



CASE STUDY

Encephalopathy associated with influenza A

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KEYWORDS

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Summary We report a 3-year-old boy with influenza A virus-associated encephalopathy. The diagnosis was based on clinical findings, magnetic resonance imaging, repeated isolation of influenza A virus from nasopharyngeal aspirate and seroconversion between acute and convalescent sera. The clinical picture was characterized by fever and aphasia followed by seizures and a rapid deterioration of consciousness 2 days later. This patient illustrates that influenza A-associated encephalopathy with severe neurological deficit can occur with atypical distribution of brain lesions during the course of the illness, while initial brain MRI and laboratory findings of cerebrospinal fluid are normal, including reverse transcription polymerase chain reaction.

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Introduction

Influenza-associated encephalopathy is a serious complication of influenza infection, mostly affecting young children.¹ The clinical picture may be very serious with sudden onset of high fever, seizures, rapidly progressive coma and death within two or three days. However, full recovery after approximately 4 weeks is also possible.^{2,3} It occurs mainly in Japanese children and has been reported rarely in western countries.^{1,4} Two hundred and two children with influenza A-associated encephalopathy were recognized in Japan between 1997 and 2001, 80.2% were aged 0-5 years.⁵ Death occurred in 31%, residual neurological deficit in 26% and full recovery in 43%. Children mainly below the age of 5

years were affected, developing encephalopathy on the first or second day that signs of influenza appeared.⁶ Recently Nikaido et al described three cases of influenza A virus-related encephalopathy developing 5-6 days after the major symptoms of the influenza A/H3N2 infection subsided.⁷ The pathogenesis and the reason why these serious complications of influenza infection occur mainly in Japan remains unknown. Twenty-one patients aged 4-78 years with influenza A-associated acute encephalopathy were reported in Austria.⁸ Several subtypes of influenza-associated encephalopathy exist including Reye's syndrome, encephalitis, haemorrhagic shock encephalopathy and acute necrotizing encephalopathy (ANE). Recently, Weitkamp et al. reported the first child who displayed clinical features of ANE in association with a documented influenza A infection.⁹ ANE is characterized by multifocal symmetric brain lesions in the thalami, putamina, cerebellar medulla,

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periventricular white matter and brainstem tegmentum.¹⁰ The neurological outcome is very poor, although a full recovery of a child with an influenza A-associated ANE is also reported.¹¹ We describe a child from the Netherlands with a severe encephalopathy during the course of an influenza A infection.

Case Study

A 3-year-old previously healthy Caucasian boy was taken to our emergency department because of altered behavior and inability to speak. He had a fever up to 40 °C for 2 days, otitis, conjunctivitis and a cough. On admission the vital signs were normal except a body temperature of 39.5 °C. The boy was awake and agitated but did not speak, did not recognize his parents and did not follow commands (Glasgow coma scale 11). Neck-stiffness and papilloedema were absent. He had no paresis, deep tendon reflexes were normal, but Babinski's sign was positive on both sides. The C-reactive protein value increased to 52 mg/l, the blood leukocyte count was $7.5 \times 10^9/l$ and the erythrocyte sedimentation rate 7 mm/h. Liver and renal function tests were unremarkable. Lumbar puncture showed leukocytes $1/\mu l$, protein 120 mg/l, glucose 4.0 mmol/l (serum glucose 5.7 mmol/l). Cerebrospinal fluid (CSF) Gram staining and cultures of CSF, blood and urine were negative. Magnetic resonance imaging (MRI) of the brain on admission was normal. Electroencephalography on admission revealed diffuse slow activity, especially in the frontal and centroparietal regions, compatible with encephalopathy. There was no epileptiform activity. As herpes encephalitis was suspected, intravenous acyclovir was started. On the third day of admission he had a partial epileptic seizure followed by several secondary generalized tonic-clonic seizures. His seizures subsided after receiving intravenous anti-epileptic therapy. The child was now unconscious with a Glasgow coma scale of 4. Noxious stimulation elicited extensor posturing. Because of respiratory distress, mechanical ventilation was necessary. This was complicated by pneumonia with a positive culture of bronchial secretion for *Haemophilus influenzae*. A second brain MRI on day 3 demonstrated a high-intensity signal involving the frontal and insular lobes bilaterally and the left temporal lobe in T₂-weighted images (Fig. 1). The early inability to speak was presumably due to involvement of the speech center located in the left frontotemporal region. A repeated lumbar puncture showed again no abnormalities. Influenza A virus

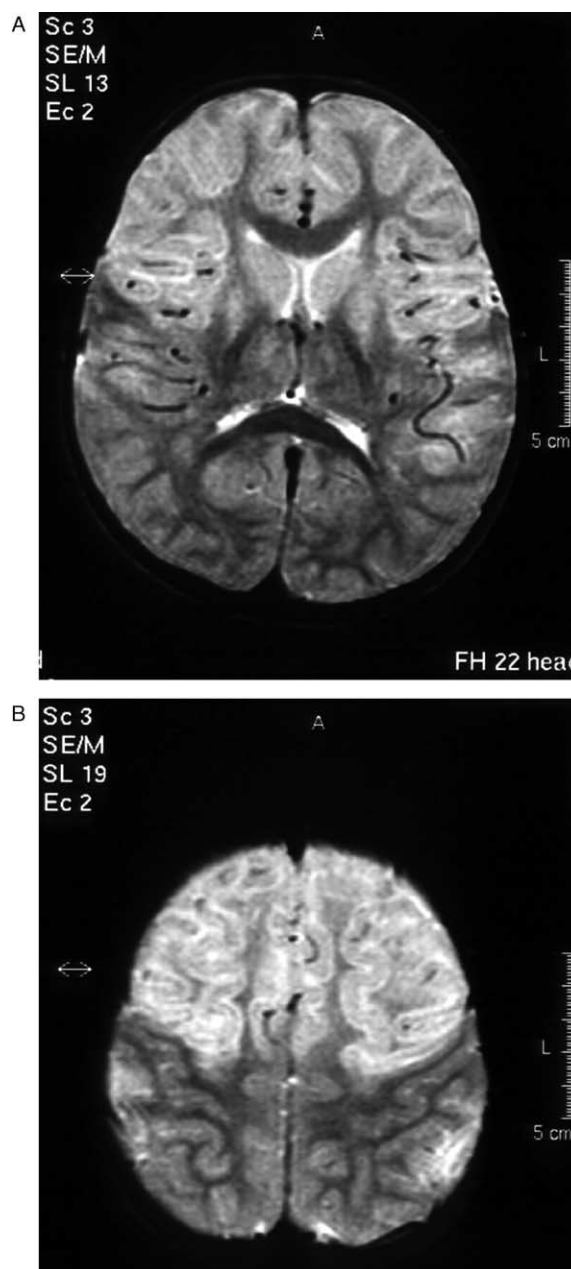


Figure 1 Brain MRI (T₂-weighted imaging). (A) Intense signal in both frontal lobes and the left temporal lobe corresponding to oedema. (B) Oedema in both frontal lobes.

was isolated from throat swabs obtained at days 1, 4 and 5 of admission. The influenza A was subtyped as H₃N₂/Moscow/10/99-like, and the hemagglutination inhibition antibody titer in sera for this subtype increased from 1/30 on day 1 of the illness up to 1/480 and 1/640 on days 9 and 19, respectively, (National Influenza Center, Rotterdam, the Netherlands). Cultures failed to demonstrate viruses in CSF. Serological studies on Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella zoster virus, mumps, measles and

Mycoplasma pneumoniae were negative. Detection of influenza A and B virus RNA in blood and CSF by reverse transcription polymerase chain reaction (RT-PCR) had negative results (Department of Molecular Biology of the University Medical Center Utrecht, the Netherlands). Biochemical blood testing revealed no enzyme defects in the urea cycle or disorders in the amino acid and organic acid catabolism.

After 7 days the child was extubated. He was alert, awake but unable to communicate verbally. Three weeks after admission he was transferred to our pediatric rehabilitation facility because of severe impaired cognitive function, mutism and behavioral disturbances. He was able to walk unassisted but the ataxia persisted characterized by a broad-based gait and dysmetria of all extremities. Three months later we noticed a slight improvement leaving him in a state of aphasia and severe cognitive deficit. Now, 2 years after admission at the age of 5 he expresses himself in short and simple sentences containing not more than 3 words.

Discussion

Influenza-associated acute encephalopathy is defined as a central nervous system involvement during the course of influenza infection.^{1,4} In our case, the diagnosis of influenza-associated encephalopathy was based on clinical features including fever, seizures and focal neurological deficits, the repeated isolation of influenza A virus from the throat and seroconversion measured in the hemagglutination inhibition assay. In influenza-associated encephalopathy CSF analyses will often show normal values or a discrete elevation of mononuclear leukocytes and a slightly increased protein level.¹² Because we found no inflammatory change in the CSF, we use the term 'encephalopathy' instead of encephalitis. Seizures develop normally within several days after the onset of fever.⁴ In 10 children (aged 22 months to 4 years, living in Nagoya, Japan) with influenza-associated encephalopathy the first symptoms of involvement of the central nervous system were generalized seizures.¹ On the contrary we found in our patient neurological deficit and behavioral disturbances before the seizures started. Despite the use of highly sensitive PCR assay, influenza A virus could be detected only in CSF specimen obtained from one of 18 patients with influenza A-associated encephalopathy.⁸ A negative result of the RT-PCR technique detecting influenza A virus RNA in CSF as in our case is also reported by Ito et al.¹³ Based upon the second brain

MRI, showing oedema mainly in the frontal lobes with sparing of the thalami and brainstem, ANE as one of the subtypes of influenza-associated encephalopathy could be excluded. The rapid and severe clinical course with brain oedema is probably mediated by several inflammatory cytokines and not by direct invasion of the brain parenchymal tissue by the virus.^{4,14} High plasma concentrations of interleukin-6 and other cytokines cause hyper-permeable vascular lesions and breakdown of the blood-brain barrier and thereby induce brain oedema.⁴ Diffuse brain oedema is associated with severe brain damage or death.¹⁵ However, we did not measure cytokin levels in CSF and blood. Although the effect of steroids on influenza A-associated encephalopathy is not known in literature, administration of steroids should be considered in these cases which could have an inhibitory effect on the presumed immunological cascade.

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