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Case Reports

Parainfluenza Infection Associated Acute Necrotising Encephalopathy: Survival Despite Initial Fulminant Neurological Presentation

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Abstract We report a 19-month-old toddler who developed and survived an episode of acute necrotising encephalopathy, as suggested by typical rapidly deteriorating consciousness and seizures (status epilepticus) associated with parainfluenza infection and typical MRI brain features of multiple symmetrical involvement of bilateral thalami, brainstem and periventricular white matter. Despite the initial fulminant course, the child survived with moderate residual neurological deficits. We hope to raise the awareness of this rare presentation of parainfluenza infections and the importance of early aggressive treatment that may substantially improve the previous notoriously high mortality rate or poor neurological outcome.

Key words Acute necrotising encephalopathy; Child; Influenza infection; Parainfluenza infection

Introduction

Acute necrotising encephalopathy (ANE) is a devastating condition affecting infants and children following viral infections. It is characterised by a fulminant clinical course with rapid onset impaired conscious state, convulsions, vomiting and a variable degree of hepatic dysfunction.[1] Multiple symmetrical brain lesions involving thalami, frequently accompanied by brainstem tegmentum, periventricular white matter, putamina and cerebellar medulla are typical MRI findings. Cases are mainly reported in Japan and Taiwan. To our knowledge, there are only two cases of ANE in children, both of which resulted in death, from our locality reported recently in 2007 and 2009 respectively.[2,3] We report a case of ANE associated with parainfluenza infection in a 19 month old boy who was treated aggressively with early intravenous corticosteroid and gammaglobulin and survived. He survived despite initial fulminant neurological presentation and poor prognostic factors. We hope to increase the awareness of this condition as early recognition with aggressive treatment may improve the outcome of this potentially fatal disease.

Case History

A 19-month-old Chinese boy who enjoyed good past health was admitted for two day history of high fever up to 41.5°C. He had no upper respiratory tract symptoms but vomited for four times and became tired on the day of admission. There was otherwise no recent illness in the preceding month. His Glasgow coma scale (GCS) was full on admission. Physical examination was unremarkable without signs of meningism except congested throat. He had repeated vomiting and his condition deteriorated quickly. At 8 hours after admission he was found comatosed with repeated tonic seizure attacks. His GCS dropped to 7/15. He was transferred to Intensive Care Unit for further management. Two doses of intravenous (IV) lorazepam

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followed by IV phenytoin were given for these seizure episodes which subsided around one and a half hour after onset. He was intubated and mechanically ventilated because of the neurological deterioration. Blood pressure, pulse rate and fundi examination did not reveal signs of raised intracranial pressure. Urgent computer tomography (CT) brain scan revealed bilateral thalamic hypodensities without gross cerebral oedema (Figure 1). Liver enzymes were markedly raised with aspartate transaminase 4187 IU/L and alanine transaminase 2289 IU/L but the serum ammonia level remained normal. Clotting profile was mildly deranged with prothrombin time 20.1 seconds (normal range 10-14 seconds), International ratio 1.72 and activated partial thrombin time 43.5 seconds (normal range 22-37 seconds). Glucose, electrolytes, blood gas, complete blood picture and C-reactive protein were normal. Chest radiograph showed no pneumonia. He was given IV cefotaxime and erythromycin for possible bacterial meningitis and/or encephalitis, and IV acyclovir for possible herpes encephalitis. Intravenous immunoglobulin 2 gram per kilogram was given as adjunct treatment for severe sepsis in critically ill patient. Fresh frozen plasma was also given to correct the clotting derangement.

On the second day of admission, his GCS further deteriorated to 4 /15. He developed generalised rigidity and hyper-reflexia. Magnetic resonance imaging (MRI) of the brain 2 days after admission showed hypointense T1/hyperintense T2 signals over bilateral thalami, basal ganglia, midbrain, posterior pons and scattered foci over periventricular white matter. There was no leptomeningeal enhancement, haemorrhage or cavitation on the initial MRI brain (Figure 2). Features were compatible with encephalitis.

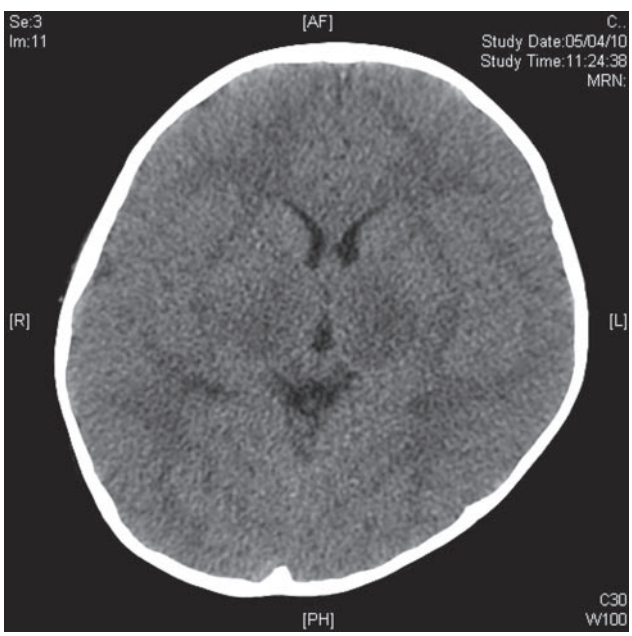
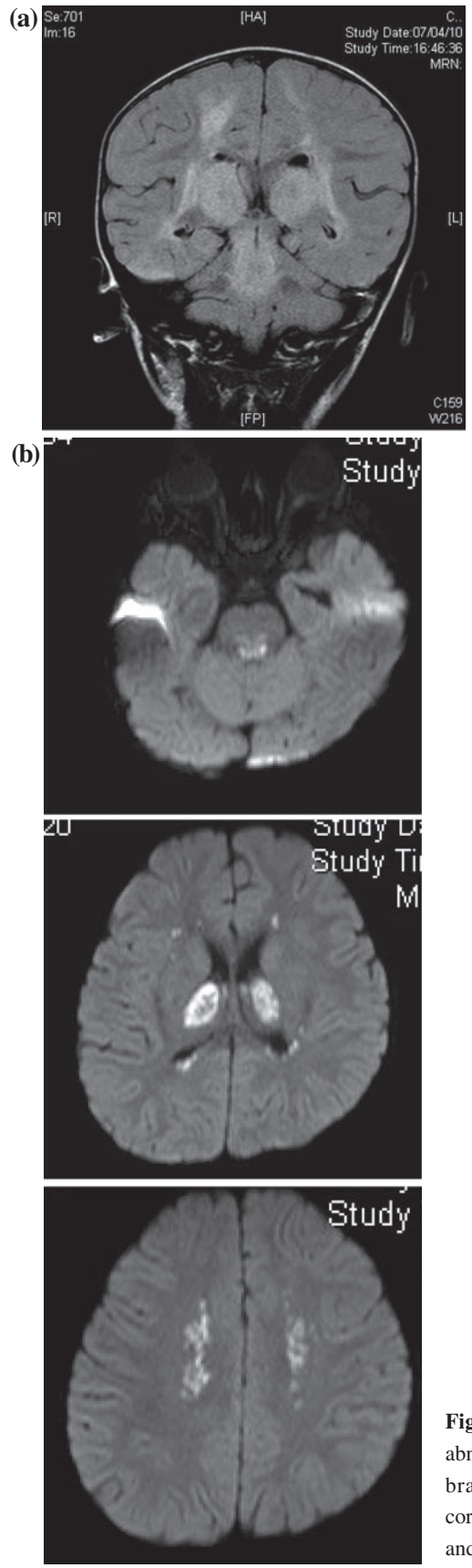


Figure 1 Plain CT brain performed on day 1 of presentation showed hypodense bilateral thalami.

Electroencephalogram (EEG) on the same day showed severe encephalopathic picture with diffuse continuous high amplitude slowing. With the MRI brain and EEG findings that suggested for acute encephalitis and encephalopathy respectively, clinical deterioration despite broad spectrum antibiotics and acyclovir treatment, parainfectious or post infectious encephalitis/encephalopathy were considered, IV dexamethasone 1.5 mg/kg/day was added. It was given for 5 days and then was tailed off. In view of the markedly deranged liver function, phenytoin was stopped and substituted by oral levetirecetam. There were episodes of limb dystonia without concurrent ictal changes on continuous video EEG monitoring. Lumbar puncture was done on day 5 of admission when patient's condition became more stable. The cerebrospinal fluid (CSF) examination showed no white blood cell on microscopy, mildly raised protein level 0.71 g/L (normal range 0.15-0.45 g/L) and normal glucose level. CSF polymerase chain reaction (PCR) for herpes simplex virus, enterovirus and Japanese B virus were all negative. Nasopharyngeal aspirate (NPA) taken on day of admission for viral immuno-fluorescent test returned positive for parainfluenza virus which was confirmed by simultaneous viral culture that yielded parainfluenza type 3. Viral cultures from stool and rectal swab were negative. Tests for Epstein Barr Virus immunoglobulin M (IgM) and mycoplasma titre were negative. Paired blood titers for viruses including other respiratory viruses and Japanese B encephalitis virus showed no significant rise. Blood, CSF and urine bacterial cultures were negative. Toxicology screen, including salicylate, was negative. Work up for inborn error of metabolism included blood for lactate, pyruvate, free fatty acids, amino acid profile, carnitine and urine for metabolic screen all showed no significant results.

He developed borderline low blood pressure on day 5, a result of blood loss into right haemothorax as a complication of subclavian central line insertion. His blood pressure responded promptly to a normal saline bolus followed by packed cell transfusion. No inotropic support was required. Subsequently, patient showed gradual improvement with GCS gradually increased to between 7-10/15 over the next 2 days. Patient was extubated on day 8 as the GCS improved to 11/15. The liver dysfunction also gradually recovered.



At this juncture, patient showed generalised rigidity, dystonia and hyperreflexia. His muscle power was MRC grade 2-3/5. There was also right VII nerve palsy. There was no speech, visual fixation or follow or social response with his relatives. He showed no sucking or swallowing.

Neuro-rehabilitation was commenced. Repeat EEG on day 12 showed improved background with less high amplitude slowing but still slower background than normal and no reactive changes were seen. There was no epileptiform discharge noted. Anticonvulsant was taken off on day 13 as there were no more seizures. Sensory evoked potential (SEP) on median nerve done on day 10 showed presence of response at Erb's points and cervical level but absence at cortical level suggesting a block at brainstem level. Visual evoked potential and brainstem auditory evoked potential showed normal results. Over the next few weeks, he showed continued improvement with return of visual fixation, social smile, and subsequently return of verbal comprehension and simple command follow. Motor improvement was also noted with decrease in dystonia and rigidity, resolution of right VII nerve palsy and improved muscle power to MRC grade 3-4/5 although he remained non-mobile.

A repeat MRI brain at 6 weeks showed residual abnormal T2/FLAIR hyperintensities in bilateral frontal and parietal white matter and cystic changes over posterior pons and right centrum semiovale. There were abnormal T1 hyperintense/T2 isointense signals over bilateral thalami representing subacute haematomata or early microcalcifications (Figure 3). No leptomeningeal enhancement or cavitation was seen.

Patient was discharged for continued rehabilitation. In the mean time, patient also received Chinese alternative medicine (herbal tea and acupuncture) and hyperbaric oxygen therapy arranged by parents.

His oral feeding ability improved and was able to completely oral feed by 9 weeks. He was last assessed at 31 month old, 12 months post illness. He could walk with K walker. The muscle power was MRC grade 4/5 and there was mild hypertonia with hyperreflexia. Limited horizontal eye movements and intermittent vertical downward

Figure 2 (a) Initial MRI performed on day 3. Coronal FLAIR image demonstrated abnormal hyperintense T2 signal in periventricular white matter, bilateral thalami and brainstem. (b) Diffusion weighted images showed restricted diffusion in the corresponding areas in the posterior pons, bilateral thalami, periventricular white matter and centrum semi ovale.

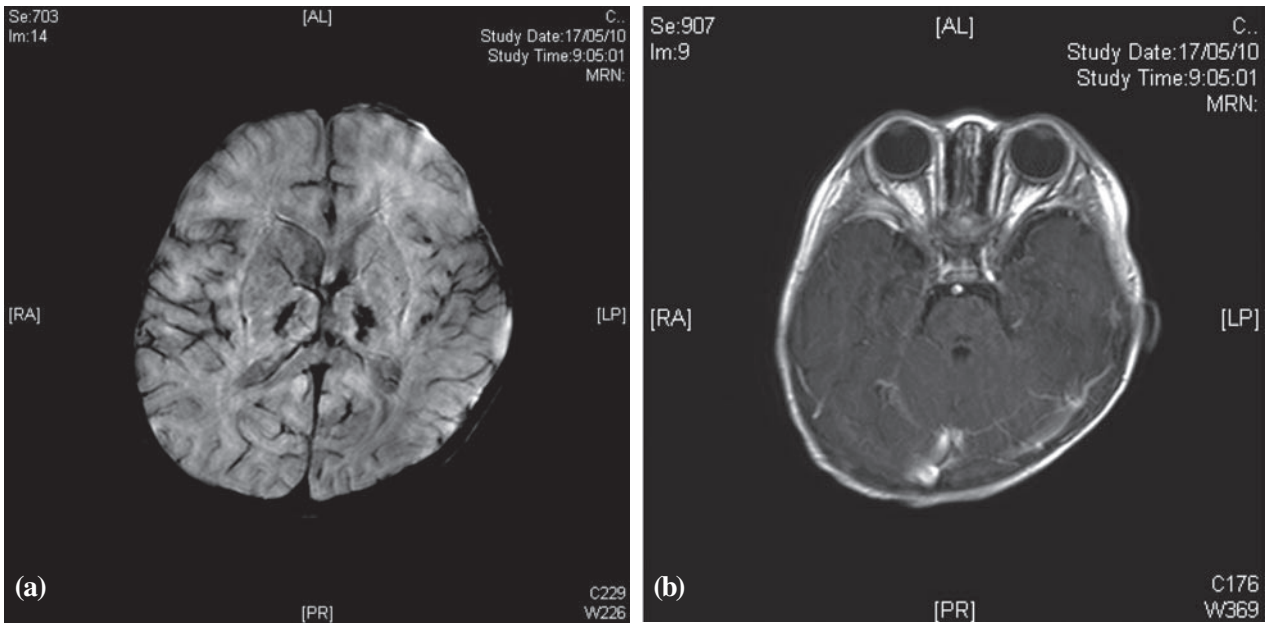


Figure 3 (a) MRI performed on day 42: Susceptibility artefacts on susceptibility-weighted sequence suggest presence of subacute haematomata or early microcalcification at the thalami. (b) Post-contrast T1-weighted image showed non-enhancing hypointense foci at the posterior pons, corresponding areas appear hyperintense on T2-weighted images and hypointense on FLAIR sequence, compatible with cystic changes.

nystagmus were noted but he showed good visual fixation. He demonstrated pincer grasp and could put spoon with food into mouth. He communicated using single words (~10 single words so far) and could identify 20 body parts and common objects.

Discussion

Acute necrotising encephalopathy (ANE) was first described by Mizuguchi et al in 1995.[1] It is a specific type of acute monophasic encephalopathy characterised by bilateral symmetrical lesions predominantly observed in thalami and brain stem. It affects children of both sexes from the age of 5 months to 11 years, typically <5 years in most published cases.[4] Majority of the cases occur in Asia, mainly Japan and Taiwan[5] and so far over 240 cases have been reported in Asia. There are far less cases reported in Europe and North American. The exact incidence of ANE remains unknown.[6]

It typically presents in previously healthy children 2-4 days (range from 1-15 days), after onset of viral infections. The children have high fever and repeated vomiting followed by rapidly deteriorating course with seizures and impairment of consciousness. Delirious behavior is sometimes seen during the early stage of disease. Coma can occur within 24 hours of presentation while seizures can become intractable.[1,5,7-9] Abnormal physical findings include decorticate or decerebrate postures, long tract signs, deep tendon hypereflexia, babinski sign, instant miosis and papilloedema while meningeal signs and abnormal involuntary movements are usually not seen.[10] Our case shared the typical clinical presentations with 2 day history of viral illness with high fever, vomiting followed by sudden deterioration to impairment of consciousness and repeated seizures in a typically aged patient There are case reports of milder atypical ANE cases.[11] As stated before, most cases (90%) are linked to preceding infections[5] e.g. upper respiratory tract infections and gastroenteritis, with influenza A (H3N2) and influenza B as the most common viral causes. Influenza A accounts up to 24% of the reported cases.[11] Other less common infective causes reported include human herpes virus 6 and 7, herpes simplex virus, parainfluenza, varicella zoster, rubella, measles and mycoplasma infection.[5] With such link to viral infections, most cases of ANE occur in the winter time. In our case, parainfluenza virus was yielded from NPA. Although the child did not have typical upper respiratory tract symptoms of cough and runny nose, the presence of high fever, vomiting and congested throat without other recent illness

in the preceding month suggested an acute parainfluenza infection and hence we suggested the association of ANE with parainfluenza infection in this case.

Laboratory findings in ANE are non specific. There is variable degree of elevation of serum aminotransferases level, from mild to up to >7000 IU/L in some reported cases.[7] The serum ammonia level is normal and there is no hypoglycemia. Thrombocytopenia, haematological pictures resembling disseminated intravascular coagulopathy, metabolic acidosis, hypoproteinemia, raised serum creatinine kinase and urea are possible laboratory findings.[10,12] CSF commonly show increased protein level but no pleocytosis.[1,5] EEG show generalised diffuse slow wave activity in acute stage.

Imaging studies provide the hallmark features of this encephalopathy which is multifocal, symmetric brain lesions affecting bilateral thalami, brainstem tegmentum, periventricular white matter, putamina and cerebellum.[13] Thalami involvement is presumably present in all cases.[1,14] In the acute stage, CT scans show low attenuation in these areas while MRI lesions are characterised by prolonged T2 and T1 relaxation times. Contrast enhanced T1-weighted images show mild contrast enhancement usually in the margin of bilateral thalami and in some cases around the pontine tegmenta, the deep cerebral and cerebellar white matter.[5,10] CT images may be normal in the very early phase of ANE[15] but CT and MRI usually demonstrate the lesions within 2 days after the onset. Diffusion weighted MRI may enhance the sensitivity in the very early phase or in mild ANE cases[9] while diffusion tensor MRI, an emerging new technique, may even be more sensitive than diffusion weighted one.[16] Over the first few weeks, lesions often show shortening of both the T1 and T2 signal on MRI images representing petechial haemorrhage[17] which may progress later to atrophy and cystic encephalomalacia over time. Complete resolution of MRI lesions can occur in mild atypical cases.[8]

Autopsy findings show symmetrical multifocal necrotic brain lesions in areas detected on imaging as mentioned above. The involved areas show oedema and congestion without direct viral invasion or parainfectious demyelination. There is evidence of local break down of blood brain barrier without necrosis of blood vessels.[1,17] Microscopic examination show necrotic neurons and glial cells with perivascular petechial haemorrhage and swelling of oligodendrocytes. There is little inflammatory reaction and meninges are free from inflammation.[17]

Diagnosis is based on the typical clinical presentation and characteristic neuroimaging findings. Mizuguchi et al who first described this disease entity proposed the diagnostic criteria as: (1) acute non-inflammatory encephalopathy with alteration in level of consciousness with CSF leukocyte count less than or equal to 8/mm^3 (2) demonstration of multi-focal symmetrical lesions including the thalami on CT images (3) absence of any other reasonable explanation for the cerebral abnormalities.[1] Clinical differential diagnoses include encephalitis, toxic shock syndrome, haemolytic uremic syndrome, Reye syndrome, haemorrhagic shock encephalopathy syndrome and heat stroke. Radiological or pathological differential diagnoses include Leigh encephalopathy, glutaric academia, methyl malonic aciduria, infantile bilateral strial necrosis, carbon monoxide poisoning, viral encephalitis, acute disseminated encephalomyelitis, acute haemorrhagic leukoencephalitis, arterial or venous infarct.[8] Our case showed the typical presentation of very rapid neurological deterioration 2 days after onset of febrile illness with characteristic imaging findings of symmetrical brain lesions over bilateral thalami and brainstem. The absence of CSF pleocytosis, mildly raised CSF protein, elevated serum aminotransferases, thrombocytopenia and documented parainfluenza infection supported the diagnosis. Though clinically differentiation may be difficult, the absence of CSF pleocytosis, normal CRP makes viral encephalitis less likely. Japanese B encephalitis, one of our initial differential diagnoses, may have similar MRI brain appearance. However the lack of CSF pleocytosis, the brainstem involvement and symmetrical thalami appearance on MRI brain render this diagnosis less likely. This diagnosis was also later ruled out by the negative serology. Reyes syndrome was ruled out at a very early stage because of lack of hypoglycemia or hyperammonemia despite raised serum aminotransferases. Leigh disease was unlikely also with the absence of lactic acidosis. The lack of significant shock and haemorrhage makes haemorrhaghic shock and encephalopathy unlikely.

The exact pathogenesis of ANE is unknown but it is increasingly believed to be due to cytokine storms induced by viruses especially the influenza viruses, which usually occur within 24 to 48 hours. It accounts for the short interval between the ANE presentation and the onset of viral infection. Interleukin 6 and tumor necrosis factor alpha are found markedly elevation in serum and CSF of ANE cases that support the cytokine storm theory.[18,19] This result in neurotoxicity and breakdown of blood brain barrier causing oedema, congestion and haemorrhage which may account for part of the disease process in ANE.[12] However, the basis for the predilection to involve the thalamus, brainstem and

cerebellum and the genetic or epigenetic factors that predispose Asian especially the Japanese and Taiwanese to ANE remains unknown.[10,12] Recurrent and familial ANE cases linked to RANBP2 gene mutations have been reported but these mutations are not documented in sporadic or isolated ANE cases.[20]

There is no specific treatment to ANE. Early use of high dose corticosteroid (e.g. iv methylprednisolone 30 mg/kg for 3 days or iv dexamethasone 0.6 mg/kg for 2-4 days given within 24 hours after the onset of ANE) was shown to improve outcome in those without brainstem lesions in a recent study. Outcome of those with brainstem lesion had been reported to be poor by Mizuguchi. Okumura demonstrated that there was no difference in outcome regardless of the time of steroid use in this group.[21] Other treatment strategies were mainly experience from case reports and include antiviral therapy, large dose intravenous gammaglobulin, antiviral therapy, anticytokine therapy, plasmapheresis, hypothermia, carnitine, coenzyme Q10 and pyridoxine but their success was uncertain. With use of active treatment like steroid and advancement in intensive supportive care, there was an overall improvement in the ANE mortality rate.[6] Prognosis of ANE was generally grave in the past with 70% dying within a few days from onset of fever.[10] Mortality improved to around 30% in 1990s[1,5] and further improve to 15% recently.[6] In surviving cases, recovery may begin around the sixth to the tenth day and neurological functions continue to improve for several months.[1] Most cases are left with variable degree of neurological deficits and only infrequent cases <10% show complete recovery.[22] Poor prognostic factors include age less than 2 years, high serum aminotransferases level, high CSF protein and brainstem involvement.[5,11,17,21] In our case, intravenous gammaglobulin was given on the first day after acute deterioration as adjunct treatment in critically ill patient with sepsis and steroid on the third day of acute deterioration (the 5th day from onset of fever and illness). Recovery was noted since the fifth day of acute deterioration despite the initial rapid neurological deterioration to comatose state. Continuous clinical improvement was noticed despite he had all the poor prognostic factors of young age, high serum aminotransferases level, high CSF protein and brainstem involvement. We do not know about the role of alternative medicine namely acupuncture and hyperbaric oxygen in this case, but our case might demonstrate the potential benefit of high dose steroids and intravenous gammaglobulin in improving the outcome of this devastating disease. In Okumura[21] study, steroid was demonstrated to improve the outcome when given within 24 hours from onset to those ANE cases without brainstem improvement but not to those with brainstem involvement. In their study, the outcome was poor in 15 out of the 17 cases of ANE with brainstem involvement. However, practically it can be difficult to administer steroid within 24 hours from onset of ANE as many important investigation results e.g. CSF results, imaging especially MRI may not be readily available within 24 hours and steroid treatment could be dangerous in patient who are immuncompromised and in those with disseminated infections especially fungal ones. Nevertheless, ANE should be suspected early when children, especially <5 years old, with high fever, coryzal symptoms and vomiting presented with sudden neurological deterioration and CT brain (which are usually readily available) showed symmetrical signal changes over bilateral thalami. It is worth considering steroid as adjunct treatment early especially in desperate situation and even it is given greater than 24 hours later from onset of ANE.

In conclusion, acute necrotising encephalopathy has its characteristic clinical and neuroimaging features. Because of the potential benefit of early steroid use in this rare but devastating condition, early recognition and early consideration of use of steroid and aggressive intensive supportive care is important for optimal outcome.

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