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Case Report

# Acute necrotizing encephalopathy associated with novel influenza H1N1 (pdm09) infection: MRI and correlation with brain necropsy

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**Abstract.** In the United Kingdom, 2010 saw the second anticipated rise in the number of cases of novel influenza A H1N1 pdm09 ("swine flu"). Fatal outcomes largely relate to pulmonary sequel with fatal frank intracranial complications occurring much less frequently. Acute necrotizing encephalopathy is one such complication with a variable, but sometimes fatal, outcome. The condition has been reported largely in the East Asian pediatric population and is a very infrequent and elusive diagnosis largely because of the lack of recognition of the radiological appearances. The present case was diagnosed as a result of correlation of peri-mortem magnetic resonance imaging appearances of the brain with neuropathological findings at formal autopsy and brain necropsy: the virus was detected through reverse transcriptase polymerase chain reaction analysis and necropsy demonstrated classical features of necrosis in affected brain parenchyma with notable absence of inflammatory infiltrate. The report seeks to highlight the salient radiological feature of symmetrical hemorrhagic bilateral thalamic lesions - the presence of this particular feature in the appropriate clinical setting should prompt consideration of this radiologically elusive diagnosis.

Keywords: Encephalopathy, influenza A (H1N1) pdm09, swine flu

## 1. Introduction

Acute necrotizing encephalopathy (ANE) is an acute encephalopathy with distinct imaging features initially described in 1995 by Mizuguchi et al. [1] and, at that time, occurring predominantly in Japanese children. Subsequently, there have been occasional reports described affecting children in other East Asian countries and ultimately non-Asian children in Western countries [1,2]. One of the associations with ANE, which has become apparent is influenza A (H1N1) pdm09 infection. The most salient imaging appearances of ANE on computed tomography (CT) and magnetic resonance imaging (MRI) are symmetrical, frequently hemorrhagic necrotizing lesions in the thalami, as well as frequent involvement of the brain stem, cerebellum and sometimes the cerebral hemispheric white matter. The present case is of such a diagnosis associated with novel influenza A H1N1 infection revealed through MRI correlated with brain necropsy and virological findings at formal autopsy.

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## 2. Case report

A 5-year-old Bangladeshi boy presented to the Accident and Emergency with a 2 d history of malaise with a cough and irritability during which time he received ibuprofen and paracetamol administered orally. There was no history of salicylate administration prior to admission. On the morning of presentation, his mother found him sleepy with his eyes rolled back. On admission to Accident and Emergency, he was pyrexial and his Glasgow Coma Scale was between 8 and 10. His extremities were notably cold and he had a slight tachycardia. Clinically, he seemed to be fitting and was therefore given buccal midazolam followed by, owing to difficulty with intravenous access, intra-osseous lorazepam before being commenced on intra-osseous phenytoin. At this time past medical history revealed that the child had been born at 29 wk gestation requiring neonatal unit support for 7 wk after birth and had since suffered recurrent chest infections requiring a total of 5 admissions to the pediatric intensive care unit.

The child was intubated and given fluid resuscitation. On a presumptive clinical diagnosis of sepsis, the child was empirically commenced on intravenous ceftriaxone (a third-generation cephalosporin) and intravenous acyclovir. Blood parameters obtained at this time demonstrated a hemoglobin of 16.3 g/dL, white cell count of 15.300/$mm^3$ (differential included: neutrophils 9.600/$mm^3$, lymphocytes 4.300/$mm^3$, monocytes 1.100/$mm^3$), platelets of 94,000/$mm^3$, prothrombin time of 24 sec, international normalized ratio of 2.4 and activated partial thromboplastin time of 39 sec. Serum sodium measured 139 mmol/L, urea 8.8 mmol/L and creatinine 59 micromol/L. C-reactive protein was 49 mg/L on admission. Initial blood culture results were negative at this time.

Unenhanced CT brain was performed before he was transferred to the pediatric critical care unit and commenced on an adrenaline and noradrenaline

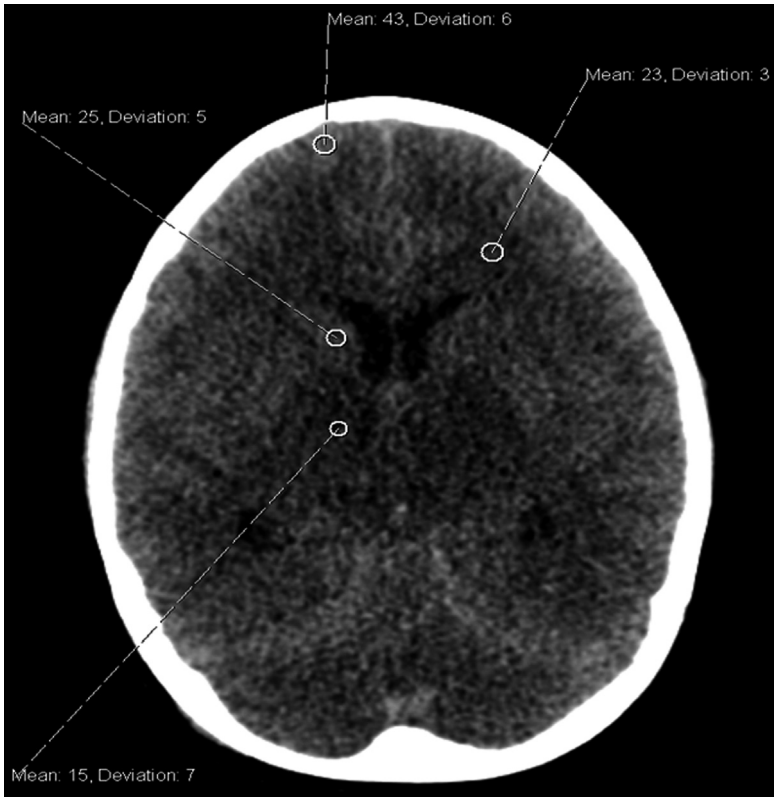


Fig. 1. Axial non-contrast computed tomography brain image through the level of the thalami: There is symmetrical low attenuation change affecting the thalami with mild edematous swelling and compression of the third ventricle as a result. (The relative mean values [with standard deviation] of Hounsfield units of affected thalamus, unaffected head of the caudate nucleus and unaffected frontal cortical grey matter and white matter are indicated with appropriate regions of interest).

intravenous infusion because of a labile blood pressure. CT revealed cerebral swelling and edema with more focal symmetrical low attenuation affecting the thalami and evidence of early cerebellar tonsillar herniation (Fig. 1). Neurosurgical opinion sought at this time was against any neurosurgical intervention. Lumbar puncture was not obtained in light of the CT appearances. Despite continued aggressive medical resuscitation and intensive hemodynamic support, the child's Glasgow Coma Scale deteriorated and pupils became fixed and dilated over the course of the next 3 h. MRI was performed during this period of time (Figs. 2A–2D). This revealed bilateral symmetrical lesions in the thalami, which exhibited predominantly T1 and T2 prolongation associated with restricted diffusion on the diffusion-weighted sequences. Similar but smaller areas of signal change were also identified within the centrum semiovale white matter and the cerebellar parenchyma. These appearances were on a background of moderate generalized cerebral and cerebellar edema and brain swelling. Within the thalamic lesions, some patchy T2 shortening was also evident suggesting an evolving necrotic component; blooming susceptibility artifact within these areas on a gradient recalled echo T2 sequence confirmed the presence of hemorrhagic products at these sites. Subsequently, brain stem death was confirmed approximately 14 h after hospital admission. The following day, formal post-mortem was performed. The necropsy findings were commensurate with the peri-mortem MRI findings: gross brain swelling was observed with evidence of macroscopic petechial hemorrhage in the thalami and cerebellum with evidence of associated coagulative necrosis (Figs. 3A and 3B). No inflammatory collections or meningeal inflammation were identified. Influenza A H1N1 was subsequently detected from lung and cardiac tissue by reverse transcriptase polymerase chain reaction (PCR) analysis but not from cerebrospinal fluid (CSF) or cerebral tissue. Herpes viral strains and adenovirus were not detected in CSF or on PCR analysis.

The radiological findings and confirmatory pathological features were consistent with novel influenza A H1N1 pdm09 associated acute necrotizing encephalopathy.

## 3. Discussion

First reported in the Far East in Japan, ANE is a relatively rare condition with the majority of recorded cases reported in Japanese, Korean and Taiwanese children and typically in children under 5 yr of age. It is a rare complication of influenza A infection and has been linked to other infections including mycoplasma, herpes simplex virus, influenza B and human herpes virus-6 [3,4]. The prevalence in East Asian children suggests genetic and environmental factors. However, the exact etiology and pathogenesis of ANE remains unclear and immune-mediated or metabolic etiologies have been proposed [3–5]. The present case is unusual because the child affected by ANE was of Bangladeshi origin, but was born and raised in the United Kingdom, and suffered cerebral palsy (as well as recurrent respiratory infections) as a pre-morbid condition.

The clinical course of ANE can be rapidly progressive as in the present case. Patients can present with fever and non-specific upper respiratory tract symptoms such as cough, diarrhea or vomiting which progress rapidly to neurological dysfunction [1,6,7]. Mizuguchi et al. [1] established a number of criteria for the diagnosis of this rare condition, which included acute encephalopathy with rapid deterioration of consciousness; absence of serum hyperammonemia; CSF pleocytosis with elevated CSF protein; neuroimaging studies showing symmetric multifocal lesions involving the thalami; the clinical absence of other disease processes resembling ANE such as prolonged hypotension, hypoxia, metabolic and neurodegenerative diseases [7]. Attempted treatment options described (with varying degrees of benefit) include oseltamavir, corticosteroids and intravenous gamma globulin, which were not administered in the present case. However, therapeutic management is largely aimed at supportive treatment [6,8].

The most distinctive neuroimaging findings in ANE documented in previous reports and highlighted in the present case are symmetric. Thalamic signal abnormality Other sites of involvement include brain stem tegmentum, periventricular white matter, capsular white matter, putamen and cerebellum [4]. Hemorrhagic signal related to coagulative necrosis prior to cavitation has been known to occur in the central component of affected deep grey matter, most notably the thalamic [1–13]. Post-contrast sequences acquired following administration of intravenous gadolinium demonstrate ring enhancement around the hemorrhagic areas. Porto et al. [10] reported magnetic resonance spectroscopy findings in a case of ANE. The spectroscopy was marked by reduction of the neuronal marker N-acetyl aspartate (NAA) consistent with neuronal damage and elevation of myoinositol (mI) and choline (Cho) suggesting

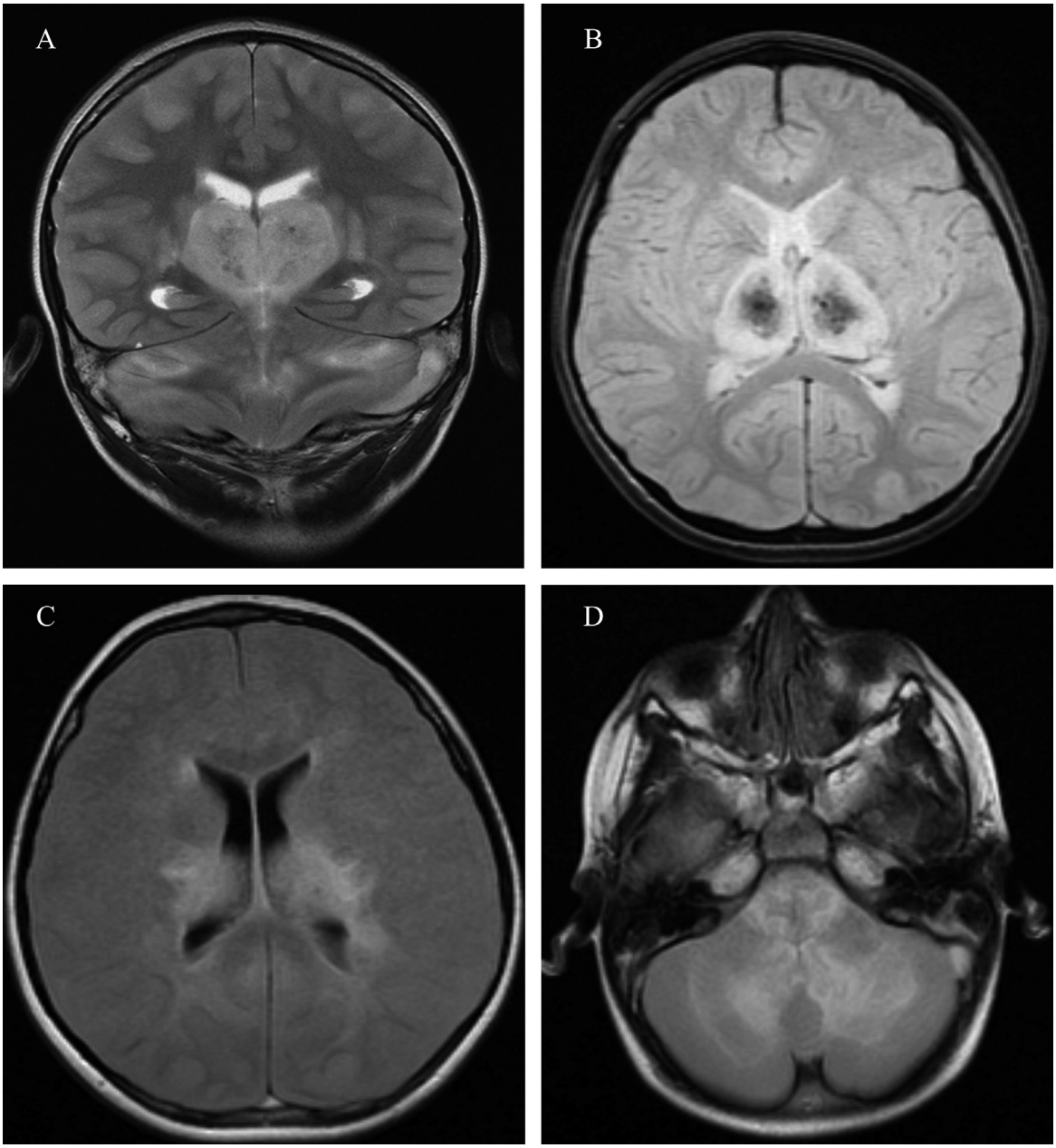


Fig. 2. (A) Coronal T2-weighted sequence demonstrates edematous symmetrical swelling of the thalami bilaterally with petechial hypointense necrotic foci within. There is also patchy high T2 signal abnormality affecting the capsular white matter, the cortical mantle and subcortical white matter, and the cerebellar hemispheric parenchyma bilaterally. Early cerebellar tonsillar descent is present. (B) Axial gradient recall echo T2-weighted sequence through the thalami and third ventricle. The hypointense early blooming in the edematous thalami confirms the necrotic hemorrhagic nature of the underlying etiology. (C) Axial fluid attenuated inversion recovery sequence through the level of the bodies of the lateral ventricles demonstrates generalized cerebral swelling and relatively symmetrical abnormal high T2 signal abnormality in the deep white matter with involvement of the periventricular white matter and corona radiata of both cerebral hemispheres. (D) Axial T2-weighted sequence through the posterior fossa at the level of the pontomedullary junction. Abnormal symmetrical T2 signal abnormality is present in the brain stem and the cerebellar hemispheric parenchyma.

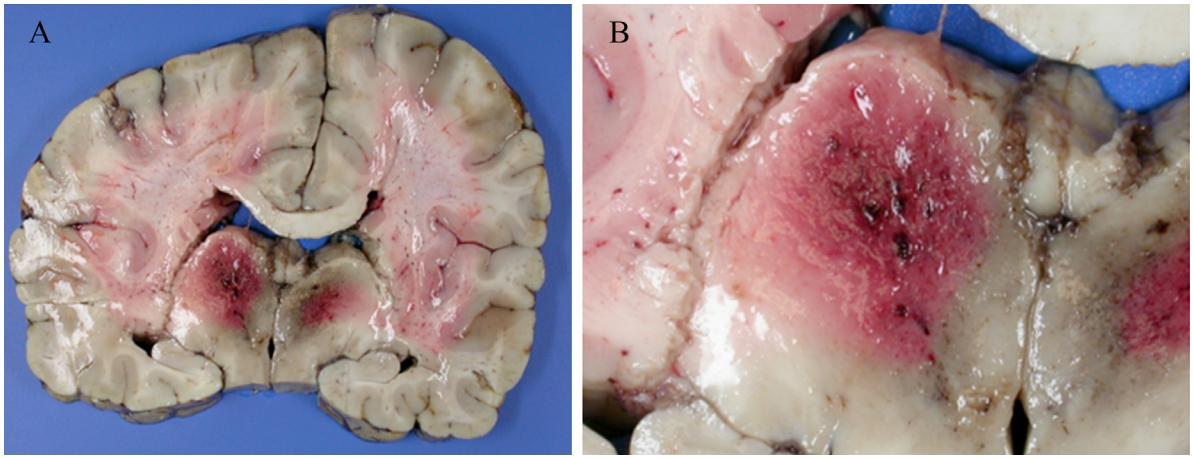


Fig. 3. Coronal section photographs of unfixed brain necropsy. (A) Sectioning through the body of the corpus callosum demonstrating relatively symmetrical coagultive necrosis in the superficial and periventricular deep white matter of both cerebral hemispheres and the thalami. Note the close correlation with the post-mortem magnetic resonance imaging appearances in figure 1 particularly in relation to the hemorrhagic necrotic changes in the thalami. (B) Magnified view of the macroscopic changes in the thalami, with focal petechial hemorrhagic necrosis affecting the thalamic parenchyma.

demyelination and reactive astrocytosis; a lactate peak was absent.

The pathologic findings recorded at necropsy in the present case correlating with the MRI findings included gross evidence of focal hemorrhage in the thalami, coagulative necrosis affecting neurons and glial cells in the affected sites. There was notable absence of perivascular or meningeal inflammatory infiltrates and relative absence of reactive inflammatory infiltration around the areas of necrosis. This particular feature highlights the disease process as an encephalopathic one, distinct from an encephalitic one. In reported cases, influenza A has seldom been identified in CSF by PCR analysis; this negative finding, together with the association of similar radiological and histopathological findings with other infective etiologies such as mycoplasma and influenza B, suggest that ANE represents an autoimmune-mediated response rather than **the result of** direct viral invasion of the CNS [6,9].

The radiological differential diagnoses worthy of consideration on MRI findings include those which may produce symmetrical lesions of the deep cerebral grey matter: Haemolytic uremic syndrome, inborn errors of metabolism, hypoxic-ischemic encephalopathy, carbon monoxide poisoning, acute disseminated encephalomyelitis, arterial or venous infarction and viral encephalitides, in particular, those of the flavivirus group such as Japanese encephalitis and West Nile encephalitis. These entities usually have distinguishing clinical and laboratory findings. Reye's syndrome is a strong consideration in the clinical differential diagnosis in the absence of neuroimaging. The MRI appearance (in addition to a clinical history clarifying the absence of aspirin ingestion) can be particularly helpful in discounting this syndrome, given that the most common neuroimaging appearances in Reye's are generalized cerebral edema without focal symmetrical deep grey matter lesions [1]. Also included in the differential for bithalamic signal abnormalities are arterial or venous infarctions. There was no evidence for infarct in this case and no venous thrombosis was identified at imaging or necropsy.

We present radiological and pathological findings of a case of ANE secondary to influenza A H1N1pdm09. H1N1pdm09 ANE is seen more commonly in children of East Asian descent and with predisposing morbidities, and should be considered with MRI findings of bithalamic signal abnormalities progressing to hemorrhage.

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