# Letters

## ACUTE ENCEPHALOPATHY IN CHILDHOOD ASSOCIATED WITH NOVEL INFLUENZA A H1N1 VIRUS INFECTION: CLINICAL AND NEUROIMAGING FINDINGS

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Editor,

The emergence of the novel H1N1 influenza virus resulted in numerous infected children. There appears to have been an increase in the likelihood of an intensive care admission particularly for pregnant women. We report the first United Kingdom case of acute necrotising encephalitis (ANE) in a child associated with the H1N1 virus.

A healthy 4 year old Caucasian girl presented to hospital with seizures. She had a 48 hour history of low grade fever, vomiting and rhinorrhoea. On admission, she was febrile (38.9°C) and was observed to have a herpetic lesion on her lip. She was fully immunised as per the UK schedule with no infectious contacts and an unremarkable family history. She remained in generalised status epilepticus despite benzodiazepine therapy. She received an intravenous load of phenytoin and was intubated and ventilated. Her initial blood results showed a white cell count of 14.7 x $10^9$ (neutrophils 10.9 x $10^9$, lymphocytes 3.2 x $10^9$), C reactive protein of 31mg/L, glucose 8.2mmol/L, normal renal, liver function and coagulation. She was given intravenous aciclovir, ceftriaxone and oral oseltamivir. A lumbar puncture demonstrated a cerebrospinal fluid (CSF) opening pressure of 38cm water. CSF was acellular with protein 0.53g/L (normal range 0.10-0.38g/L) and glucose 3.6mmol/L.

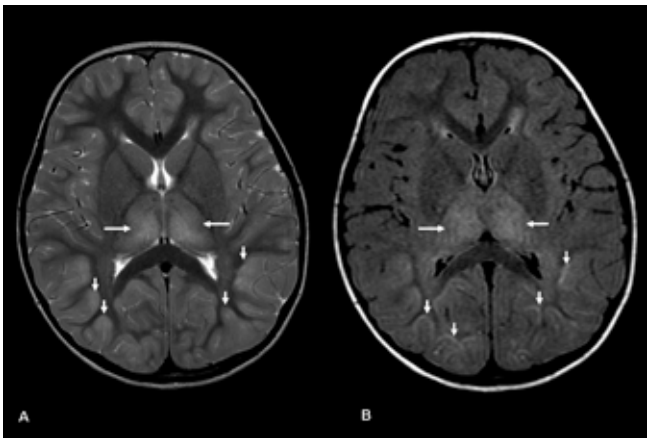


*Figure 1*. Axial T2-weighted and FLAIR images at the level of the basal ganglia show T2 hyperintensity and swelling of the thalami (long arrows) and cortical/subcortical high signal within the parieto-occipital regions bilaterally (short arrows).

She had an unenhanced Computerised Tomography (CT) brain examination, which was unremarkable except for mild cerebral swelling and some subtle low density change in the thalami. A Magnetic Resonance Imaging (MRI) examination was recommended to clarify further.

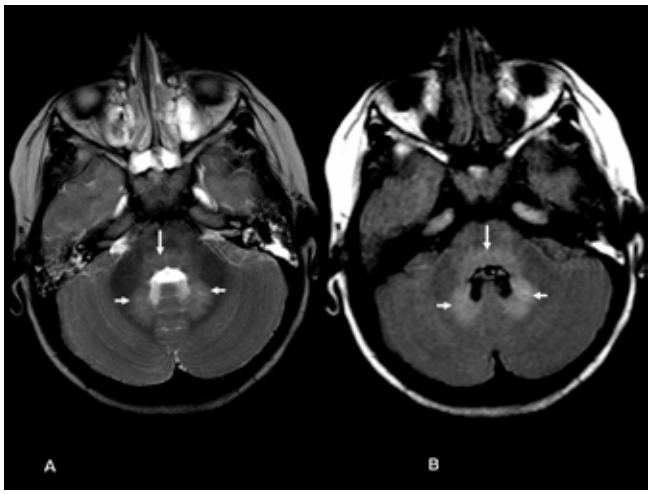


*Figure 2*. Axial T2-weighted and FLAIR images at the level of the pons show T2 hyperintensity within the pontine tegmentum (long arrows) and dentate nuclei bilaterally (short arrows).

She had no further seizures and was extubated the next morning. She remained encephalopathic with lower limb hypertonia, hyperreflexia and upgoing plantars and required reintubation. MRI brain scan on day 3 revealed symmetrical high signal changes on T2 weighted and Fluid Attenuation and Inversion Recovery (FLAIR) images involving the dentate nuclei, dorsal pons, midbrain and thalami with subcortical white matter high signal predominantly in the parietal and occipital regions (Figures 1 and 2). No abnormal contrast enhancement was observed. On diffusion weighted imaging (DWI), only minor patchy diffusion restriction was noted in the cerebral white matter, but the thalami, brain stem or cerebellum did not show any evidence of diffusion restriction. T2-weighted gradient echo images did not show any evidence of haemorrhage. Electroencephalogram was encephalopathic with no epileptiform activity.

Throat swab and broncho-alveolar lavage returned positive for H1N1 by RNA PCR. CSF was negative for H1N1 by PCR. All other plasma and CSF serology were negative. Scrapings of her lip lesion were positive for Herpes Simplex Virus Type 1. Serial platelet count, liver function and coagulation remained within normal limits.

The clinical and imaging findings were compatible with acute necrotizing encephalopathy (ANE). She was treated with intravenous immunoglobulin on day 4 (2g/kg over 2 days) and intravenous zanamivir on day 5 (20mg/kg for 5 days). This was made available on a compassionate basis from GlaxoSmithKline. She made a rapid recovery and neurological examination at day 8 was completely normal.

## DISCUSSION

ANE was first described in 1995 by Mizuguchi et al in Japan[1]. ANE is an acute onset encephalopathy which often presents with characteristic neuroimaging features of multiple, symmetrical deep grey-matter lesions involving the thalami, cerebral white matter, internal capsule, putamen, upper brainstem tegmentum cerebellum and medulla[2].

ANE has been associated most commonly with influenza A and B viruses[2]. To the authors' knowledge, this is the first childhood case in the United Kingdom of ANE in association with novel H1N1 virus.

There are few reports of neurological complications of H1N1 in children. In 2009, Evans et al in Texas reported 4 children with influenza like illness, seizures and altered mental state. They had H1N1 positive nasopharyngeal aspirates although no evidence of infection within the CSF. Electroencephalograms in 3 patients were abnormal. Neuroimaging in all 4 showed non-specific changes and no suggestion of ANE. All 4 patients recovered with no neurological sequelae at discharge[3]. More recently, there have been a few published cases of ANE during the current H1N1 pandemic, with imaging findings similar to our case, both from Europe/Eurasia[4,5] and North America[6,7]. The rapid neurological deterioration with a minimal respiratory prodrome and seizures described in these reports was comparable to the case we present. These case reports also describe a similar pattern of involvement of the thalami, dorsal brain stem and cerebellum, with variable involvement of the cerebral white matter, except for the case described by Haktanir[5] where there was bithalamic and perirolandic cortical involvement. This case report had limited clinical information but appears to have presented in a similar way to the others. MRI findings in the case report describing fatality by Martin et al[6], showed extensive white matter change and cerebral swelling, presumably leading to raised intracranial pressure and herniation, findings that were much less extensive in our patient. Ornitti et al[4] describe diffusion restriction with haemorrhage in the thalami and diffusion restriction in the cerebellum and white matter, which presumably explains the residual damage noted on follow up and the protracted neurological recovery. Although we do not have radiological follow up in our case, the absence of restricted diffusion or haemorrhage within the thalami, brain stem or cerebellum on the day 3 MRI, together with the prompt clinical recovery, would probably indicate less severe residual damage in these areas, if any.

ANE has not been universally associated with a good outcome. In a Japanese review of 89 children with ANE, 53 (59.6%) had proven influenza virus. Thirty-three (37.1%) died and 17(19.1%) had neurological sequelae[8]. Elevated interleukin six has been associated with adverse neurological outcome in the Japanese literature on ANE, it was elevated at 441pg/ml in this case however it is of uncertain significance as other interleukins were also elevated. One possible explanation is sample transit time.

Unlike other reported cases, this child did not have CSF pleocytosis, abnormal liver function or coagulopathy. However, she did have a raised CSF protein which is typical. It has been suggested that children with normal CSF protein and liver function tend to recover well. Normal CSF protein seems to have the strongest correlation to a good outcome[9]. Correlation of MRI findings and clinical outcomes has resulted in the development of a radiological scoring system which may be helpful.[10] The possibility of familial encephalitis was considered in this case but there was no relevant family history.

There is no specific therapy for ANE. Corticosteroids, dexamethasone, intravenous methylprednisolone, intravenous immunoglobulin and plasmapharesis have been used in different centres with variable long term outcomes[9]. In this case, intravenous immunoglobulin was given for its potentially beneficial non-specific immunemodulatory effects. This decision was aided further by the reluctance to use steroids in the presence of Herpes Simplex type 1 virus positive skin lesion. Other similar cases published recently have demonstrated ongoing neurological deficits.[4,5]

Intravenous zanamivir is an unlicensed treatment with currently unknown efficacy and has not been described in other published case reports of ANE associated with H1N1 in children. In this case, given the clinical and neuroimaging findings supporting a diagnosis of ANE and its potential severity, intravenous zanamivir was given after 4 days of oral oseltamivir. The patient did not have any adverse effects and demonstrated a full neurological recovery. This virus may re-emerge in the coming months.[11] For the vast majority of children it appears to have been a mild even asymptomatic infection, however monitoring is required to assess the prevalence of neurological sequelae of this particular strain of influenza.

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