

Fatal influenza A (H3N2) and *Campylobacter jejuni* coinfection

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ABSTRACT

The rapid diagnosis and subtyping of influenza is particularly important in areas where avian influenza (H5N1) is present. The ability to recognise both typical and atypical presentations of influenza is also critical in such settings. A six-month-old male child who visited a H5N1-affected area subsequently died from a severe febrile diarrhoeal illness with minimal respiratory symptoms, and was initially diagnosed with influenza A of an unknown subtype. The final microbiological results showed a highly unusual combination of influenza A (H3N2) and *Campylobacter jejuni* infection.

Keywords: avian influenza, *Campylobacter jejuni* infection, H3N2 subtype, influenza A virus

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INTRODUCTION

Influenza and *Campylobacter* spp. commonly affect children in tropical countries, but are likely to be underdiagnosed.^(1,2) Malaysia experienced localised outbreaks of avian influenza (H5N1) in birds in 2004 and 2006, with no human cases.⁽³⁾ Humans infected with H5N1 may present atypically, for example with diarrhoea, rather than respiratory symptoms.⁽⁴⁾ We describe a child who had fever and diarrhoea and had recently visited an area affected by H5N1.

CASE REPORT

A previously healthy six-month-old male infant of Indonesian origin presented at Kajang Hospital, Selangor, Malaysia, with a two-day history of fever, cough and rhinorrhoea, and one day of severe watery diarrhoea. He also had three brief episodes of generalised tonic-clonic convulsions. On admission, he was febrile and unresponsive, with an unrecordable pulse and decreased skin perfusion. He was tachypnoeic, and the lung fields were otherwise clear. A diagnosis of acute gastroenteritis with hypovolaemic shock was made. He was resuscitated with fluids and inotropes, and intubated. Intravenous penicillin and cefotaxime were commenced to cover possible bacterial sepsis. Initial investigations revealed a normal complete blood count, including a white cell count of $5.2 \times 10^9/L$ (neutrophils 61%, lymphocytes

33%, monocytes 5%, eosinophils 1%), C-reactive protein 1.0 mg/dL, deranged clotting indices including an international normalised ratio of 2.78, sodium 153 mmol/L, urea 14.1 mmol/L and creatinine 130 $\mu\text{mol/L}$. Arterial blood gases showed severe metabolic acidosis, with a pH of 6.97, and base excess -26.4 mmol/L . The chest radiograph appeared normal.

Further questioning revealed that the patient and his family had visited relatives in Gombak, a nearby town in the same state, a week ago. At the time (February 2006), there was an outbreak of H5N1 among village chickens in Gombak, with ongoing culling of all domestic birds and active surveillance for human and bird cases.⁽³⁾ The patient had no apparent history of direct exposure to birds. His mother reported a mild, non-specific febrile illness five days prior to his admission. The patient was urgently transferred on the same day to the Paediatric Intensive Care Unit at the University Malaya Medical Centre, Kuala Lumpur, for further care. Stool culture, lumbar puncture, and nasopharyngeal aspirate for respiratory viruses were carried out. The cerebrospinal fluid (CSF) showed 2,160 red cells/ μL , 60 neutrophils/ μL , glucose 6.8 mmol/L (serum glucose 7.1 mmol/L), and raised protein of 2.65 g/L. Influenza A virus was detected in the nasopharyngeal aspirate using the respiratory viral screen indirect immunofluorescence assay (Chemicon, USA). Attempts to subtype with specific H1, H3 and H5 immunofluorescence assays, using monoclonal antibodies provided by the World Health Organisation, produced negative results. This may have been because the influenza A subtyping immunofluorescence assay is recommended for use on virus isolates, rather than clinical specimens. The specimen was sent to the Veterinary Research Institute (VRI) in Ipoh for polymerase chain reaction (PCR) analysis, as the VRI was the main laboratory investigating H5N1 avian outbreaks. Meanwhile, the patient deteriorated, despite aggressive intensive care, and died the following morning.

The stool culture subsequently yielded *Campylobacter jejuni*. PCR for the influenza virus subtype identified influenza A (H3N2) in the nasopharyngeal aspirate, while tests for H5N1 were negative. Four days later, influenza A (H3N2) grew in cell cultures inoculated with the nasopharyngeal aspirate. The subtype was confirmed by haemagglutination inhibition. No organisms were isolated

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from the CSF or blood, including the influenza virus and *Campylobacter* spp. The cause of death was recorded as hypovolaemic shock resulting from acute infective gastroenteritis, due to influenza A and *Campylobacter* spp.

DISCUSSION

Avian influenza strains may carry any of the reported subtypes of haemagglutinin (H1–H16) and neuraminidase (N1–N9) surface proteins. Human influenza strains only have H1, H2 or H3, and either N1 or N2. Avian influenza (H5N1) has now spread globally from its Asian origins. Current circulating human subtypes are H1N1 and H3N2.⁽⁵⁾ In the case described, before final confirmation of H3N2, we were faced with a severely ill child who had laboratory-confirmed influenza A of an undetermined subtype, and had recently visited a H5N1-affected area. Although most cases of H5N1-infected humans have had direct contact with sick birds, there are occasional human cases which report being merely present in areas with affected birds, without direct contact with the birds.⁽⁴⁾ Furthermore, although no direct contact with birds was reported in this case, the presence of *Campylobacter* spp. suggested possible contact with chickens, or at least with contaminated poultry products.⁽²⁾ Therefore, at the time, there was concern that this could be the first case of human H5N1 infection seen in Malaysia.

The case raised several important points. Firstly, both human influenza and H5N1 may present atypically, with mild or absent respiratory symptoms and unremarkable chest radiographs, as well as predominant non-respiratory features such as diarrhoea, fits and apparent sepsis, as in this case.^(4,6-8) In Vietnam, a fatal case was reported of a child presenting with diarrhoea, followed by seizures and coma, with an initially normal chest radiographs; influenza A (H5N1) was later isolated from several sites, including CSF and a rectal swab.⁽⁷⁾ It is therefore critical to be able to recognise atypical presentations in patients at risk of avian influenza.

Coinfection with *Campylobacter* spp. undoubtedly complicated the clinical picture, as both pathogens may cause a similar presentation. It was not possible to determine the relative contribution of each organism towards the patient's death, as a postmortem was not conducted. Respiratory viral infections, most notably influenza, are well-known to predispose to severe bacterial coinfections, usually sepsis or respiratory infections due to *Staphylococcus aureus* or *Streptococcus pneumoniae*.⁽⁶⁾ Several mechanisms of this "lethal synergy" are suggested, including viral immunosuppression leading to increased susceptibility to bacterial invasion.⁽⁹⁾ Concomitant bacterial gastroenteritis is rare, and coinfection with *Campylobacter* spp. has not been previously described with the influenza virus, so this case is highly unusual.

This case highlights the importance of rapid laboratory diagnosis and subtyping of influenza, to facilitate infection control⁽¹⁰⁾ and public health decisions. This is particularly important in areas where both human and avian influenza are present, such as Southeast Asia. Appropriate control measures for influenza cases in such settings are important to prevent onward transmission, and to minimise the risk of human influenza and H5N1 coinfection, which may result in reassortment.⁽¹¹⁾ As a recommended minimum, laboratories should offer a rapid diagnostic assay such as immunofluorescence, or preferably nucleic acid testing, which has greater sensitivity.⁽⁵⁾ If subtyping is not locally available, each laboratory should be able to access a reference laboratory offering this service. This case provides a timely reminder that human influenza may present atypically, and may be fatal in healthy children, especially in the presence of a bacterial coinfection. Up to 47% of influenza-associated childhood deaths may occur in previously healthy children.⁽⁶⁾ Furthermore, the rapid diagnosis and subtyping of influenza is of critical importance in a setting where avian influenza is present.

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