CASE REPORT

Acute necrotising encephalopathy in a child with H1N1 influenza infection: a clinicoradiological diagnosis and follow-up

Sangeetha Yoganathan,¹ Sniya Valsa Sudhakar,² Ebor Jacob James,³ Maya Mary Thomas¹

¹Department of Neurological Sciences, Christian Medical College, Vellore, Tamilnadu, India

²Department of Radiodiagnosis, Christian Medical College, Vellore, Tamil Nadu, India

³Department of Pediatrics, Christian Medical College, Vellore, Tamilnadu, India

Correspondence to
Professor Maya Mary Thomas,
maya@cmcvellore.ac.in

Accepted 6 December 2015

SUMMARY

Acute necrotising encephalopathy of childhood (ANEC) is a fulminant disorder with rapid progressive encephalopathy, seizures and poor outcome. It has been reported in association with various viral infections. We describe the clinicoradiological findings and short-term follow-up in a child with H1N1 influenza-associated ANEC. Laminar, target or tricolour pattern of involvement of the thalami was seen on apparent diffusion coefficient images. Our patient had significant morbidity at discharge despite early diagnosis and management with oseltamivir and immunoglobulin. Repeat imaging after 3 months had shown significant resolution of thalamic swelling, but there was persistence of cytotoxic oedema involving bilateral thalami. She was pulsed with intravenous steroids and maintained on a tapering schedule of oral steroids. This report emphasises the need for a high index of suspicion to establish early diagnosis, promotion of widespread immunisation strategies to prevent influenza outbreak, and more research to establish standard treatment protocols for this under-recognised entity.

BACKGROUND

The incidence of severe influenza-associated neurological complications was estimated to be 1.2 per 100 000 persons ill with H1N1 during the 2009 outbreak and high frequency was observed among children and Asian Pacific patients.¹ A large national-based study found that less than 10% of children with influenza infection had neurological complications such as febrile seizures, encephalopathy, encephalitis or acute necrotising encephalopathy of childhood (ANEC).² Other reported complications were myositis, Guillain-Barre syndrome and Reye's syndrome.³

ANEC is an under-recognised neurological complication that can occur in influenza infection. It is a rare fulminant disorder with rapid progressive encephalopathy resulting in altered mental status, seizures and poor outcome. Less than five cases of ANEC were reported from the Indian subcontinent and less than 250 cases have been reported from Asia.^{4–7} In contrast, a 2-year surveillance study from Britain identified 4 cases of ANEC among 25 patients with influenza-associated neurological manifestations. Although the incidence of ANEC reported in this study was 15%, there were only four cases diagnosed in the 2-year surveillance period, implying the rareness of the entity. All four

patients had H1N1 influenza virus infection and neurological complications were reportedly more common in influenza A than B viruses.⁸ We describe the clinical presentation, laminar pattern of thalamic involvement in the neuroimaging and short-term follow-up in a child with H1N1 influenza-associated ANEC.

CASE PRESENTATION

A girl aged 4½ years was born first in birth order to a non-consanguineously married couple and her premorbid development was normal. She had not been immunised with influenza vaccine. She presented with a history of cough and coryza for 4 days and fever for 2 days. She had one episode of upward gaze on the second day of febrile illness followed by an altered sensorium and a progressive drop in the sensorium. There was no family history of encephalopathy or seizures. There was no history of recent travel, but there was an outbreak of influenza A infection during the same period.

Anthropometric assessment was normal. She was unresponsive with decorticate posturing and her Glasgow coma score (GCS) was 5/15. Doll's eye response was present. Bilateral pupils were constricted and reacting to light. The fundus was normal and there was no facial weakness. The tone was increased in all limbs and deep tendon reflexes were depressed. Bilateral plantar responses were extensor. Signs of meningeal irritation were absent. The airway was intubated in the emergency room due to the poor sensorium.

INVESTIGATIONS

CT of the brain had revealed a marked symmetrical swelling and hypodensity of the thalami and dorsal pons (figure 1A, B). MRI of the brain (figure 2A, H) had confirmed the thalamic and dorsal pontine involvement with symmetric swelling and heterogeneous signal changes. Diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) images (figure 2B–D) showed the characteristic tricolour or target pattern in thalami with a central intermediate signal, a middle layer of intense restricted diffusion of cytotoxic oedema and a peripheral layer of hyperintense signal suggesting vasogenic oedema. Restricted diffusion and long repetition time (TR) hyperintensity were also seen involving the caudate nuclei, posterior putamen, hippocampi and amygdala in symmetric distribution (figure 2A, B, G, H). Susceptibility-weighted images

CrossMark

To cite: Yoganathan S, Sudhakar SV, James EJ, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-213429

Figure 1 CT axial images at initial presentation (A and B) showing marked symmetrical thalamic swelling (white arrow) and hypodensity and dorsal pontine hypodensity (black arrow). Repeat CT after 2 weeks (C) showing reduction of thalamic swelling with persistent peripherally enhancing hypodensity (white arrow).

(SWI) had shown bilateral symmetric blooming of the thalami suggesting haemorrhagic foci (figure 2E) and blooming was also seen in the dorsal pons. Vermis and deep cerebellar white matter were involved with long TR hyperintensity. No abnormal enhancement was seen in these involved areas (figure 2F). MR spectroscopy (MRS) had shown a large lactate peak in the thalamus (figure 3).

Blood counts, liver function, renal function and coagulation parameters were normal. Screening for an inborn error of metabolism was negative. The nasopharyngeal swab for influenza virus (H1N1) was positive. Cerebrospinal fluid (CSF) analysis revealed 5 cells, and glucose of 53 mg/dL, protein of 152.4 mg/dL, lactate of 1.2 mmol/L and PCR for herpes simplex virus, adenovirus, enterovirus, human herpes virus-6, cytomegalovirus,

Epstein-Barr virus and Japanese encephalitis were negative. The blood-borne virus screen was negative. CSF and blood serology for Japanese encephalitis were negative. CSF serology or PCR for the influenza virus was not performed due to the lack of facilities for testing at our centre. Testing for RANBP2 mutational analysis of two exons (exons 12 and 14 transcript ID-ENS00000283195) where common disease-causing variants like p.T585M, p.T653I and p.I656V are clustered was performed and the proband did not have any disease-causing variants.

DIFFERENTIAL DIAGNOSIS

On the basis of the clinical, radiological and laboratory features, a diagnosis of ANEC was established and other differentials to be considered are internal cerebral vein thrombosis, Reye's

Figure 2 MRI of the brain showing thalamic swelling and hyperintensity (red arrow in A) and haemorrhage (SWI, red arrow in E). DWI and ADC images (B and C) showing restricted diffusion with the target pattern illustrated in overlay (D). No contrast enhancement is seen (F). Also note the symmetrical putamen hyperintensity and restriction (black arrow in A and B) and caudate restriction (white arrow in B). DWI (G) image showing symmetric restriction of the hippocampi, amygdala (white arrow in G) and dorsal pons (black arrow in G). FLAIR image (H) showing hyperintensity of the dorsal pons (black arrow) and vermis (white arrow in H). ADC, apparent diffusion coefficient; DWI, Diffusion-weighted images; FLAIR, fluid-attenuated inversion recovery; SWI, susceptibility-weighted images.

Figure 3 MRS of the brain in the acute phase showing lactate peak at 1.3 parts per million (ppm).

syndrome, vascular occlusion, tumour, haemorrhage of the thalamus, Leigh disease, organic aciduria, acute haemorrhagic leucoencephalitis, acute disseminated encephalomyelitis (ADEM), osmotic myelinolysis, Wernicke encephalopathies, hypoxic or traumatic brain injury.

TREATMENT, OUTCOME AND FOLLOW-UP

The child was initiated on intravenous immunoglobulins (IVIG) from day 2 of admission and had received IVIG 400 mg/kg/day for 5 days. In addition, she was treated with oseltamivir for 5 days and also acyclovir till CSF was proven negative for herpes encephalitis. She was loaded and maintained with phenytoin for seizure control. She was weaned off from the ventilator after 15 days and was in a vegetative state at the time of discharge. Neurorehabilitation measures were initiated and nutrition was maintained through nasogastric feeding. Repeat CT after 2 weeks (1 C) had shown a reduction of thalamic swelling with persistent peripherally enhancing hypodensity.

During follow-up at 3 months, she had an appropriate emotional response and was responding to her mother's call. Bilateral ptosis, restriction of horizontal gaze and bifacial weakness were observed. Pupillary reflexes were normal. Spasticity had reduced and she had mild generalised dystonia with distal athetoid movements. She was fully dependent for all activities of daily living.

Repeat MRI of the brain (figure 4A, F) after 3 months had shown significant resolution of the swelling and signal changes. Thalami showed central and medial hyperintensity with small areas of persistent restricted diffusion (figure 4B). Disappearance of the diffusion restriction was observed in the bilateral hippocampi and caudate regions. The post contrast study showed intense symmetric irregular areas of enhancement (figure 4E). T1 image (figure 4D) showed an intermediate signal in some areas suggesting a possible subacute stage of haemorrhage, but the enhancement and restricted diffusion was not confined to these areas, thus suggesting possible persistent inflammation. Signal changes were also seen in the dorsal pons (figure 4F) and posterior putamen (figure 4E). SWI (figure 4C) had shown a significant interval reduction of blooming and mild hypointensity of the thalami.

The visual evoked potential was normal. Brainstem evoked response revealed peripheral pathway dysfunction. Somatosensory evoked potential of tibial nerves was suggestive

of dorsal column dysfunction. Nerve conduction parameters were normal. She was given a pulse of intravenous methylprednisolone 30 mg/kg/day for 5 days in view of persistent cytotoxic oedema involving bilateral thalami followed by a tapering schedule of oral steroids. Neurorehabilitation measures were continued.

DISCUSSION

ANEC is a rare neurological entity characterised by bilateral thalamic necrosis and most cases are reported from East Asia.⁹ It occurs sporadically in previously healthy infants and children less than 11 years of age.¹⁰ Recurrences have been reported in children with mutations in RAN-binding protein two gene.¹¹ ANEC has been reported following infection with herpes simplex, human herpes virus, influenza A virus, influenza B virus, parainfluenza virus, varicella zoster, reovirus, rotavirus, enterovirus, measles, coxsackie A9 and mycoplasma.¹²

Criteria proposed by Mizuguchi for the diagnosis of typical ANEC are acute onset encephalopathy following a viral illness with rapid neurological deterioration, increased CSF protein without pleocytosis, neuroimaging findings of bilateral symmetrical involvement of the thalami, putamen, internal capsule, brainstem, cerebellum and periventricular white matter, elevation of serum transaminases, normal blood ammonia and exclusion of other bacterial or viral infections, Leigh disease, Reye's syndrome, ADEM and vasculitis.⁹ Our case qualified all the criteria except the presence of elevated transaminases.

Neurological manifestations in children and adults with influenza result from a cytokine storm, adaptive cell-mediated immune responses or unknown pathophysiology. It is speculated that following a viral infection, there is an increase in the inflammatory mediators such as interleukin-1, interleukin-6 and tumour necrosis factor α .¹³ A cytokine storm following viral infection leading to systemic immune response could possibly explain the pathogenesis and clinical presentation in patients with ANEC.^{12 14} Although CSF PCR for H1N1 influenza was not performed in our case, a previous observation of rare isolation of the influenza virus from CSF has supported the hypothesis that ANEC reflects a cytokine storm mediated central nervous system injury.¹⁵ Acute onset manifestations are febrile seizures, movement disorder, benign encephalopathy, mild encephalopathy with reversible splenic lesions, acute encephalopathy syndromes, acute encephalopathy with biphasic seizures

Figure 4 Follow-up MRI after 3 months showing resolution of thalamic swelling with persistent hyperintensity (white arrow in A) and small focus of restricted diffusion (white arrow in B). SWI (white arrow in C) shows mild hypointensity. Comparison of precontrast T1 (D) with postcontrast T1 (E) image depicts intense heterogeneous enhancement. Small non-enhancing hypointense focus is seen in the left posterior putamen (black arrow). T2 axial image (F) shows resolution of swelling with persistent hyperintensity of the dorsal pons (black arrow). SWI, susceptibility-weighted images.

and late reduced diffusion, acute infantile encephalopathy predominantly affecting the frontal lobes, acute shock with encephalopathy and multiorgan failure and acute haemorrhagic leucoencephalopathy. Subacute onset manifestations are Guillain-Barre syndrome, transverse myelitis, ADEM, cerebellitis and myositis. Late onset manifestations are parkinsonism and encephalitis lethargica. Comparison of patients with the 2004–2008 seasonal influenza and the 2009 pandemic H1N1 influenza had shown the heightening of neurological complications such as encephalopathy, focal deficits and electrographic abnormalities in the latter.¹⁶

MRI findings described in the acute phase of patients with influenza-associated encephalopathy were diffuse cerebral oedema, signal changes in the deep grey nuclei, splenium, subcortical white matter and cortical grey matter.¹⁷ Classical neuroimaging findings described in ANEC include bilateral symmetrical involvement of the thalami, putamen, internal capsule, brainstem, cerebellum and periventricular white matter.⁹ Our patient had the above described classical imaging findings and MRS performed in the acute phase showed a lactate peak in our case, which is in concordance with other reports, although the elevated glutamate/glutamine peak reported previously in ANEC was not observed in our patient.^{18 19} An elevation of lipids was proposed to result from cell membrane damage or disintegration and elevated glutamate would result from an increase in excitatory neurotransmitters. Although our patient had an elevated lactate peak, her acylcarnitine profile was normal and CSF lactate was not elevated, and therefore genetic studies for mitochondrial cytopathies were not pursued. Laminar, target or tricolour

pattern of involvement of the thalami is typically seen most obviously on ADC images.²⁰ Central haemorrhage and necrosis, surrounding cytotoxic oedema and vascular congestion and peripheral vasogenic oedema forms the pathological basis for this appearance. A composite scoring system was devised for patients with ANEC by Wong *et al*²¹ who observed a positive correlation between the MRI brain findings and clinical outcome. Follow-up imaging in the survivors had shown significant regression of lesions with residual changes like cortical atrophy, cystic changes and haemosiderin deposition.¹² Follow-up imaging in our patient had shown significant resolution of signal abnormalities with persistent cytotoxic oedema in the bilateral thalami and previous reports have rarely described persistent inflammation in the follow-up imaging, which might explain the incomplete recovery.

There are no standard guidelines for the management of ANEC. Treatment of ANEC with antiviral drugs, immunoglobulin, methylprednisolone, dexamethasone, plasmapheresis, antithrombin III and therapeutic hypothermia has been tried.^{12 22} Our patient was treated with supportive measures, mechanical ventilation, IVIG in the acute phase and oseltamivir for influenza A infection. The role of steroid therapy in ANEC is controversial. Steroid was deferred in the acute phase in our case due to active influenza virus infection and nosocomial sepsis. It was added up later in view of the persistent cytotoxic oedema in the follow-up imaging.

There is a high incidence of mortality and morbidity in patients with ANEC and complete recovery was documented in less than 10%.²³ Functional recovery following rehabilitation had been reported in the literature and time for recovery was

variable. Significant neurological morbidity despite early diagnosis and management enlightens the need for more research to elucidate the pathophysiology and establishment of better treatment protocols. Influenza is a vaccine preventable disease and widespread immunisation strategies should be promoted in South East Asian countries, although the role of vaccine in protection against ANEC needs to be explored.

Learning points

- ▶ Acute necrotising encephalopathy of childhood (ANEC) is a rare under-recognised parainfectious disorder associated with influenza virus infection.
- ▶ Bilateral symmetrical involvement of the thalami, putamen, internal capsule, brainstem, cerebellum and periventricular white matter in a child with acute encephalopathy should raise suspicion for ANEC.
- ▶ Laminar, target or tricolour pattern of involvement of the thalami is typically seen most obviously on apparent diffusion coefficient images.
- ▶ Immunotherapy may be beneficial as a cytokine storm following a virus infection is the underpinned pathophysiology.
- ▶ Influenza is a vaccine preventable disease and widespread immunisation strategies should be promoted in South East Asian countries.

Acknowledgements The authors acknowledge Sathish Kumar from the Department of Paediatrics who helped in the clinical care of the patient and Gautham Arunachal from the Department of Medical Genetics who helped in the molecular diagnostics.

Contributors SY and EJ provided clinical care to the patient. SY and SS prepared the initial manuscript. EJ revised the manuscript. MMT critically reviewed the manuscript and supervised the patient care. All authors approved the final manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Glaser CA, Winter K, DuBray K, *et al.* A population-based study of neurologic manifestations of severe influenza A(H1N1)pdm09 in California. *Clin Infect Dis* 2012;55:514–20.
- 2 Muhammad Ismail HI, Teh CM, Lee YL, National Paediatric H1N1 Study Group. Neurologic manifestations and complications of pandemic influenza A H1N1 in Malaysian children: what have we learnt from the ordeal? *Brain Dev* 2015;37:120–9.
- 3 Davis LE, Koster F, Cawthon A. Neurologic aspects of influenza viruses. *Handb Clin Neurol* 2014;123:619–45.
- 4 Yadav S, Das CJ, Kumar V, *et al.* Acute necrotizing encephalopathy. *Indian J Pediatr* 2010;77:307–9.
- 5 Kulkarni R, Kinikar A. Encephalitis in a child with H1N1 infection: first case report from India. *J Pediatr Neurosci* 2010;5:157–9.
- 6 Narra R, Mandapalli A, Kamaraju SK. Acute necrotizing encephalopathy in an adult. *J Clin Imaging Sci* 2015;5:20.
- 7 Mastroyianni SD, Gionnis D, Voudris K, *et al.* Acute necrotizing encephalopathy of childhood in non-Asian patients: report of three cases and literature review. *J Child Neurol* 2006;21:872–9.
- 8 Goenka A, Michael BD, Ledger E, *et al.* Neurological manifestations of influenza infection in children and adults: results of a National British Surveillance Study. *Clin Infect Dis* 2014;58:775–84.
- 9 Mizuguchi M. Acute necrotizing encephalopathy of childhood: a novel form of acute encephalopathy prevalent in Japan and Taiwan. *Brain Dev* 1997;19:81–92.
- 10 Marco EJ, Anderson JE, Neilson DE, *et al.* Acute necrotizing encephalopathy in 3 brothers. *Pediatrics* 2010;125:e693–8.
- 11 Neilson DE, Adams MD, Orr CM, *et al.* Infection-triggered familial or recurrent cases of acute necrotizing encephalopathy caused by mutations in a component of the nuclear pore, RANBP2. *Am J Hum Genet* 2009;84:44–51.
- 12 Wu X, Wu W, Pan W, *et al.* Acute necrotizing encephalopathy an under recognized clinicoradiologic disorder. *Mediators Inflamm* 2015;2015:79257.
- 13 Ichiyama T, Isumi H, Ozawa H, *et al.* Cerebrospinal fluid and serum levels of cytokines and soluble tumor necrosis factor receptor in influenza virus-associated encephalopathy. *Scand J Infect Dis* 2003;35:59–61.
- 14 Kansagra SM, Gallentine WB. Cytokine storm of acute necrotizing encephalopathy. *Pediatr Neurol* 2011;45:400–2.
- 15 Akins PT, Belko J, Uyeki TM, *et al.* H1N1 encephalitis with malignant edema and review of neurologic complications from influenza. *Neurocrit Care* 2010;13:396–406.
- 16 Ekstrand JJ, Herbener A, Rawlings J, *et al.* Heightened neurologic complications in children with pandemic H1N1 influenza. *Ann Neurol* 2010;68:762–6.
- 17 Ishida Y, Kawashima H, Morichi S, *et al.* Brain magnetic resonance imaging in acute phase of pandemic influenza A (H1N1) 2009—associated encephalopathy in children. *Neuropediatrics* 2015;46:20–5.
- 18 Aydin H, Ozgul E, Agildere AM. Acute necrotizing encephalopathy secondary to diphtheria, tetanus toxoid and whole-cell pertussis vaccination: diffusion-weighted imaging and proton MR spectroscopy findings. *Pediatr Radiol* 2010;40:1281–4.
- 19 Goo HW, Choi CG, Yoon CH, *et al.* Acute necrotizing encephalopathy: diffusion MR imaging and localized proton MR spectroscopic findings in two infants. *Korean J Radiol* 2003;4:61–5.
- 20 Albayram S, Bilgi Z, Sencuk H, *et al.* Diffusion-weighted MR imaging findings of acute necrotizing encephalopathy. *AJNR Am J Neuroradiol* 2004;25:792–7.
- 21 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.
- 22 Yamamoto H, Okumura A, Natsume J, *et al.* A severity score for acute necrotizing encephalopathy. *Brain Dev* 2015;37:322–7.
- 23 Mizuguchi M. Acute necrotizing encephalopathy of childhood. *Ryokibetsu Shokogun Shirizu* 2000;(30 Pt5):527–30.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow