Chapter 2
Acute Necrotizing Encephalopathy Mimicking ADEM

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Case Presentation

A 3-year-old girl presented in status epilepticus. At the time of presentation, she had no notable past medical history and was well until 1 day prior to admission when she awoke with an elevated temperature (39.4 °C). At that time, she also had rhinorrhea and cough. Throughout the day, her parents noted decreased energy and physical activity. In the evening of the first day of her illness, the patient's father found her unresponsive and noted generalized muscle rigidity with both arms extended. She was taken to an outside hospital where examination noted decerebrate posturing, rotatory nystagmus, and urinary incontinence. Initial evaluation with brain CT showed bilateral thalamic hypodensities. Cerebrospinal fluid was reportedly normal. For initial stabilization, she was intubated, treated with intravenous phenytoin and ceftriaxone, and transferred to a tertiary care center where she was admitted to the pediatric intensive care unit.

Initial evaluation showed a comatose child with decerebrate posturing after stimulation. Deep tendon reflexes were brisk in all extremities, and plantar response was extensor bilaterally. EEG obtained on admission showed numerous electrographic seizures without clinical correlate occurring independently from bilateral posterior regions. The background electrographic activity was slow and disorganized.

Gadolinium-enhanced brain MRI obtained on admission was most notable for diffuse hyperintense T2 signal and marked swelling in the thalami bilaterally (Fig. 2.1). There was also hyperintense T2 signal in the cortex of the frontal, posterior parietal, and occipital lobes. Additional hyperintense T2 signal was seen within the brainstem involving the midbrain and the pons. There was no enhancement of the lesions. The diffusion-weighted images delineated small foci of restricted

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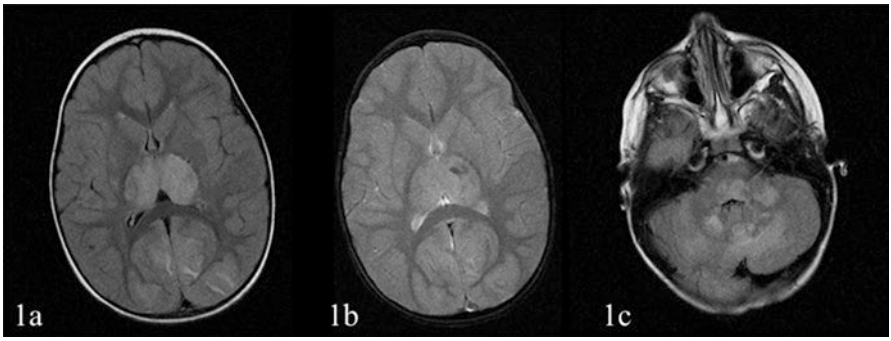

Fig. 2.1 (**a**) T2-weighted FLAIR image demonstrates marked swelling and diffuse symmetric signal abnormality of bilateral thalami and occipital cortex. (**b**) The MPGR sequence delineates patchy foci of hypointensity in the left thalamus suggesting microhemorrhage. (**c**) The T2-weighted FLAIR image demonstrates multiple signal abnormalities in the brainstem and cerebellum

diffusion in the thalami and bilateral occipital lobes. The multiple planar gradient recalled (MPGR) sequence demonstrated small patchy foci of hypointensity in the left thalamus suggesting microhemorrhage. Brain MRA and MRV studies were normal.

Repeat CSF examination on admission showed zero white cells, one red blood cell, elevated protein 77 mg/dL, and normal glucose 70 mg/dL. IgG index was elevated at 0.78 (normal < 0.7), and no oligoclonal bands were seen. She had normal serum lactate, ammonia, amino acids, acylcarnitine, LDH, ACE, and ferritin as well as normal urine organic acids. Antibody studies for ANA, ANCA, SSA, SSB, NMO-IgG, thyroid peroxidase, and thyroglobulin were negative. Mutation analysis of mtDNA polymerase (*POLG*) was normal.

The patient was initially treated with high-dose intravenous corticosteroids for a presumed diagnosis of ADEM. After consulting with neuroimmunology, acute necrotizing encephalopathy (ANE) was alternatively suspected, and testing for influenza and other respiratory viruses was recommended. Nasopharyngeal swab PCR testing was positive for influenza A. There was otherwise no bacterial or fungal growth in the blood and cerebrospinal fluid cultures. Based upon the clinical history, MRI findings, and positive influenza A test, she was diagnosed to have ANE. In addition to corticosteroids, she received IVIG 2 g/kg as well as antiviral treatment with oseltamivir.

Throughout her hospitalization, she remained quite somnolent and developed generalized spasticity with dystonia. Her EEG obtained 3 weeks from her presentation showed severe background slowing but no epileptiform features. Following her acute treatment, she spent several months in the inpatient rehabilitation unit and continued to make some improvements in her neurological function. By 6 months from the time of her presentation, her speech was fluent, but she remained with intellectual deficits, right hemiparesis, and generalized dystonia and was not able to ambulate without assistance.

Clinical Questions

1. What is acute necrotizing encephalopathy?
2. What are the similarities and differences of clinical presentation between ADEM and ANE?
3. What are the atypical imaging features for ADEM in this case?
4. How does the prognosis differ between ANE and ADEM?

Diagnostic Discussion

1. Acute necrotizing encephalopathy (ANE) is a rare but distinctive disorder characterized by fever, seizures, and rapid progression to coma just after the onset of a viral infection. The first cases were initially reported in Asia by Mizuguchi et al. with several additional cases subsequently described worldwide [1]. The MRI hallmark is represented by symmetrical lesions in the thalami, brainstem tegmentum, cerebellum, and periventricular white matter. Marked involvement of bilateral thalami is a distinctive feature of ANE and is often accompanied by microhemorrhages. Additional lesions may involve the cortical and deep gray matter as well as the deep white matter and spinal cord [2]. Another distinguishing feature of ANE is the presence of deep and cortical gray matter microhemorrhages, which tend to spare the white matter [3]. The T2-weighted gradient echo imaging or the susceptibility-weighted imaging (SWI) is particularly useful in demonstrating these petechial hemorrhages in ANE.
   Although the exact pathogenesis of ANE remains obscure, the most prevalent hypothesis is that individuals suffering from ANE often have an exaggerated immune response to various viral infections by producing elevated pro-inflammatory cytokines resembling systemic inflammatory response syndrome (SIRS) [2]. The "cytokine storm" results in systemic symptoms, such as liver dysfunction, acute renal failure, shock, and disseminated intravascular coagulation. In the central nervous system, it leads to brain injury through alteration of blood vessel wall permeability without wall disruption [2].
   Most cases of ANE are sporadic; however, the observation of multiple cases in the same family with recurrent episodes of ANE led to the identification of a genetic form of the disorder, called ANE1, and to the discovery of the causative mutation in *RANBP2* [4]. A nuclear pore protein, Ran-binding protein 2, is encoded by the gene and has numerous roles throughout the cell cycle. In neurons, it is detected in association with microtubules and/or mitochondria, suggesting roles in intracellular trafficking or energy metabolism [4]. It may also affect other processes including viral entry, antigen presentation, cytokine signaling, immune responses, and blood-brain barrier maintenance [4].
2. Although ANE and ADEM both occur in children, there are some differences. ANE tends to have a higher occurrence in infants compared to ADEM. Whereas

ADEM typically develops during the postinfectious period up to several days after the initial signs and symptoms of infection have resolved, ANE occurs during the early febrile period of the viral infection and runs a fulminant course with the rapid development of coma, as demonstrated in the presented case. Further distinction of ANE from entities such as viral encephalitis can be clinically difficult. However, in contrast to CNS infection and most cases of ADEM, ANE tends not to have a CSF pleocytosis [2, 5].

3. The necrotizing nature of the lesions reflected by the presence of petechial or microhemorrhages in the deep and cortical gray matter and symmetric involvement of bilateral thalamic structures should be considered as atypical for ADEM in this patient. Bi-thalamic involvement is seen in 100% of the patients with ANE. In contrast, it only occurs in 30–50% of ADEM patients and is usually asymmetric [6]. Another distinguishing feature of ANE, rarely seen in ADEM, is the presence of microhemorrhages on MRI. These are consistent with the pathophysiological cascade from edema to petechial hemorrhage and resulting cell necrosis and cavitation [2]. It is uncommon for lesions in ADEM to have such a degree of necrosis, as most of the lesions in this disease do not have hemorrhage and tend to demonstrate complete resolution on follow-up MRI.
4. ADEM overall has a favorable prognosis with a complete recovery rate reported in 57–94% of patients [6]. In contrast to ADEM, the neurological outcome of ANE has been reported to be very poor. It has an estimated mortality rate of about 30%, and less than 10% of patients recover completely [2]. The genetic form of acute necrotizing encephalopathy is fatal in some patients. However, the majority recovers but may experience varying degrees of neurodevelopmental impairments to include cognitive and motor difficulties [7]. Approximately 50% of patients will experience a recurrent encephalopathy that often results in further neurodevelopmental disabilities.

Clinical Pearls

1. In ANE, CSF analysis typically shows no pleocytosis, but CSF protein can be markedly elevated.
2. Microhemorrhages and symmetric bi-thalamic lesions are frequently seen in ANE, which are not typical of ADEM.
3. While ADEM has near-complete resolution with a favorable clinical prognosis, ANE lesions usually leave significant sequela characterized by severe neurological deficits.
4. It is important to consider the relapsing genetic form of ANE secondary to pathologic mutations in *RANBP2,* particularly in infants who continue to have relapses without recovering completely.

References

1. Mizuguchi M, Abe J, Mikkaichi K, et al. Acute necrotising encephalopathy of childhood: a new syndrome presenting with multifocal, symmetric brain lesions. J Neurol Neurosurg Psychiatry. 1995;58:555–61.
2. Wu X, Wu W, Pan W, et al. Acute necrotizing encephalopathy: an underrecognized clinicoradiologic disorder. Mediat Inflamm. 2015;1–10.
3. Wong AM, Simon EM, Zimmerman RA, et al. Acute necrotizing encephalopathy of childhood: correlation of MR findings and clinical outcome. AJNR Am J Neuroradiol. 2006;27:1919–23.
4. Neilson DE, Adams MD, Orr CMD, et al. Infection-triggered familial or recurrent cases of acute necrotizing encephalopathy by mutations in a component of the nuclear pore, RANBP2. Am J Hum Genet. 2009;84:44–51.
5. Bergamino L, Capra V, Biancheri R, et al. Immunomodulatory therapy in recurrent acute necrotizing encephalopathy ANE1. Brain and Development. 2012;34:384–91.
6. Tenembaum S, Chitnis T, Ness J, for the International Pediatric MS Study Group. Acute disseminated encephalomyelitis. Neurology. 2007;68(Suppl 2):S23–36.
7. Neilson DE, Heidi S, Feiler HS, et al. Autosomal dominant acute necrotizing encephalopathy maps to 2q12.1-2q13. Ann Neurol. 2004;55:291–4.

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