Case report

# A bad dose of the 'flu

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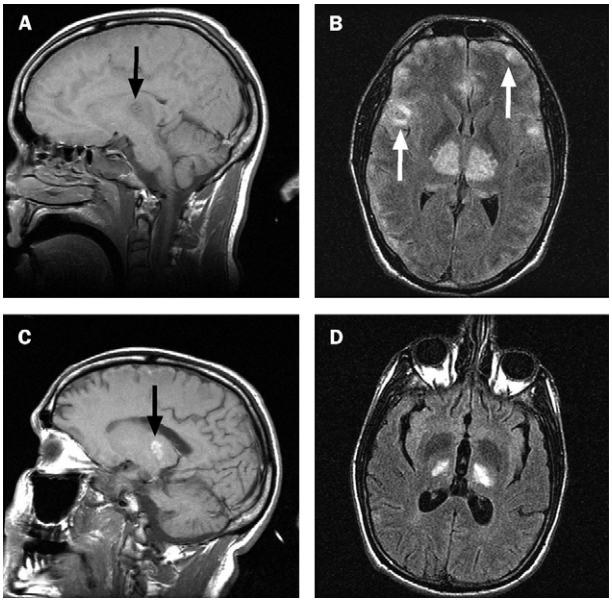
In the winter of 2002, a 29-year-old man was admitted to our intensive care unit. He had become unwell and confused over the preceding 2 days and had a grand mal seizure. On admission, he was febrile, tachycardic, hypoxaemic, and had a Glasgow Coma Scale score of 5/10. We intubated and ventilated him. Blood tests showed leucocytosis ($21\times10^9$/L; mainly polymorphonuclear leucocytes), serum creatinine 0·18 mmol/L, raised transaminases, and a creatine kinase of 1865 U/L. We did a lumbar puncture; opening pressure was 270 mm $H_2O$, and the cerebrospinal fluid (CSF) had no white cells, 4 red cells/μL, glucose 4·6 mmol/L, and protein 0·87 g/L. We did PCR for influenza and herpes simplex viruses and screened for salicylates, amphetamines, and cocaine; these tests were negative. There was no carbon monoxide in the blood. Brain CT showed no abnormalities, but MRI showed bilateral, symmetric lesions in the thalami and hyperintense changes on T2-weighted images in the midbrain, anterior pons, and medulla tegmentum; there were asymmetrical changes in the frontal cortices, left hippocampus and uncus, and right temporal cortex (figure A, B). No contrast enhancement was seen and the cerebral veins appeared patent. A throat swab taken on admission cultured influenza A/Moscow/10/99 (H3N2) virus, a prevalent strain in New Zealand.

On the basis of our patient's presentation, culture results, and the MRI showing such widespread vasogenic and cytotoxic oedema, we diagnosed acute necrotising encephalopathy, secondary to influenza. Despite treatment with acyclovir, oseltamivir, and methylprednisolone, the patient remained unwell and required ventilation for a further 3 weeks. Complement fixation testing confirmed acute influenza A infection by a four-fold increase in antibody titre. Repeat MRI showed that the thalamic lesions which had been hypointense on T1 had become hyperintense (a sign of petechial haemorrhage), while some of the T2 signal abnormalities had partially resolved (figure C, D). Neurological recovery was protracted and when last seen, in May, 2003, he was staying in a rehabilitation home and was coherent but remained tetraparetic and dysarthric.

Acute necrotising encephalopathy was first described in a series of Japanese children who presented sporadically between 1979 and 1995.[1] All the children developed coma and seizures following a short febrile illness; mortality was 28% with neurological sequelae in 63% of survivors. 148 Japanese patients developed this complication during the 1998–99 winter influenza epidemic; 130 were infected with influenza A (H3N2).[2] Massive cerebral oedema with no inflammatory cell infiltration or viral nucleoprotein was found on postmortem examinations, and only a few patients had viral RNA in the CSF. Such findings, and the rapid onset of the encephalopathy, suggest that direct viral invasion of the brain may not be the main pathogenic mechanism.[3] The virus may set off an exaggerated cytokine response which causes vascular damage throughout the body, breakdown of the blood-brain barrier, and multi-organ failure.[4] The host's normal interferon production may be curtailed by certain lethal influenza A viruses.[5] Acute necrotising encephalopathy may occur after subtle antigenic changes in circulating viruses or, unpredictably, in predisposed individuals.




**Sagittal T1 and axial T2 FLAIR MRI of the brain**
Oedema in the right thalamus (A, arrow), symmetric bilateral hyperintense lesions in the thalamus and patchy changes in the cortex (B, arrows). 3 weeks later, hyperintense lesions persist in the thalamus and superior cerebral cortex; T1-weighted, (C) and T2-weighted, (D).

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