

## **Influenza associated encephalitis/encephalopathy (IAE) in children**

Dr Gulam Khandaker

University of Sydney, National Centre for Immunisation Research and Surveillance and The Children's Hospital at Westmead.

**Word count: 965**

Encephalitis is a complex neurological syndrome caused by inflammation of the brain, which is uncommon but potentially devastating.<sup>1</sup> Although encephalitis may be caused by a variety of agents, both infectious and non-infectious (eg. immune-mediated), direct viral infection is one of the commoner causes.<sup>2</sup> Influenza-associated acute encephalopathy has been described in children, and can cause long term neurologic sequelae and death. Clinically it presents with altered level of consciousness, disorientation, and seizures within a few days after the onset of fever and respiratory symptoms.<sup>3-5</sup> However, in some cases, symptoms of influenza may be subtle<sup>6</sup> and the neurologic symptoms may be transient but in others rapid progression to necrotizing encephalitis, deep coma, and death may occur.<sup>3-5</sup> The pathogenesis of IAE is unclear and direct CNS viral invasion is rarely reported.<sup>3-5,7,8</sup> In this essay we described the epidemiology and pathophysiology of IAE in children and share our experiences during the 2009 influenza pandemic.

**Definition: Encephalitis** can be defined both clinically and pathologically. **Clinically** it comprises of altered level of consciousness for >24 hours, including lethargy, irritability or a change in personality and behaviour and  $\geq 2$  of the following features: fever or history of fever ( $\geq 38^{\circ}\text{C}$ ), seizures and/or focal neurological findings (with evidences of brain parenchyma involvement), CSF pleocytosis ( $>4$  WBC/ml), electroencephalogram findings compatible with encephalitis, abnormal results of neuroimaging in keeping with encephalitis.<sup>9</sup>

A **pathological definition** of encephalitis requires the presence of nonpyogenic inflammatory infiltrates, commonly in the form of T lymphocytes and microglia, within the brain. This may also involve the meninges (meningoencephalitis) and spinal cord (myelitis).<sup>9</sup>

**Encephalopathy** is defined as altered level of consciousness for more than 24 hours, including lethargy, irritability or change in personality and behaviour.<sup>10</sup>

**Epidemiology of influenza associated encephalitis/encephalitis:** One of the largest cohort of IAE has been reported from Japan. Between 1994 and 2002 in Hokkaido, Japan, 89 children were reported to develop IAE with a mean age of 3.8 years.<sup>5</sup> One US study showed that the proportion of encephalopathy in children hospitalised with laboratory confirmed pandemic influenza was 1.7%.<sup>11</sup> Another Australian study from the Children's hospital at Westmead in 2007 found 1.6% (2 of 122) of hospitalised children with laboratory-confirmed seasonal influenza had encephalitis.<sup>12</sup> A comprehensive literature review on the 2009 pandemic influenza related neurologic complications identified 23 published papers presenting original data on influenza neurologic complications including IAE (9 cases of encephalitis, 25 cases of encephalopathy).<sup>6</sup>

During the 2009 influenza pandemic a national surveillance of influenza neurologic complications at 6 major paediatric hospitals in Australia identified 7 cases of IAE. Majority of those (5 of 7) had pre-existing health conditions. Of the 2 patients who were previously well, one developed pneumonia with empyema and had an asystolic arrest secondary to

tension pneumothorax but survived with hypoxic encephalopathy. Another presented with a focal seizure and later developed generalised seizures and encephalopathy. Five (71.4%) of the 7 encephalitis/encephalopathy cases needed intensive care unit (ICU) admission, one of whom died (14.3%). All except one were aged over 5 years of age. 5 children with encephalitis/encephalopathy had a lumbar puncture. Influenza virus was not isolated from any sample. One had low cerebrospinal fluid (CSF) protein (0.13 g/L) and the rest did not have any CSF abnormalities.<sup>6</sup>

**Case report:** One of the seven cases reported in the earlier section was a previously healthy 5-year-old boy who developed fever (38.4°C), ascending paralysis, ophthalmoplegia, and drowsiness and became quadriplegic and comatose within 24 hours of symptom onset. He was admitted to the Children's hospital at Westmead and an MRI demonstrated high signal in the medulla and cervical cord on T2-weighted sequences and areas of high signal in the right frontal and left posterior periventricular white matter. A RT-PCR on nasopharyngeal swab confirmed as influenza A/H1N1 2009. However, H1N1 RNA was not detected in CSF by RT-PCR. Serology for other infectious agents including cytomegalovirus, Epstein-Barr virus, enterovirus, rubella, herpes simplex virus [HSV], M pneumoniae and CSF PCR (HSV-1 and HSV-2, enteroviruses) were tested negative. The child also had normal CSF glucose, protein, without any CSF pleocytosis. He was treated with oseltamivir for 5 days. Methylprednisolone (30 mg/kg/day for 3 days) and IV immunoglobulin (2 g/kg over 2 days) were also commenced. The child's consciousness level improved within 48 hours of treatment, and his motor function showed significant improvement within 2-week of his hospital stay. A month after his initial admission, he had some mild left arm weakness without any other sequelae.<sup>13</sup>

**One proposed pathophysiology of IAE:** The pathophysiology of influenza associated encephalopathy is poorly understood and may involve viral invasion of the CNS, pro-inflammatory cytokines, metabolic disorders, or genetic susceptibility.<sup>14</sup> Without direct CNS invasion by the virus pro-inflammatory cytokines (ie, interleukins and tumor necrosis factor) released as result of systemic inflammation can reach the brain in a number of ways: via peripheral afferents (ie, the vagus nerve), entry through leaky circumventricular areas in the blood-brain barrier, or active transport. Once in the brain, the cytokine signal stimulates microglia to secrete inflammatory mediators (ie, cytokines, chemokines, and proteases) from its monocytes and macrophages. These local inflammatory mediators can affect neuronal function and synaptic plasticity by increasing oxidative stress and weakening astrocytic tight junctions. They also increase metabolism and reuptake of neurotransmitters (ie, serotonin, noradrenalin, and dopamine) and stimulate the hypothalamic-pituitary-adrenal axis<sup>15</sup> which could be responsible for a range of cognitive and affective symptoms in encephalitis/encephalopathy. IAE in children mostly represent a parainfectious encephalopathy which is likely immune-mediated.

**Conclusion:** Through our experiences we know that IAE is not uncommon in children and can be life threatening and disabling. Absence of CSF pleocytosis and detectable virus by PCR/culture in CSF during IAE may supports an immune mediated or autoimmune mechanism of influenza associated encephalopathy. More research is needed to completely understand the pathophysiology of IAE in children which will help to develop targeted therapy and preventive measures.

## References:

1. Dale RC, Brilot F, Banwell B. Pediatric central nervous system inflammatory demyelination: acute disseminated encephalomyelitis, clinically isolated syndromes, neuromyelitis optica, and multiple sclerosis. *Curr Opin Neurol*. 2009;22:233-40.
2. Thompson C, Kneen R, Riordan A, Kelly D, Pollard AJ. Encephalitis in children. *Arch Dis Child*. 2012;97:150-61.
3. Studahl M. Influenza virus and CNS manifestations. *J Clin Virol*. 2003;28:225-32.
4. Morishima T, Togashi T, Yokota S, Okuno Y, Miyazaki C, Tashiro M, et al. Encephalitis and encephalopathy associated with an influenza epidemic in Japan. *Clin Infect Dis*. 2002;35:512-7.
5. Togashi T, Matsuzono Y, Narita M, Morishima T. Influenza-associated acute encephalopathy in Japanese children in 1994-2002. *Virus Res*. 2004;103:75-8.
6. Khandaker G, Zurynski Y, Buttery J, Marshall H, Richmond PC, Dale RC, Royle J, Gold M, Snelling T, Whitehead B, Jones C, Heron L, McCaskill M, Macartney K, Elliott EJ, Booy R. . Neurologic complications of influenza A(H1N1)pdm09: surveillance in 6 pediatric hospitals. *Neurology* 2012 (in press).
7. Kawada J, Kimura H, Ito Y, Hara S, Iriyama M, Yoshikawa T, et al. Systemic cytokine responses in patients with influenza-associated encephalopathy. *J Infect Dis*. 2003;188:690-8.
8. van Zeijl JH, Bakkers J, Wilbrink B, Melchers WJ, Mullaart RA, Galama JM. Influenza-associated encephalopathy: no evidence for neuroinvasion by influenza virus nor for reactivation of human herpesvirus 6 or 7. *Clin Infect Dis*. 2005;40:483-5.
9. Granerod J, Cunningham R, Zuckerman M, et al. Causality in acute encephalitis: defining aetiologies. *Epidemiol Infect* 2010; 138:783-800.
10. Glaser CA, Gilliam S, Schnurr D, et al. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998-2000. *Clin Infect Dis* 2003; 36:731-742.
11. Baltagi SA, Shoykhet M, Felmet K, Kochanek PM, Bell MJ. Neurological sequelae of 2009 influenza A (H1N1) in children: a case series observed during a pandemic. *Pediatr Crit Care Med* 2010; 11:179-84.
12. Lester-Smith D, Zurynski YA, Booy R, Festa MS, Kesson AM, Elliott EJ. The burden of childhood influenza in a tertiary paediatric setting. *Commun Dis Intell* 2009; 33:209-15.
13. Webster RI, Hazelton B, Suleiman J, Macartney K, Kesson A, Dale RC. Severe encephalopathy with swine origin influenza A H1N1 infection in childhood: case reports. *Neurology*. 2010;74:1077-8.
14. Wang GF, Li W, Li K. Acute encephalopathy and encephalitis caused by influenza virus infection. *Curr Opin Neurol* 2010; 23:305-11.
15. Khandaker GM, Jones PB. Cognitive and functional impairment after severe sepsis. *JAMA*. 2011;305:673-4.