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A Tragic Case of 'Flu'

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Abstract We report a 5-year old boy with influenza A-associated acute necrotising encephalopathy. This is the first reported case in Hong Kong. The diagnosis was based on clinical features, neuroimaging findings and isolation of influenza A virus from nasopharyngeal aspirate. The disease is characterised by fever, seizure, rapid deterioration in consciousness and radiologic involvement of bilateral thalami and cerebellum. Paediatricians taking care of children should be aware of this exceedingly rare but emerging presentation of influenza infections.

Key words Acute necrotising encephalopathy; Influenza

Introduction

Influenza infection does not only cause acute febrile respiratory illness. Potential fatal complications such as myocarditis, rhabdomyolysis and lower respiratory syndromes that result in respiratory failure can develop. Neurologic complications have been reported for over 100 years. The majority of patients have relatively minor symptoms such as headache or easy fatigue. Influenza-associated encephalopathy is a serious complication of influenza infection mostly affecting children. Several subtypes of influenza-associated encephalopathy exist that include Reye's syndrome, encephalitis, haemorrhagic shock encephalopathy and acute necrotising encephalopathy (ANE). The latter is characterised by rapidly progressive course and poor neurological outcome.[1] We describe a comatose child that was subsequently diagnosed to have acute necrotising encephalopathy complicating influenza infection.

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Case Report

A 5-year old previously healthy Chinese by presented to our intensive care unit in generalised status epilepticus. He had a 2-day prodrome of fever, rhinorrhoea, cough and vomiting. There was no history of influenza vaccination, recent travel, ill contacts or exposure to drugs such as aspirin. On examination, he was febrile, tachycardic and had a Glasgow Coma Score of 3. Oxygen saturation was 97% in room air. Blood pressure was 97/57 mmHg. There was no neck rigidity. Pupils were pinpoint and showed sluggish response to light. He was flaccid. Deep tendon reflexes were intact and planter was extensor bilaterally. Examination of other systems was unrevealing. Blood tests sowed leucocytosis (21 x 10^9/L, neurtrophil predominant), alanine transaminases 423 U/L, creatinine kinase 175 U/L, lactic dehydrogenase 19810 U/L, troponin 0.13 ng/ml and ammonia 35 umol/L. Platelet and coagulation profiles were normal Serum salicylate was undetectable. Brain CT

revealed cerebral oedema and multifocal lesions in bilateral thalami, brainstem and cerebellar white matter (Figures 1 & 2). Electroencephalogram showed diffuse slow waves indicating diffuse cortical dysfunction. Lumbar puncture was withheld in view of the critical situation of the child. Direct immunofluorescent testing of the nasopharyngeal aspirate was positive for influenza A and was later confirmed by culture to be H3N2. Other virus studies including Epstein-Barr, herpes simplex, varicella-zoster, mumps and mycoplasma pneumoniae were all negative. Seizure was abolished by intravenous diazepam and phenytoin. Patient was intubated and ventilated. Despite treatment with acyclovir, oseltamivir, cefotaxime, hyperventilation and mannitol infusion, the child remained comatose. Pupils became fixed and dilated 6 hours after hospitalisation. Blood pressure became labile requiring boluses of fluid and inotrophic support. Central diabetes insipidus set in and body temperature became unstable. He finally succumbed. Parents refused post-mortem examination.

Discussion

Acute necrotising encephalopathy was first described in 1995 by Mizuguchi et al., in a series of Japanese children between 1979 and 1995.[1] Children with this syndrome presented with fever, seizure, and alteration in mental status that rapidly progress to coma. Neuroimaging features are characterised by massive cerebral oedema, multifocal, symmetrical brain lesions that affect thalamus, brainstem tegumentum, periventricular white matter and cerebellar medulla.[1] Mortality was 31% and neurological sequalae was 63% in survivors. Children mainly below 5 years were affected.[2] The disease can be differentiated from Reye's syndrome by absence of elevated serum ammonia. Clinical features, neuroimaging findings and isolation of influenza virus supported the diagnosis of influenza-associated ANE in our patient. We believe this is the first reported case of ANE complicated influenza infection in Hong Kong.

Pathogenesis of ANE is unknown. Isolation of virus from cerebrospinal fluid has been rare.[3] Influenza A virus could

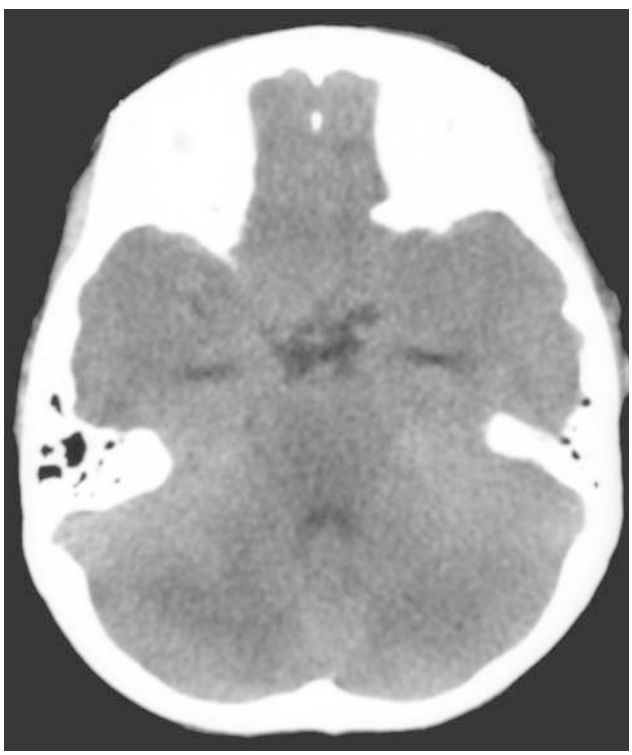

Figure 1 CT scan brain shows multifocal hypodense lesions in cerebellum and brainstem.

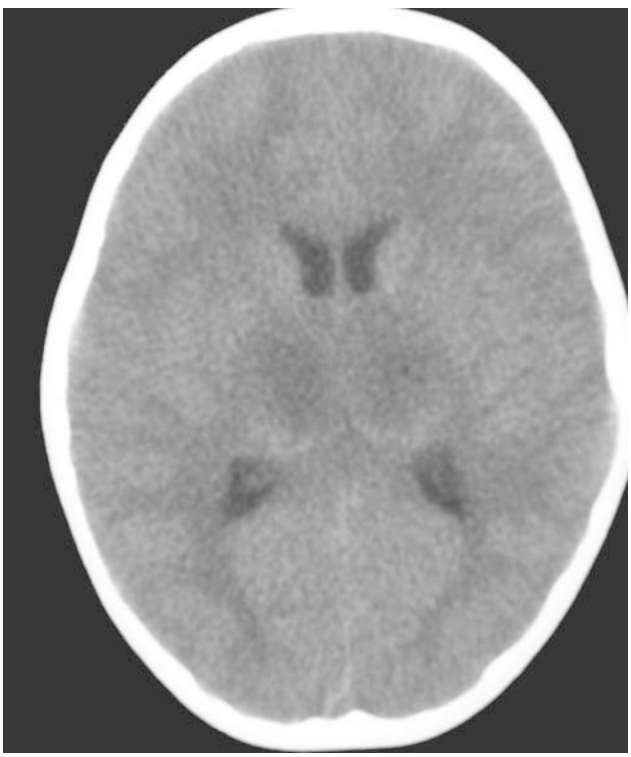

Figure 2 CT scan brain shows hypodense lesions in bilateral thalami.

only be detected in the CSF in one of the 18 patients with influenza A-associated encephalopathy.[4] Autopsy findings revealed vascular congestion, swollen oligodendrocytes, necrosis of neurons, rarefaction of tissues and lack of infiltration of inflammatory cells.[5] The catastrophic clinical course, massive cerebral oedema and the pathological findings suggest exaggerated cytokine response. Direct viral invasion of brain may not be the main mechanism.[6] Genetic predisposition and subtle antigenic changes may be involved in the pathogenesis as well.[7]

It is unclear whether influenza vaccination would have prevented or attenuated influenza-associated encephalopathy.[8] Passive immunisation of mice protected them from influenza encephalopathy.[9] Japan had been providing influenza vaccination to most school children, but the program was discontinued in 1994. Shortly afterwards, 148 Japanese patients developed this complication during the 1998-1999 influenza epidemic.[3] It is tempting to link these two events together.[10] Besides, ANE occurs mainly in children younger than 5 years that had few prior influenza infections. Antibody induced by vaccination or prior infections might have protected children against ANE.

Of equal controversy is the efficacy of anti-viral treatment. There is a lack of randomised, controlled study in the value of anti-viral agents in effecting the neurologic outcome of influenza. Steroid in ANE is ambiguous in literature. Steroid maybe beneficial if cytokine response is believed to be the main culprit. Supportive care, anti-viral therapy, methylprednisolone pulse therapy and large dose of IgG reduced the mortality of influenza-associated encephalopathy (T Morishima, personal communication). Treatment of influenza B-associated encephalopathy with oseltamivir and cerebrospinal fluid clearance has been described.[11]

To conclude, we reported an exceedingly rare but fatal complication of 'flu'. When paediatricians manage children with encephalopathy or encephalitis, potentially treatable viruses are not only herpes simplex or varicellar-zoster, influenza virus can be an important agent especially during the flu season.

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