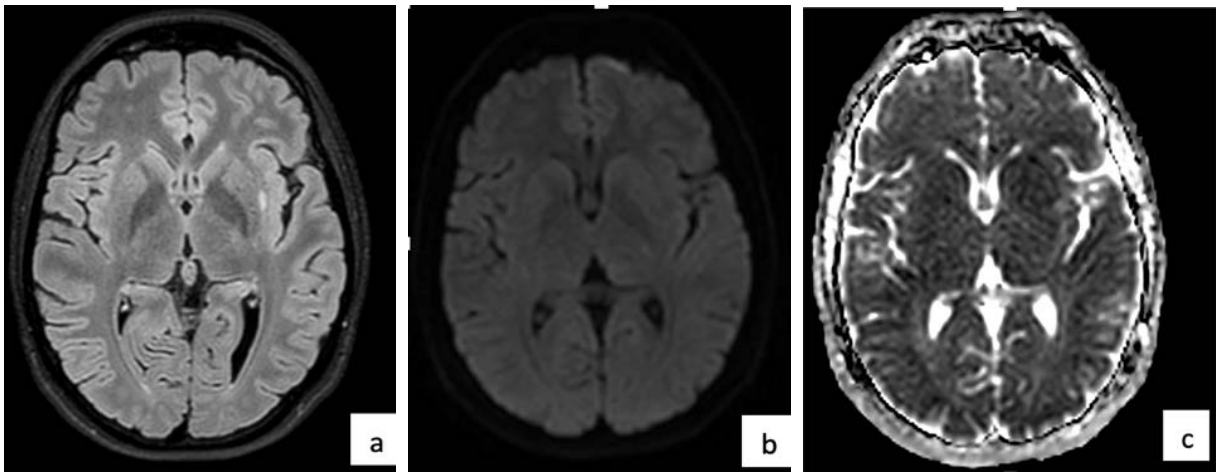

Figure 4 (a-c): In the follow-up examination performed three months later, the previously reported pathological areas were no longer detected. Specifically, no signal alterations were observed in the FLAIR (a), diffusion-weighted (b), or ADC map (c) sequences. A small residual hyperintense focus in the left external capsule was noted on FLAIR, likely representing stabilized sequelae, but it was not detectable in (b) and (c).

KEYWORDS

Acute necrotizing encephalopathy; magnetic resonance imaging; neuroradiology; brain; case report.