Recurrent aseptic meningitis in a child

Chi-Yeung CHU 朱志揚1, Man-Ting SOO 蘇文庭2, Daniel Kwok-Keung NG 吳國強3
1Department of Radiology, Pamela Youde Nethersole Eastern Hospital; 2Department of Paediatrics, Kwong Wah Hospital, Hong Kong

Introduction

Influenza is a common infection among children and the elderly, causing significant morbidity and mortality. The influenza virus may affect not only the respiratory tract, but also the central nervous system. We present here a child with two episodes of aseptic meningitis, one of which associated with influenza A virus. The literature on recurrent aseptic meningitis and influenza-related meningitis is reviewed.

Case report

A 10-year-old Chinese boy who lived in Saipan first presented in September 2003 for fever, headache and neck rigidity. Cerebrospinal fluid (CSF) showed elevated white blood cells of 40/mm³ with lymphocyte predominance (59%) and red blood cells 100/mm³. Lumbar puncture was done, and it revealed a pressure of 15 cmH₂O, protein of 0.32 g/L and glucose of 3.2 mmol/L (59% of serum level). Bacterial culture, acid-fast bacilli culture and polymerase chain reaction (PCR) for Mycobacterium tuberculosis and herpes simplex of CSF were negative. Blood culture, Mantoux test, throat swab and nasopharyngeal aspirate (NPA) immunofluorescence for respiratory viruses (adenovirus, influenza, parainfluenza and respiratory syncytial virus) were all negative. Paired serology tests for influenza, mycoplasma, varicella-zoster, herpes simplex, and mumps showed no rise in titres from admission to two weeks later. Since no causative organism was identified, he was diagnosed as aseptic meningitis and discharged two weeks later.

He presented to us again in March 2005 with fever and headache for ten days, with vomiting for three days. Before admission, he received treatment in Saipan and was given amoxicillin for 3 days. Plain computed tomography (CT) of the brain was normal. For both admissions, he did not have recent contact history or other travels.

On admission, he was febrile but not toxic-looking. Physical examination was normal except mild neck rigidity. Intravenous cefotaxime 200 mg/kg/day was given empirically. Plain CT brain and magnetic resonance imaging (MRI) of the brain were normal. Lumbar puncture showed an opening pressure of 18 cmH₂O. CSF showed a raised white cell count of 76/mm³ with lymphocyte predominance (76%) and red blood cells of 9/mm³, while the protein and glucose content was 0.51 g/L and 2.6 mmol/L (plasma glucose level 6.8 mmol/L) respectively. Again, CSF was negative for bacterial culture, viral culture, acid-fast bacilli culture, latex agglutination and PCR for Mycobacterium tuberculosis and herpes simplex. His white cell count was raised (15.3 x 10⁹/L), with neutrophil predominance (12.6 x 10⁹/L) and a normal lymphocyte count. Blood culture was negative for bacteria and fungus. Autoimmune markers (including anti-nuclear antibodies, anti-DNA antibodies and rheumatoid factor) were negative. Nasopharyngeal aspirate was negative for influenza A and B. Blood smear for malaria and monospot test were negative. Paired serological tests for varicella-zoster, herpes simplex, enterovirus, mumps, Japanese B encephalitis, dengue, rickettsia, mycoplasma and leptospirosa all showed no rise in titres after two weeks. However, the serum titre of influenza A antibody showed a fourfold decrease from 1:160 to 1:40 after four weeks.

He remained well despite mild neck rigidity and headache. No seizure or change in mental state or behaviour was noted. He continued to run a low-grade fever while on antibiotics, which were stopped after seven days. The fever started to subside twelve days after admission, i.e. fever for a total of 22 days. A second lumbar puncture done 13 days later was normal, with a white cell count of 5/mm³. The antibody titre against influenza A was performed on the second CSF, and
turned out to be normal. Lymphocyte subset and lymphocyte proliferation assay were normal, and he did not have any anatomical defects such as in the skull base, sinuses or middle ear. He was discharged after hospitalisation for 21 days, and remained well on follow-up 10 days later.

**Discussion**

Our patient had two episodes of aseptic meningitis. No organism was found in the first, but there was indirect evidence for influenza A in the second episode. We suspect that this is not a case of two random instances of infection, because recurrent aseptic meningitis is an unusual clinical scenario with differential diagnoses like congenital or acquired structural anomalies, infections, autoimmunity, immunodeficiency idiopathic causes.

In retrospect, the illness course of our patient appeared similar to the one reported in 1944 by Mollaret\(^1\) although the typical microscopic finding had not been looked for. Its clinical presentation was recurrent episodes of meningismus, headache and fever, separated by symptom-free episodes. Each episode lasted from a few days to three weeks, and generally resolved without any clinical intervention. Transient neurological symptoms might occur in some patients but the symptoms resolved with the resolution of the infection. The course of disease, although protracted, was benign and the recurrent attacks usually resolved after a period of three to five years.\(^2\) The reason for the recurrent nature of this type of meningitis was not known.

Examination of the CSF during an episode showed a pleocytosis, sometimes several thousand cells per microlitre, with lymphocytes, neutrophils and so-called “Mollaret” cells. These are large, friable cells with faintly staining vacuolated cytoplasm, originally thought to be endothelial but are now considered to be activated macrophages and are not pathognomonic of the disorder.\(^3\) Although not always identified in patients, herpes simplex virus (mainly HSV-2) was the most common agent causing Mollaret’s meningitis,\(^4\) with or without a history of genital herpes. The diagnosis was usually obtained only by positive PCR in HSV-2, whereas antibody analysis was not clinically useful. It was not clear from the literature whether other viruses might play a role in those cases where HSV was not identified. In our patient, no herpes simplex virus was detected in his CSF in both episodes, and no underlying anatomical or immunological defects were identified. In the second episode of illness, one might argue that the child had received antibiotics for three days and the CSF glucose was low. However, the paired viral titre suggested that influenza A was highly suspected, although the exact microbiological diagnosis could not be confirmed despite our investigations.

Influenza-related illnesses constitute a substantial proportion of hospitalisation and outpatient consultation among children.\(^5\) Estimated incidence of respiratory and circulatory deaths associated with influenza is 0.4-0.6/100,000 in people aged 0 to 49 years, 7.5/100,000 in people aged 50 to 64 years, and 98.3/100,000 in people of 65 years and above.\(^6\) A wide spectrum of clinical manifestations exists, ranging from sub-clinical illness to respiratory tract infection, myocarditis and meningoencephalitis.\(^7\) Meningitis caused by influenza virus was reported to occur in only 0.9-2.4% of in-patients with influenza infection.\(^7,8\)

Central nervous system (CNS) manifestations of influenza infection include encephalopathy, encephalitis, Guillain-Barre syndrome and transverse myelitis.\(^7\) When compared to parainfluenza virus and adenovirus, influenza A infection is associated with a higher incidence of febrile seizure admissions and of repeated seizures in the same febrile episode.\(^7\) During the months of peak activity, influenza may account for 35-44% of febrile seizure admissions.\(^9\) Patients with CNS manifestations due to influenza can have different presentations, such as seizure and change in mental state.\(^7,10\) The commonest presenting symptom in influenza-related meningitis is meningism,\(^8\) as in our patient.

Our patient presented with two episodes of aseptic meningitis, with clinical features of meningitis, CSF pleocytosis with lymphocyte predominance and a negative CSF culture. A concomitant four-fold decrease in serum antibody titre against influenza A suggested that influenza virus was the cause of the second episode of aseptic meningitis. We suspect that the absence of positive test for influenza A antigen on NPA and the lack of increase in CSF influenza A titre might be attributed by the late sample collection (day 12 of fever).

Diagnosing CNS manifestations due to influenza is a challenge, since the evidence of viral infection is usually
Case Report

not identified in the CNS. Influenza A virus was detected by PCR in the CSF in 5 of 7 patients with documented influenza-associated encephalitis or encephalopathy in one study, but not in others. Serological testing is another useful method for the diagnosis of influenza A virus infection. Interleukin-6 and other cytokines were proposed as the main mediators for CNS manifestations in influenza infection. Recurrent meningitis can be caused by infections, structural lesions, medications and chronic inflammatory diseases. Any underlying predisposing factors should be sought, including congenital CSF fistula, immunodeficiency or traumatic CSF fistula.

While it is believed that the majority of patients with CNS manifestations recovered fully and quickly, some reported otherwise: in a series of 21 patients with CNS involvement by influenza virus (six of them less than 18 years old), 10 of them had neurological sequelae (three of them less than 18 years old), and among the three patients below the age of 18 years with influenza meningitis, one had neurological sequelae while the other two patients had multiple focal lesions on MRI brain which were distributed asymmetrically over the cerebral cortex, thalamus, pons, or corpus callosum, characteristic of postinfectious demyelinating encephalitis. Vaccination is cost-effective in preventing influenza infection among children. In a meta-analysis, inactivated influenza vaccine and live-attenuated influenza vaccine had 65% and 79% efficacy against influenza infection respectively. However, it remains unclear whether the use of influenza vaccination can prevent or decrease the neurological complications due to influenza. The majority of influenza infections are self-limiting and do not require antivirals. Antivirals, such as amantadine, rimantadine, and neuraminidase inhibitors (zanamivir and oseltamivir), may at most shorten the course of illness if given early. It is unknown whether antivirals have any definite role in CNS manifestations of influenza A infection.

Conclusion

We present a case of recurrent aseptic meningitis, with one episode due to influenza A infection. The patient made a complete recovery without any neurological sequelae. The reason for the predisposition to recurrent aseptic meningitis is not known. Subtle immunological defects cannot be ruled out.

References