CASE REPORT

A severe neurological complication of influenza in a previously well child

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SUMMARY

We describe a case of a 3-year-old girl who was admitted with encephalopathy and a right-sided hemiparesis secondary to acute influenza A. She was up-to-date with the Australian National Immunisation Program (which does not routinely include the seasonal influenza vaccine). After initial treatment with intravenous antimicrobials and acyclovir, a brain and spinal cord MRI demonstrated extensive focal necrotic and haemorrhagic changes in keeping with acute necrotising encephalopathy (ANE). She was started on a course of oseltamivir and intravenous pulse methylprednisolone, followed by an oral weaning regimen of prednisolone. After an intense period of rehabilitation, she has made a remarkable recovery. Genetic testing has since confirmed that this girl has the RANBP2 gene mutation, which leads to increased susceptibility of developing ANE. This case report highlights ANE as a rare but severe complication of influenza, the unfortunate complication of having the RANBP2 mutation and the importance of paediatric influenza vaccination.

BACKGROUND

Despite its perceived severity in the paediatric population, influenza can cause significant morbidity and mortality in previously well children. Neurological complications are reported to occur in up to 10% of hospitalised children, including the potentially fatal acute necrotising encephalopathy (ANE). Of all vaccine preventable diseases, influenza is the leading cause of hospitalisation among Australian children under 5 years of age. However, it is not included in the routine Australian National Immunisation Program. Annual seasonal influenza vaccination in Australia is recommended from 6 months of age, but the uptake remains low at around 15%.¹ This case reinforces the serious consequences of influenza and questions whether the seasonal influenza vaccination should be recommended universally and more assertively for the paediatric population.

CASE PRESENTATION

A 3-year-old girl with a history of failure to thrive, who was up-to-date with the Australian National Immunisation Program, presented to a metropolitan emergency department with a 5-day history of fever, coryzal symptoms and lethargy. Although her general practitioner had started oral antibiotics during the early stages of her illness, she had clinically deteriorated in the preceding 24 h with slurred speech and a fluctuating

sensorium. There was no associated neck-stiffness or photophobia. Her parents and older sister were also unwell at the time with coryzal symptoms. In the emergency department, she was confirmed to have a fluctuating Glasgow Coma Scale (9–13), with increased tone and brisk reflexes throughout. Power was unable to be accurately assessed at the time.

INVESTIGATIONS

Full blood examination demonstrated a mild lymphopenia (white cell count $4.8 \times 10^9/L$, lymphocyte $2.3 \times 10^9/L$). Initial inflammatory markers revealed C reactive protein $<5 \text{ mg/L}$ and procalcitonin $<0.06 \mu\text{g/L}$. Blood chemistry was unremarkable. CT of the brain conducted in the emergency department did not identify a cause to explain the child's clinical deterioration. Lumbar puncture was withheld, and she was started on intravenous cefotaxime, flucloxacillin and acyclovir. She was then transferred to the intensive care unit for on-going monitoring.

The following morning, a right-sided hemiplegia became apparent. Subsequent MRI (as shown in figures 1–3) demonstrated extensive focal necrotic and haemorrhagic changes in the supratentorial

Figure 1 Brain MR axial image (T2-weighted) revealing hyperintensity involving bilateral extreme capsules and putamen (diagonal arrow), and thalami (horizontal arrow).

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Figure 2 Diffusion-weighted image demonstrating areas that have centrally restricted diffusion consistent with multifocal necrosis in acute necrotising encephalopathy.

and infratentorial areas of the brain, and spinal cord (cervical spine area C4–C5) in keeping with ANE and myelitis. Areas involved included bilateral extreme capsule regions, posterior

Figure 3 Apparent diffusion coefficient series demonstrating areas that have centrally restricted diffusion consistent with multifocal necrosis in acute necrotising encephalopathy.

thalami, both hippocampi, mammillary bodies, hypothalamus, left side of the pons, dorsal medulla and cerebellar hemispheres.

A subsequent nasopharyngeal aspirate was positive for influenza A (later confirmed as AH1pdm09 influenza virus, currently included in the Australian seasonal influenza vaccination). Lumbar puncture was subsequently performed and cerebrospinal fluid demonstrated 27 white cells (10 polymorphs/17 lymphocytes $\times 10^6/L$). Bacterial culture and respiratory virus PCR on the cerebrospinal fluid were negative. Blood was sent for genetic testing.

TREATMENT

Once the diagnosis of ANE secondary to influenza A was confirmed, the child was started on a 7-day course of oseltamivir and a 3-day course of intravenous pulse methylprednisolone, followed by an oral weaning regimen of prednisolone. This was done in discussion with Infectious Diseases and Neurology specialists.

OUTCOME AND FOLLOW-UP

The child remained as an inpatient for the following 3 weeks for rehabilitation, with ongoing issues of physical and cognitive fatigue, including short-term memory deficits. She was able to communicate and mobilise independently by the time of discharge, and continued to have outpatient rehabilitation. Four months later, she remains as a bright and interactive girl with some ongoing memory deficits. Genetic studies have confirmed that the girl has the RANBP2 gene mutation, which increases the chance of developing further episodes of ANE. It is recommended that she, and the rest of her family, get vaccinated annually with the seasonal influenza vaccine. The parents will also undergo genetic testing for the RANBP2 mutation and if they have the same mutation as their affected daughter, the other siblings will be offered testing.

DISCUSSION

The neurological complications of influenza are varied, with an incidence of 4/100 000 person-years.² Neurological complications include encephalopathy/encephalitis, seizures, Guillain-Barre Syndrome, myelitis, stroke and Reye syndrome. Prospectively collected data in 2009 from six major paediatric hospitals in Australia indicated that 9.7% of all children admitted with influenza had neurological complications, with seizures being the most common neural complication from the influenza A H1N1 virus, followed by encephalitis/encephalopathy (1.4%).³

ANE is the most severe form of acute non-inflammatory encephalopathy, making up 20% of cases⁴ with influenza A as the leading cause. ANE commonly affects children aged 6–18 months and has a poor prognosis, leading to death or severe neurodisability in 70% of affected children.⁴ Genetic studies have demonstrated that an autosomal dominant mutation in the RANBP2 gene can lead to an increased risk of developing ANE.⁵ ANE most often presents 24–72 h after initial influenza symptoms, with symptoms including seizure, coma, acute encephalopathy and focal neurological deficits.⁴ Imaging is often diagnostic, with T2-weighted MRI demonstrating multiple symmetrical lesions involving the thalami, upper brainstem tegmentum, periventricular white matter, putamina and cerebellum.⁵

Although the management of ANE is primarily supportive, there is some evidence to suggest that high-dose steroids may be of some benefit.⁶

Learning points

- ▶ Neurological complications of influenza A occur in up to 10% of hospitalised patients.
- ▶ Acute necrotising encephalopathy (ANE) as a rare complication of influenza A presents a few days after the viral prodromal illness and can be accompanied by seizures, focal neurological deficits and/or acute encephalopathy.
- ▶ Specific management of ANE is primarily supportive, although oseltamivir and high-dose steroids can be used.
- ▶ The autosomal dominant RANBP2 gene mutation is associated with recurrent episodes of ANE and affected individuals should receive an annual influenza vaccine.
- ▶ This case highlights the question of whether influenza vaccination should be universally recommended for the paediatric population, especially children under 5 years of age.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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