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Case Report

Two Cases of Acute Necrotising Encephalopathy: Same Disease, Different Outcomes

KF ***Lam***, SP ***Wu***

Abstract Acute necrotising encephalopathy of childhood (ANEC) was first reported by Mizuguchi et al in 1995. We report two cases of ANEC with different outcomes, and alert our paediatricians to early identification of radiological signs in this disease for an earlier diagnosis and intervention.

Key words Acute necrotising encephalopathy of childhood; ANEC; Outcome

Introduction

Acute necrotising encephalopathy of childhood (ANEC) was first reported by Mizuguchi et al. in 1995.[1] It is defined as an acute non-inflammatory encephalopathy, usually following viral infection, most commonly influenza A, and is associated with characteristic neuroimaging findings.[2-5] The disease has a high mortality and morbidity with poor neurodevelopmental outcomes. We report two cases of ANEC with different outcomes.

Case 1

A 17-month-old Southern Chinese girl with good past health was admitted for high fever and influenza-like symptoms. She developed repeated episodes of generalised tonic-clonic seizure. Urgent computed tomography (CT) brain showed subtle hypodense signal changes in bilateral thalami and basal ganglia. Lumbar puncture was not performed in view of unstable clinical condition. Intravenous Ceftriaxone and Acyclovir were started empirically to cover possible meningoencephalitis. Phenytoin successfully brought her seizure under control. She was transferred to paediatric intensive care unit (PICU) for further management. Blood tests showed elevated alanine aminotransferase (ALT) up to 864 IU/L and aspartate aminotransferase (AST) up to 1159 IU/L. Serum ammonia was normal all along. Complete blood count, electrolytes, glucose and C-reactive protein were normal. Nasopharyngeal swab was positive for Influenza A H1 subtype. Oseltamivir 60 mg twice daily was given for 5 days. At 12 hours after admission, she developed hypertension and bradycardia, suggestive of Cushing phenomenon. Blood gas showed respiratory acidosis. She was therefore intubated and put on mechanical ventilation. Glasgow coma scale (GCS) was 5/15 at that time. CT brain was repeated 2 hours later but she developed hypotension and bradycardia requiring fluid resuscitation and 1 dose of intravenous adrenaline. CT brain showed cerebral oedema, prominent hypodense areas in white matter of bilateral cerebral and cerebellar hemispheres, as well as in brainstem, thalami and bilateral basal ganglia (Figure 1a). One dose of dexamethasone and 20% mannitol were given for cerebral oedema. She also developed hypotension and required multiple inotropes including dopamine, dobutamine and adrenaline infusions. Her GCS dropped to 3 and her pupils turned dilated and slow in constriction to light. She developed hyperglycaemia on the next day of admission and was given insulin infusion for 5 days to control the high blood glucose. She also developed

Department of Paediatrics, Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, Hong Kong, China

KF **Lam** (林競輝) *MBBS, FHKAM(Paediatrics), FHKCPaed*
SP **Wu** (胡信平) *MBBS, FHKAM(Paediatrics), FHKCPaed*

Correspondence to: Dr KF **Lam**
Email: lkf327@ha.org.hk

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diabetes insipidus with serum sodium up to 169 mmol/L on the next day of admission. Vasopressin infusion was given for 6 days. Electroencephalogram on the next day of admission showed a generally suppressed background composing of delta and theta activities with most parts of the record below 5 uV, indicating a diffuse severe cerebral dysfunction. No epileptiform discharge or electrographic seizure was detected. Magnetic resonance imaging (MRI) brain performed 6 days after admission showed bilateral multifocal asymmetrical involvement of bilateral cerebral hemispheres and cerebral white matters, basal ganglia, thalami, brainstem tegmentum, as well as long segment of cord involvement in cervical and upper thoracic spine. Diffuse cerebral oedema with uncal herniation and brainstem compression was seen (Figure 1b). Metabolic screening including plasma amino acids, urine organic acids, acylcarnitine profile were unremarkable. Her parents declined external ventricular drainage or decompression craniectomy as means to decrease intracranial pressure. Pulsed methylprednisolone at 500 mg/m^2 daily was given on the sixth day of admission for 3 days. No neurological improvement was seen and her GCS remained at 3. Brain death was certified 13 days after admission and patient eventually succumbed. Paramortem lumbar puncture was refused by parents.

Case 2

A 12-month-old Southern Chinese boy with good past health was admitted for high fever with cough, vomiting and diarrhea. Physical examination on admission showed normal GCS, normal muscle tone and negative Kernig sign. Initially he was treated as upper respiratory tract infection and acute gastroenteritis. Nasopharyngeal swab was negative for influenza viruses. Serum alanine aminotransferase was elevated to 136 IU/L and ammonia was normal. He was noted to have increased muscle tone at 7 hours after admission. Lumbar puncture was performed yielding clear cerebrospinal fluid (CSF) and a normal opening pressure. CSF examination found normal white cell count, normal glucose and raised protein of 0.83 g/L. CSF viral study for herpes simplex virus, varicella zoster virus and enterovirus was negative. Intravenous Ceftriaxone and Acyclovir were started empirically to cover possible meningoencephalitis. He subsequently developed focal seizure with impaired consciousness presented as increased right upper limb tone and right hand fisting. One dose of intravenous lorazepam was given. Urgent CT brain performed showed features suspicious of acute necrotising encephalopathy with bilateral symmetrical white matter hypodensity involving both fronto-parietal lobes and cerebellum, bilateral basal ganglia, thalami and posterior midbrain. His condition quickly deteriorated on the day of admission. He showed bradycardia, cyanosis and worsened consciousness. His GCS dropped to 3. He was thus resuscitated with mask bagging and transferred to PICU for intubation and ventilation. Neurological examination showed unequal pupil size, brisk deep tendon reflexes all over with bilateral cross adductor reflex and left Babinski sign. No recurrence of seizure was witnessed. Intravenous immunoglobulin at 2 grams/kg was given on next day when the CT brain result was known and pulsed methylprednisolone at 30 mg/kg/dose was given 2 days after admission for 5 days, followed by tapering course of oral prednisolone. Metabolic workup showed normal serum lactate, pyruvate, ammonia, plasma amino acids, acylcarnitine profile and urine organic acids. MRI brain, brainstem and spine was performed 4 days after admission and showed extensive increase in T2W hyperintense signal in bilateral thalami, posterior brainstem, periventricular white matter and bilateral medial cerebellum (Figure 2). Restricted diffusion with concentric rings appearance in bilateral swollen thalami was seen. Acute necrotising encephalopathy of childhood was diagnosed. Electroencephalogram (EEG) on the second day of admission showed a background composed of diffuse theta and beta activity with large amount of high amplitude delta activities reaching 300 uV and absence of normal sleep changes, suggesting a diffuse encephalopathy. EEG repeated on the eighth day of admission did not show interval improvement. There was some improvement in conscious state but he suffered from severe neurological morbidities including spasticity and dystonia required Baclofen and Benzhexol, feeding problem required tube feeding, abnormal brainstem auditory evoked potential and visual evoked potential. He was hospitalised for 4.5 months for treatment and rehabilitation. Subsequently he developed focal seizure at 18 months of age with EEG showing epileptiform discharge from bilateral frontal and parasagittal regions. Sodium valproate was started for seizure control.

Discussion

ANEC is relatively rare and is almost exclusively seen in East Asian infants and children.[6] Diagnostic criteria proposed by Mizuguchi et al include (1) acute

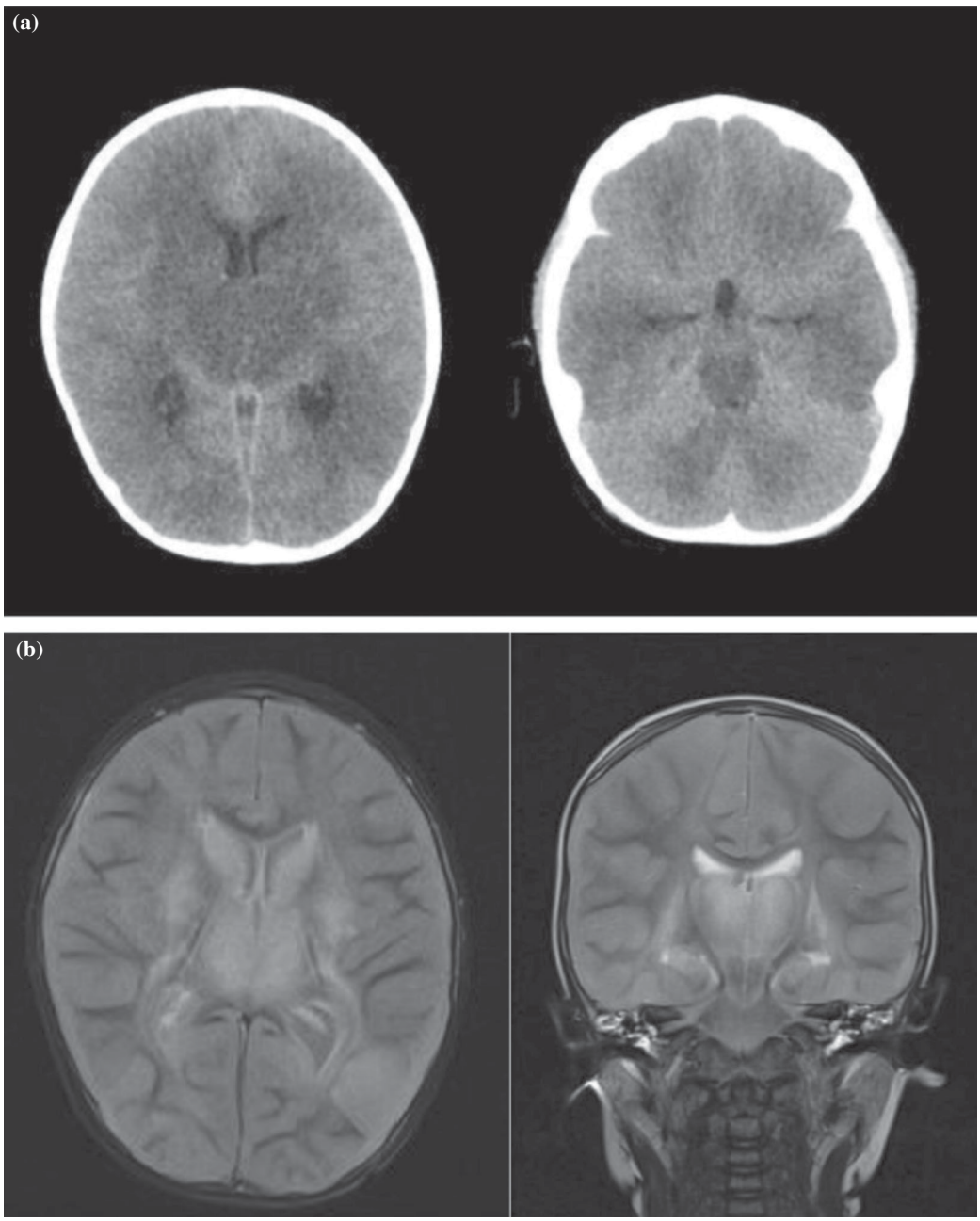

Figure 1 (a) CT brain of case 1 showing hypodense lesions in white matter of bilateral cerebral hemispheres, as well as in brainstem, thalami and bilateral basal ganglia. (b) MRI brain of case 1 showing multifocal lesion in basal ganglia, thalami, periventricular white matter and brain stem.

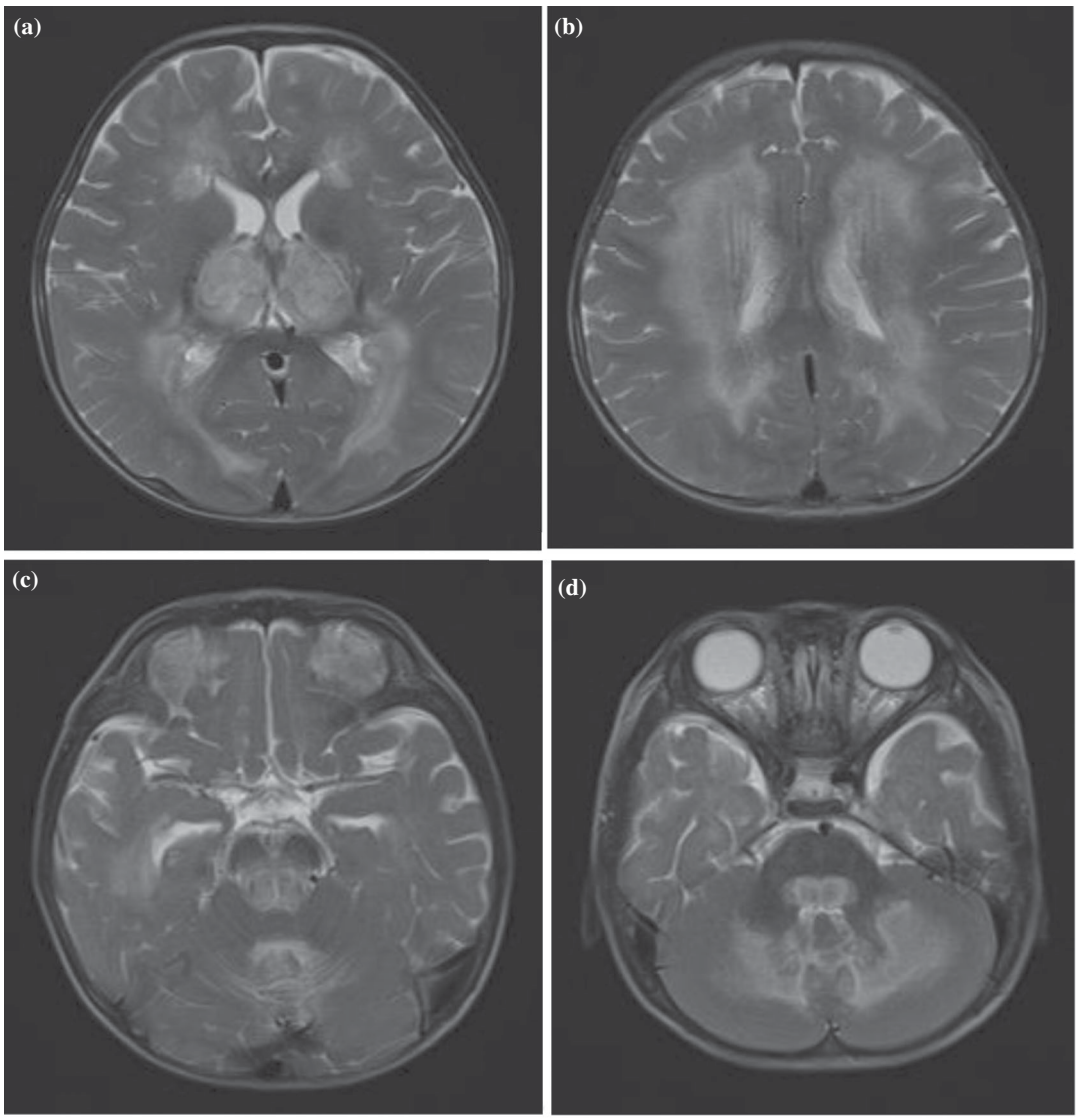

Figure 2 MRI of case 2 showing symmetric multifocal lesions at bilateral thalami with a whorl-like pattern (a), periventricular white matter (b), brain stem (c) and cerebellum (d).

encephalopathy following a febrile viral illness. Features of acute encephalopathy include seizure and rapid deterioration in level of consciousness. (2) Increase in cerebrospinal fluid protein without pleocytosis. (3) Abnormal liver function with elevation of serum aminotransferase without hyperammonaemia. (4) Neuroradiological findings of symmetric multifocal lesions involving bilateral thalami, cerebral periventricular white matter, internal capsule, putamen, upper brainstem tegmentum and cerebellar medulla.[7-9] CT brain typically shows hypodense lesions involving bilateral thalami. Being able to pick up this radiological sign is crucial in making an early diagnosis which in turn facilitates prompt treatment.

Previous study by Yamamoto et al has developed a severity score for ANEC. Brain stem involvement is one of the most important prognostic factors.[2] Treatment strategies include pulse steroid therapy and immunoglobulin.[3] A study by Okumura et al suggested that early steroid treatment is associated with better outcome in patients without brain stem lesion. The prognosis of ANEC is uniformly bad regardless of treatment in patients with brain stem lesions.[2,5]

Both of our cases have brainstem involvement but with different outcomes. The fact that the second case received earlier steroid and immunoglobulin treatment may have averted the fatal outcome, although complicated by severe neurodevelopmental morbidities.

Both cases did not receive influenza vaccination. Influenza vaccination is well-proven to reduce the prevalence of influenza-related complications. However, there is no literature supporting the same theory for ANEC as it is a rare disease. Hypothermia may lead to a favourable outcome in ANEC[10] but more research is needed to proof its benefits.

In conclusion, acute necrotising encephalopathy of childhood is a devastating disease with characteristic clinical features and neuroimaging findings. Early and aggressive therapies in patients with favourable prognostic factors may improve the outcome. The characteristic CT finding of bilateral thalamic hypodensity is valuable in alerting paediatricians to an earlier diagnosis and intervention.

Declaration of Interest

All the authors report no conflicts of interest.

References

1. Yamamoto H, Okumura A, Natsume J, Kojima S, Mizuguchi M. A severity score for acute necrotizing encephalopathy. Brain Dev 2015;37:322-7.
2. Lim HY, Ho VP, Lim TC, Thomas T, Chan DW. Serial outcomes in acute necrotising encephalopathy of childhood: A medium and long term study. Brain Dev 2016;38:928-36.
3. Okumura A, Mizuguchi M, Kidokoro H, et al. Outcome of acute necrotizing encephalopathy in relation to treatment with corticosteroids and gammaglobulin. Brain Dev 2009;31:221-7.
4. Schindler N, Ambegaonkar G. Acute necrotizing encephalopathy of childhood: an uncommon cause of childhood encephalopathy with recognisable clinical and radiological features and genetic predisposition. Arch Dis Child 2017;102:292-3.
5. Voudris KA, Skaardoutsou A, Haronitis I, Vagiakou EA, Zeis PM. Brain MRI findings in influenza A-associated acute necrotizing encephalopathy of childhood. Eur J Paediatr Neurol 2001;5:199-202.
6. Martin A, Reade EP. Acute necrotizing encephalopathy progressing to brain death in a pediatric patient with novel influenza A (H1N1) infection. Clin Infect Dis 2010;50:e50-2.
7. Mizuguchi M, Hayashi M, Nakano I, et al. Concentric structure of thalamic lesions in acute necrotizing encephalopathy. Neuroradiology 2002;44:489-93.
8. Seo HE, Hwang SK, Choe BH, Cho MH, Park SP, Kwon S. Clinical spectrum and prognostic factors of acute necrotizing encephalopathy in children. J Korean Med Sci 2010;25:449-53.
9. Wu X, Wu W, Pan W, Wu L, Liu K, Zhang HL. Acute necrotizing encephalopathy: an underrecognized clinicoradiologic disorder. Mediators Inflamm 2015;2015:792578.
10. Vargas WS, Merchant S, Solomon G. Favorable outcomes in acute necrotizing encephalopathy in a child treated with hypothermia. Pediatr Neurol 2012;46:387-9.