Acute necrotising encephalopathy of childhood: A review of two cases

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SUMMARY
Acute necrotising encephalopathy of childhood (ANEC) is an uncommon disease with characteristic clinical and imaging findings. We present two cases of ANEC secondary to Respiratory Syncytial Virus (RSV) and mycoplasma infections. An eight-month-old boy presented with features of gastroenteritis but soon developed multiple episodes of seizures. Blood and CSF cultures were negative but nasopharyngeal aspirate immunofluorescence was positive for RSV. A nine-year-old girl presented with abnormal behaviour following two days of prodromal symptoms. Her serological markers implicated mycoplasma (IgM titre 1: 640). CT brain of both patients showed bilateral symmetrical thalamic hypodensities, while MRI revealed more extensive white matter involvements.

INTRODUCTION
Acute necrotising encephalopathy of childhood (ANEC) is seen sporadically in the Far East, often with seemingly mild prodromal symptoms followed by a fulminant clinical course. There is no general consensus on the aetiology and pathophysiology of this disease. No specific treatment or preventive method has been identified and a poor prognosis with less than 10% of complete recovery is generally expected.¹ We encountered two cases at our institution involving children of separate age groups with different clinical presentations, isolated causative organisms, and neurological sequelae.

CASE REPORT
CASE 1
An eight-month-old boy presented to a district hospital with two weeks history of cough and runny nose followed by two days of fever, multiple bouts of diarrhoea and vomiting. As he was being treated for acute gastroenteritis, he developed two episodes of tonic seizures. He was then transferred to a tertiary hospital an hour away where he developed generalised a tonic-clonic seizure. On examination, GCS was 6/15. There were hypertonia and hyperreflexia of all limbs. Blood results showed leukopaenia (2.6 – 4.6 x 10⁹/L) and raised C-reactive protein (60.8mg/L). Initial computed tomography (CT) brain showed bilateral symmetrical thalamic hypodensities (Fig 1(A)). Magnetic resonance imaging (MRI) brain revealed more extensive involvements at bilateral caudate nuclei, bilateral thalami, left parieto-occipital lobe, pons and cerebellar white matter (Fig 1(B)). DWI/ADC sequence showed restricted diffusion at all the affected sites. No enhancement seen on post gadolinium images.

He was intubated and received ventilator support for three weeks before weaning to room air. Culture and sensitivity were negative for blood and CSF. CSF was clear and analysis revealed slightly reduced glucose (7.9mmol/L with plasma glucose of 14.9mmol/L) and raised protein (1.44g/L). Nasopharyngeal aspirate immunofluorescence (NPAIF) was positive for Respiratory Syncytial Virus (RSV). He received courses of IV Methylprednisolone, IV immunoglobulin and IV Ribavirin. Upon discharge from the hospital six weeks later, examination revealed head lag, no visual focus, hypertonia and hyperreflexia of bilateral lower limbs with positive clonus. He also had absent swallowing reflex and was prescribed regular nasogastric tube feeding. Follow-up consultation showed persistent developmental delay. MRI brain two months from initial presentation showed generalised cerebral atrophy. Most of the parenchymal lesions had resolved, leaving CSF cavities (Fig 1(C)). Blooming artefacts on GRE within the thalami suggest haemosiderin deposits.

CASE 2
A nine-year-old girl with underlying bronchial asthma presented with acute onset of abnormal behaviour. She had two days history of fever, cough and runny nose preceding the event. On examination, she had poor GCS (10/15), neck stiffness and brisk reflexes. She was also febrile (39.2C) and had tachycardia (124 bpm). Chest and abdominal findings were normal. Immediate laboratory findings revealed mild leukocytosis (13.3 x 10⁹/L) with raised C-reactive protein (93.4mg/L).

CT brain was performed and showed bilateral symmetrical thalamic hypodensities. MRI brain showed symmetrical thalamic T2W hyperintense signals and blooming artefacts on GRE (Fig 2). Restricted diffusion seen on DWI/ADC sequences. Smaller punctate white matter lesions were also seen at bilateral frontal lobes.
Other relevant investigations included negative blood and CSF cultures. CSF viral isolation was negative. CSF analysis showed slightly raised protein of 0.62g/L and normal glucose (3.3 mmol/L compared to plasma glucose of 5.3 mmol/L). Mycoplasma pneumoniae serology was positive (IgM titre 1:640).

She was given supportive care and started on IV Immunoglobulin, IV Methylpredisolone and IV Moxifloxacin. Repeated mycoplasma serology following treatment showed improvement (IgM titre 1:320). Her GCS improved after five days and she remained afebrile since. She was stable upon discharge at day 12 of illness. On clinic follow-up, she was found to have unsteady gait, poor short term memory and behaviour regression to five-six years of age. She could not cope with her normal school lessons and had to be referred for special education.

**DISCUSSION**

Following the constellation of clinical, laboratory and imaging findings, both children were diagnosed to have ANEC. Other conditions causing bilateral thalamic lesions such as extrapontine myelinolysis and acute disseminated encephalomyelitis (ADEM) did not fit the clinical context in both cases.

ANEC is a distinct type of encephalopathy first described in Japan in the 1990s. It had since been discovered in Taiwan, South Korea and to a lesser extent in the United States and Europe. It affects children between five months and 12 years of age.1,5

First reported as a subtype of Reye’s syndrome, it was soon thought to be neurological sequelae from influenza infection. However, other aetiologies have been implicated, namely the...
human herpesvirus-6, measles, herpes simplex, parainfluenza and mycoplasma. Recent studies suggest possible immune-mediated or metabolic causes. To our knowledge, association with the Respiratory Syncytial Virus (RSV) has never been made.

Traditionally, there is a predictable but fulminant clinical course. Onset of encephalopathy is preceded by prodromal illness like upper respiratory tract infection, skin rash or acute gastroenteritis. Convulsions and coma follow after 3-15 days of unresolving prodromes. There will be variable rise in liver enzymes, C-reactive protein and CSF protein but there is usually positive viral or bacterial isolation. Initial reports suggested that death occurs in a third of patients while up to two-thirds of survivors would suffer from residual neurological deficits of varying severity. No specific treatment or preventive method has been identified and a poor prognosis with less than 10% of complete recovery is generally expected. However, a recent Korean study of 14 cases revealed no mortality and more than half of the patients had little or no sequelae. The improved prognosis was later corroborated by analysis of 12 patients in Taiwan. Radiological imaging plays an important role to aid in diagnosis of ANEC. Most distinctive imaging finding would be bilateral, symmetrical abnormalities of the thalami with possible associated brainstem, internal capsule, basal ganglia and cerebellum involvement. Follow-up scans would show near-total resolution of initial abnormalities with haemorrhagic foci, generalised atrophy or localised cystic encephalomalacia. Poorer prognosis is associated with haemorrhage and cavitation.

We have presented two cases of ANEC survivors in different paediatric age groups. Despite avoiding death, both suffered debilitating neurological consequences.

CONCLUSION
Early recognition and diagnosis of this poorly understood but well documented condition will facilitate potential life-saving treatments and supportive therapies.

REFERENCES