Unusual presentation of more common disease/injury

Viral encephalitis associated with pandemic 2009 (H1N1) influenza A

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Summary

Encephalitis has been described as a rare complication of pandemic 2009 (H1N1) influenza A infection in children and adolescents. This report is on two adult patients who presented with encephalitis in relation to acute H1N1 influenza. Encephalitis is therefore also a potential complication of pandemic 2009 (H1N1) influenza infection in adults.

BACKGROUND

Encephalitis during influenza infection is a rare complication described mostly during epidemics.^{1 2} The majority of the reported cases have been in children, especially in Japan,³ but cases in older patients have also been described.⁴ In previous reports no viral RNA has been detected in the cerebrospinal fluid (CSF), but increased levels of cytokines in the CSF have been documented.⁴ This suggests the pathogenesis of encephalopathy to be cytokine mediated. Clinical manifestations are diverse, from short seizures and abnormal behaviours to rapid evolution through decreased consciousness to coma.^{4–6} In relation to pandemic 2009 (H1N1) influenza A virus (H1N1v), neurological complications have been reported in the literature in four children⁶ and one adolescent.⁷ We report two adult patients with acute H1N1v infection and encephalitis. The cases appeared during a local epidemic from October to November 2009, when 82 cases of H1N1v infection were confirmed among patients admitted to Helsinki University Central Hospital, Helsinki, Finland, an adult tertiary centre serving about 1 million inhabitants.

CASE PRESENTATION

Case 1

A 55-year-old previously healthy man felt dizzy during the day prior to his admission and was later found convulsing symmetrically. Out-of-hospital emergency care gave intravenous benzodiazepine for prolonged epileptic seizures. His family members had had influenza-like symptoms during the preceding days.

On admission he was unconscious, response to pain was abnormal flexion/withdrawal and his upper limbs were convulsing. Plantar reflexes were positive. He had a fever of 38.5°C. His white cell count (WCC) was 5.9×10^9 cells/litre, level of plasma C reactive protein was <3 mg/litre and his kidney and liver functions were normal. CSF tests showed

there were no erythrocytes, and the WCC (2×10^6 cells/litre), glucose (4.5 mmol/litre) and protein (360 mg/litre) were normal. A cranial CT scan and chest x-ray were normal.

He was treated with fosphenytoin, intubated and transferred to an intensive care unit (ICU). He was treated with propofol for status epilepticus and anticonvulsive treatment with levetiracetam and fenytoin were administered. His clinical characteristics suggested encephalitis. Empirical antimicrobial treatment was administered with ceftriaxone, doxycycline and aciclovir. Because of the family history, and the regional epidemic of H1N1v, oseltamivir was also initiated.

The next day, his WCC was 11×10^9 cells/litre, C reactive protein level 169 mg/litre (normal <10 mg/litre) and a chest x-ray showed pneumonia considered to be caused by a virus or aspiration. The H1N1v RNA status of nasopharyngeal and tracheal samples was shown to be positive via the reverse transcription (rt)PCR method. (H1N1)-rtPCR was later performed on CSF collected at admission, but no viral RNA was detected. CSF PCR testing for Herpes simplex virus (HSV) and Varicella zoster virus (VZV) was also negative. Bacterial staining and culture of CSF and blood were negative. Serum and CSF antibody testing for acute mycoplasma, HSV1 and 2, VZV, *Borrelia burgdorferi* infection and for tick-borne encephalitis were negative. On day 3 an electroencephalogram (EEG) showed generalised waveform abnormalities typical of encephalitis without any epileptic activity.

After H1N1v infection was verified, oseltamivir was continued to complete a 5-day total course. Ceftriaxone was continued for pneumonia. Treatment for epilepsy was fosphenytoin/fenytoin for 5 weeks and levetiracetam to be continued for at least 3 months.

On day 4 the patient was extubated. On day 7 his chest x-ray was normalised. On day 14 his WCC, C reactive protein level, EEG and cerebral MRI findings were normal.

After extubation the patient was at first agitated and disoriented. Over the following days cognition improved. On discharge on day 19, he still had minor cognitive impairment. At 2 months later he subjectively reported being recovered but a neuropsychological control examination has not been carried out yet.

Case 2

A 71-year-old man was admitted because of altered mental status and seizures. He had a history of pulmonary sarcoidosis and pancreatitis, but was on no regular medication. Over the few days before admission he had had cough, headache and nausea. On the day of admission he had become confused and had had a short collapse. Out-of-hospital emergency care reported a fever of 38°C and altered consciousness level; he was drowsy, did not cooperate adequately and had two short seizures. After the second seizure he was intubated and sedated with propofol.

On admission he was unconscious and haemodynamically stable. He had lactataemia (lactate level 6.6 mmol/litre) and slight acidosis (pH 7.38, base excess -6.2 mmol/litre). His WCC was leucopenic (2.1×10^9 cells/litre, neutrophils 1.3×10^9 cells/litre) and C reactive protein level was 4 mg/litre. His kidney and liver functions were normal. His CSF WCC was 4×10^6 cells/litre and lactate level was 2.53 mmol/litre (normal 1.1–2.2 mmol/litre). Protein and glucose concentrations were normal. His chest x-ray was normal and a cranial CT scan revealed only slight vascular degeneration.

On arrival he was treated with dexamethasone and ceftriaxone because of suspected bacterial meningitis, but the results of initial examinations and the clinical characteristics suggested viral encephalitis so treatment with oseltamivir and aciclovir was administered. Fosphenytoin was administered as anticonvulsive treatment. He was transferred to an ICU. No signs of systemic bacterial infection developed: blood leucocyte levels remained relatively low (2.1–7.1 cells/litre, neutrophils 1.3–3.4 cells/litre), there was no bacterial growth in blood or urine cultures on admittance, and chest x-ray and cranial CT showed no signs of bacterial pneumonia or sinusitis. C reactive protein levels remained normal (4–8 mg/litre) in the first week of treatment.

A tracheal sample for influenza H1N1 collected on day 1 was positive on rtPCR. CSF staining and cultures were negative, as well as viral PCR testing for influenza A H1N1v, HSV and VZV. Blood cultures were negative, and serum and CSF antibody testing for acute mycoplasma, HSV1 and 2, and VZV infection were negative. EEGs on days 2 and 5 showed generalised waveform abnormalities indicating encephalitis. The EEG on day 10 was improved, but still abnormal.

After H1N1v infection was verified, oseltamivir was continued to complete a 6-day total course. Treatment for epilepsy with fosphenytoin/fenytoin was to be continued for at least 3 months.

There were no signs of recurrent convulsion after admission, but because of the patient's altered consciousness he could not be extubated until day 4. His clinical condition improved and his fluctuating confusion gradually decreased. On day 5 he was transferred to a neurological ward and on day 12 to a private hospital for further rehabilitation. At 2 months later he was returned home. He subjectively felt he had slight memory impairment after the episode.

DISCUSSION

In relation to H1N1v, encephalitis has been reported in four children,⁵ but not previously in adults. We report two men aged 54 and 71 years admitted to hospital because of altered mental status and seizures after a short period of influenza-like symptoms. Both fulfilled the diagnostic criteria for encephalitis with findings of fever, altered mental status >24 h, seizures and typical EEG findings.⁶ Additionally, criteria for this condition to be caused by H1N1v were met; that is, encephalitis within 5 days of influenza-like symptom onset, positive tests for H1N1v and no evidence of an alternative aetiology.⁶ In our cases no viral RNA was found in the CSF. This is in accordance with previous studies.^{1–8} Our patients were men, as are the majority of reported patients with neurological involvement during seasonal influenza.^{1–7} The clinical manifestations were similar to those described earlier in relation to seasonal influenza A or B, but more severe than on average, or the four cases with H1N1v reported in children.^{1–6} Appearance of 2 cases of encephalitis among 82 cases of hospitalised patients with influenza in our centre was much more than would be expected from the rate of 0.5–1.5 encephalitis cases per 1000 hospitalised influenza positive persons reported from Sweden¹ and is nearly as frequent as the reported 6 cases among 407 patients with influenza in Austria.² Novel influenza A (H1N1) virus infection should be considered as an aetiological agent of viral encephalitis in adults also.

Learning points

- ▶ Encephalitis during influenza infection is a rare complication described mostly during epidemics.
- ▶ Clinical manifestations are diverse, ranging from short seizures and abnormal behaviours to rapid evolution through decreased consciousness to coma.
- ▶ Activated cytokine response may be important factor in pathogenesis.
- ▶ Novel influenza A (H1N1) virus infection should be considered as an aetiological agent of viral encephalitis in adults.

Competing interests None.

Patient consent Obtained.

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