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CASE REPORT

Imaging Findings and Clinical Perspectives of Acute Necrotising Encephalopathy: Report of Two Cases

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INTRODUCTION

First coined by Mizuguchi[1] in 1997, acute necrotising encephalopathy (ANE) is a severe, uncommon type of encephalopathy with distinctive imaging and clinical features and a global distribution. Despite ongoing studies, the exact pathogenesis of ANE is yet to be determined and is still classified as an idiopathic disorder. It is hypothesised that the disease is an immune response to a prior, mostly viral, infection. With two illustrative cases, we showcase the current understanding of the pathogenesis, clinical and radiological presentation of the disease as well as the latest treatment strategies.

CASE 1

A 2-year-old boy with good past health developed fever and upper respiratory symptoms for 1 day. His symptoms deteriorated overnight and he developed generalised seizure. He was then urgently admitted to the Accident and Emergency Department where the seizure was aborted with anticonvulsant therapy. He was transferred to the paediatric intensive care unit for further care.

A nasopharyngeal swab for rapid antigen test was positive for influenza A. Despite empirical treatment with vancomycin, rocephin, acyclovir, and oseltamivir, the patient developed breakthrough seizure. An urgent contrast magnetic resonance imaging (MRI) revealed symmetrical T2 and fluid attenuated inversion recovery hyperintensities with restricted diffusion over bilateral thalami, white matter, and brain stem (Figure 1a-c). Bilateral thalami were markedly swollen with central hypo-enhancement (Figure 1d). Features were suggestive of ANE.

The patient was started on intravenous pulse steroid but his neurological condition deteriorated rapidly. A follow-up computed tomography (CT) scan of the brain showed diffuse cerebral oedema with effacement of bilateral cerebral sulci and cisterns. Evidence of coning was also observed. An urgent bilateral craniotomy and decompression were performed. Despite the surgical management, the patient's condition remained poor. Neurologically, the patient showed minimal brain stem response and scored 4 (E1V1M2) in the Glasgow Coma Scale. On day 5 after admission, the patient succumbed.

CASE 2

A 6-year-old boy with good past health presented with high fever, upper respiratory symptoms and transient episodes of confusion. An urgent CT scan of the brain performed on admission revealed no abnormality. A

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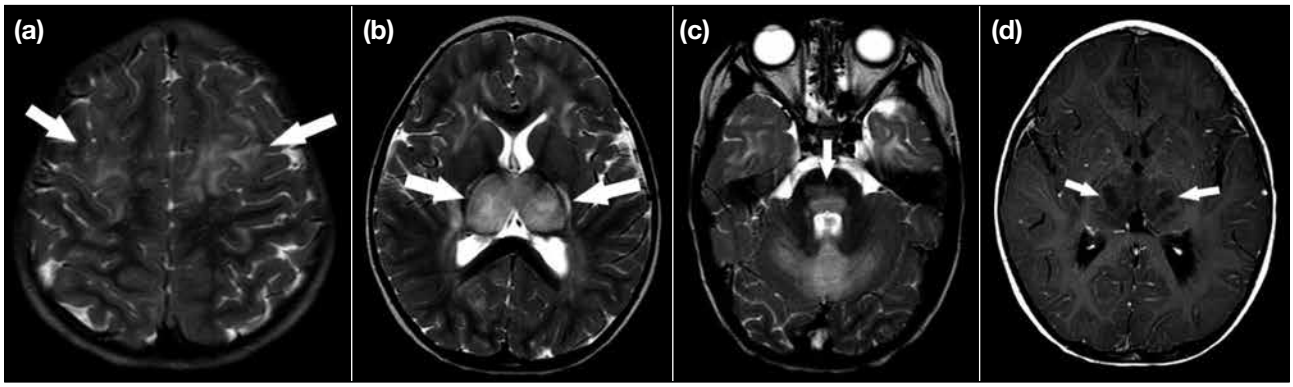

Figure 1. A 2-year-old boy with acute necrotising encephalopathy. T2-weighted axial image showing abnormal hyperintensities at (a) bilateral cerebral white matter, (b) bilateral thalami, and (c) brain stem. (d) T1-weighted axial post-contrast image showing bilateral thalamic symmetrical hypoenhancing lesions.

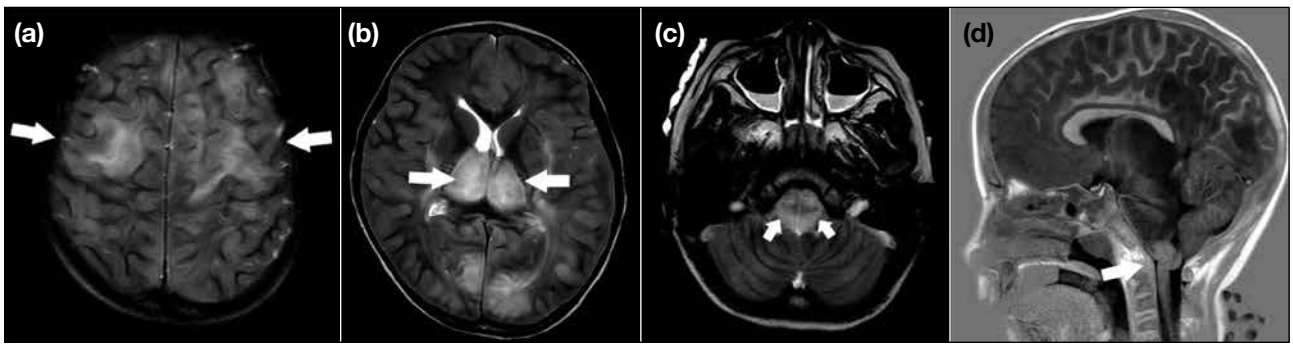

Figure 2. A 6-year-old boy with acute necrotising encephalopathy. T2-weighted axial image showing hyperintensities and swelling at (a) bilateral cerebral white matter, (b) bilateral thalami, and (c) brain stem. (d) T1-weighted inversion recovery sagittal image showing significant swelling at the thalamus and brainstem with kinking of the cervicomedullary junction.

rapid antigen test on nasopharyngeal swab was positive for influenza A.

The patient's level of consciousness deteriorated rapidly: Glasgow Coma Scale score dropped from 15 to 4 over 7 hours. MRI performed 12 hours after admission revealed bilateral symmetrical T2 hyperintensities in the thalamus and brain stem (Figure 2a and b). Associated bilateral cerebral and cerebellar white matter hyperintensities were also observed (Figure 2c). Features were suggestive of ANE. There was significant swelling at the thalamus and brain stem with kinking of the cervicomedullary junction (Figure 2d). Crowding of the foramen magnum was evident.

A neurosurgical opinion was sought and the boy was deemed too ill to benefit from surgery. He remained comatose with no obvious return of any brainstem function despite all medical support. The patient was certified dead on day 12 after admission.

DISCUSSION

Pathogenesis and Aetiology of Acute Necrotising Encephalopathy

The most widely accepted cause of ANE is hypercytokinaemia.[2] Patients with ANE mount an exaggerated immune response to infection by releasing a high level of cytokines. There is evidence that the level of various inflammatory mediators, including different interleukins (IL-6, IL-15, IL-1β, IL-10), tumour necrosis factor-α as well as interferon-γ,[2-4] is raised in the serum as well as the cerebrospinal fluid. This causes multiple system failure.[1]

Both environmental and host factors seem to play a role in a predisposition to ANE.

A number of different infections are associated with ANE and different pathogens have been reported, including viruses and bacteria.[2,5] Influenza virus is the most common culprit.

There have been some recurrent cases reported within certain families, suggesting a genetic predisposition.[5] In recurrent cases, missense mutations in Ran-binding protein 2 were identified as the susceptibility alleles.[5]

Clinical Presentation of Acute Necrotising Encephalopathy

In general, the clinical presentation of ANE can be classified into three stages: the prodromal stage, the acute encephalopathy stage, and the recovery stage.

The presentation in the prodromal stage is highly variable, due to the wide range of antecedent pathogens possible. Symptoms may include fever, upper respiratory symptoms, gastroenteritis, or skin rashes. Patients with ANE may also present with more severe symptoms including shock, disseminated intravascular coagulation and even multiple organ failure.[5]

As the disease progresses, the acute encephalopathy stage ensues during which neurological symptoms will manifest rapidly. Seizures, an altered level of consciousness and focal neurological deficits may occur. The patient usually requires intensive care support.

Although majority of the cases result in high morbidity and mortality, milder forms with recovery have also been reported.[5]

Radiological Findings and Imaging Differential Diagnoses of Acute Necrotising Encephalopathy

Contrary to the highly non-specific clinical presentations, imaging features of ANE can usually help to narrow down the differential diagnosis.[5] The list of differential diagnoses is limited when rapid neurological deterioration is taken into account.

The typical imaging presentation of ANE is multiple symmetrical lesions with supra- and infra-tentorial brain involvement. The thalami, brain stem, cerebral white matter, and cerebellum[1,2] are typical sites of involvement. Spinal cord involvement is also occasionally reported.[5] Among them, bilateral thalami involvement is the most distinctive feature of ANE.[1]

It is also common for imaging features of ANE to change over the clinical course.[1,5] Significant oedema is seen in the early phase. On CT, the lesions will show up as symmetrical hypodense foci with mass effect. On MRI, the lesions will have a low T1 signal and high T2 signal. There will also be fluid restriction on diffusion-weighted imaging and apparent diffusion coefficient.[5]

As the disease progresses, imaging features change. Oedema will subside and features of petechial haemorrhage and necrosis may appear. On CT, this will appear as new heterogeneous hyperdense foci within the previously seen hypodensities.[1,5] On MRI T1-weighted image, there will be new hyperintensities within the pre-existing hypointense lesions, while on T2-weighted image they will show up as a hypointense centre surrounded by a high signal rim.[5] Susceptibility weight images and T2* gradient echo imaging are more able to show the petechial haemorrhage that will appear as low signal foci with blooming artefact.[5] The classically described ANE imaging features of concentric structures, tricolour pattern, or target-like appearance can be seen on apparent diffusion coefficient images. The centre of the lesion shows high signal with a hypointense rim suggesting cytotoxic oedema. A further outer rim of hyperintensity suggests vasogenic oedema.[5,6]

With specific imaging features of ANE and a rapid neurological decline, the imaging differential diagnoses of ANE are limited. Entities that need to be considered include acute disseminated encephalomyelitis, Reye's syndrome and Leigh's syndrome. Acute disseminated encephalomyelitis is associated with multiple bilateral brain lesions bilaterally. Nonetheless the lesions do not typically affect the brain symmetrically as in ANE. Although Reye's syndrome and Leigh's syndrome may present with symmetrical brain lesions, both entities are characterised by the presence of lactic acidosis.

In both of our cases, the later imaging features were not well demonstrated due to the rapid clinical course. Unfortunately both patients succumbed before follow-up imaging was available. However, the typical early imaging features of ANE were well demonstrated.

Diagnostic Criteria of Acute Necrotising Encephalopathy

Diagnosis of ANE is made if both clinical and imaging findings are present and when similar-presenting diseases have been excluded. Mizuguchi[1] have outlined the diagnostic criteria (Table).

Management and Prognosis of Acute Necrotising Encephalopathy

There is no definitive recommended treatment for

Table. Proposed diagnostic criteria for acute necrotising encephalitis by Mizuguchi.[1]

1. Acute encephalopathy present with rapid consciousness deterioration and convulsion followed by a viral febrile illness
2. Elevated protein level without increase in lymphocyte count in cerebrospinal fluid
3. Elevation of serum alanine aminotransferase level without increase ammonia level
4. Neurological findings compatible with bilateral thalami, cerebral periventricular white matter, internal capsule, putamen, upper brain stem tegmentum, and cerebellar medulla involvement

Exclusion of similar illness

A. Clinical
- Toxic shock syndrome
- Haemolytic uraemic syndrome
- Reye syndrome
- Haemorrhagic shock
- Heat stroke

B. Imaging
- Leigh encephalopathy
- Glutaric acidaemia
- Methyl malonic aciduria
- Infantile bilateral striatal necrosis
- Wernicke encephalopathy
- Acute disseminated encephalomyelitis
- Acute haemorrhagic leukoencephalitis
- Severe hypoxia
- Toxins resulting in symmetric bilateral basal ganglia necrosis, including:
  - Carbon monoxide, methanol
  - 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
  - Cyanide
  - Manfanese, carbon disulphide
  - Tegretol
- Other diseases with symmetric bilateral basal ganglia involvement, including:
  - Osmotic myelinolysis
  - Canavan disease
  - Methylmalonic acidaemia
  - Wilson disease
  - Juvenile Huntington disease
  - Hallervorden–Spatz syndrome

ANE. The mainstay of treatment is intensive care and symptomatic treatment.

Theoretically, intravenous steroids, immunoglobulin, and plasmapheresis should be effective in view of the postulated immunological aetiology.[5,7] High-dose steroid is the most widely documented treatment. Administration of steroids within 24 hours of symptom onset is proposed to be related to an improved outcome.[5] Therapeutic hypothermia has also been mentioned as a supportive treatment.[5]

Despite treatment, ANE has a grave prognosis. The mortality rate is reported to be about 30%. Complete neurological recovery is observed in fewer than 10% of patients and many survivors develop long-term neurological sequelae.[1,5]

CONCLUSION

Acute necrotising encephalitis is a severe neurological complication of a common infection. The exact pathogenesis is incompletely understood. The prognosis of ANE is generally poor, although recent studies have shown that starting treatment early may have a great impact on the final outcome. Prompt diagnosis is vital to ensure early treatment. The diagnosis of ANE is mainly based on clinical and radiological features after exclusion of other diseases with similar presentation.

The two cases we describe had typical imaging findings and clinical presentation. One important limitation of our case sharing is a lack of radio-pathological correlation. In both patients, the cause of death was stated as ANE and autopsy was waived in the absence of any other suspected cause.

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