

# The first case of H5N1 avian influenza infection in a human with complications of adult respiratory distress syndrome and Reye's syndrome

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**Abstract:** Avian influenza virus was not known to cause systemic infection in humans before. We report a 3-year-old boy with good past health who developed pneumonia caused by H5N1 avian influenza A virus (A/Hong Kong/156/97). The virus was isolated from a tracheal aspirate. There were complications of Reye's syndrome, adult respiratory distress syndrome, and multiple organ system failure. He had a history of receiving aspirin. His adult respiratory distress syndrome did not respond to endotracheal surfactant replacement therapy. He died 6 days after admission. Clinicians should be alert to the importance of a new human influenza strain.

**Key words:** adult respiratory distress syndrome; H5N1 avian influenza; Reye's syndrome.

Influenza A virus is known to infect a variety of animals including pigs, horses, birds, and seals as well as humans.<sup>1</sup> Previous studies revealed that all subtypes of influenza A virus, including haemagglutinin antigen H1 to H15 and neuraminidase N1 to N9, could be found in birds.<sup>2</sup> Although severe H5 subtype avian influenza infection in birds occurred rarely, there are two reported outbreaks of severe disease caused by the H5 subtypes. One outbreak of the H5N2 subtype occurred in chickens in Pennsylvania in 1983<sup>3</sup> and another of H5N1 subtype in turkeys in Norfolk, England in 1991.<sup>4</sup> So far, the only reported human infections caused by the avian influenza virus were two cases of conjunctivitis caused by avian H7 subtype.<sup>5,6</sup> We report the case of a 3-year-old boy infected by avian influenza A H5N1 subtype who developed multiple complications. This is the first case reported in the literature of systemic infection in a human caused by the avian influenza A virus.

## CASE REPORT

The patient was the second child in a Chinese family and had an unremarkable perinatal history. He had been healthy previously. He developed a fever up to 40°C on 10th May 1997, and episodes of abdominal pain. Antibiotics and antipyretics including aspirin were prescribed by a private practitioner. He was admitted to a private hospital on 13th May 1997. Physical examination showed pharyngitis with bronchial inflammatory changes on chest X-ray. Throat swab and urine cultures were sterile. There was leukopaenia of  $2.0 \times 10^9/L$  (neutrophil count  $0.9 \times 10^9/L$ , lymphocyte count  $0.84 \times 10^9/L$ ). Left shift and 9% band forms were observed. ESR was 13 mm/h and the ALT was 64 iu/L. He received intravenous amikacin and cefotaxime. However, he gradually became irritable with more severe abdominal pain. Viral

titres or cultures were not performed. He was referred to Queen Elizabeth Hospital on 16th May 1997 for further management.

Examination showed an irritable child who was febrile and fully conscious with no neck rigidity. His abdomen was soft. Cardiovascular, neurological and chest examination were essentially normal. His throat was mildly congested, and an exudate was present. He was commenced on intravenous ampicillin and gentamicin. A complete blood count showed a leukopaenia of  $1.3 \times 10^9/L$ . The ALT was 140 iu/L; amylase concentrations were normal, and his blood glucose was 4.7 mmol/L.

He deteriorated on the night of 17th May 1997 and was very irritable and confused. He developed a high temperature and his SaO<sub>2</sub> was 80% despite 3 L/min nasal oxygen. He was hyperventilating, with decreased air entry over the left chest. The clinical picture was compatible with severe sepsis with a Reye-like picture. He was intubated and ventilated with positive pressure. Ceftazidime as well as metronidazole were added. A chest X-ray demonstrated consolidation of the left lung with increased right hilar infiltrate which suggested severe pneumonia. Arterial blood gas estimation showed low PaCO<sub>2</sub> and PaO<sub>2</sub>. The oxygenation index (OI = mean airway pressure  $\times$  FiO<sub>2</sub>/PaO<sub>2</sub>  $\times$  100) just after intubation was 32.7.

A CT scan of brain showed no cerebral oedema. Electroencephalography demonstrated encephalopathic changes. Echocardiography revealed only minimal tricuspid incompetence and mitral incompetence, with a right sided pleural effusion. There was persistent leukopaenia, and liver enzymes remained raised with ALT up to 518 iu/L (ref. 5–45) and AST up to 2410 iu/L (ref. 20–60) on 18th May. His bilirubin was 20  $\mu$ mol/L (ref. < 23). Serum ammonia was 29  $\mu$ mol/L (ref. 12–50). Lactate was 1.4 mmol/L (ref. 0.7–2.1). Urine for metabolic screening was negative. There was diffuse pulmonary infiltrate on chest X-ray with refractory hypoxaemia.

A clinical diagnosis of fulminant sepsis with adult respiratory distress syndrome was made. The oxygenation index later rose to 47.2. Endotracheal surfactant replacement therapy was initiated and 16 mL of survanta were instilled. Oxygenation index before surfactant was 62.7. He developed a pneumothorax 1 h after commencement of surfactant. Conventional ventilation

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was changed to high frequency oscillatory ventilation. A total of four doses of survanta (16 mL + 8 mL + 8 mL + 8 mL) were given over 2 days, with no improvement in oxygenation. He developed repeated pneumothoraces, a pneumomediastinum, and subcutaneous emphysema. Intravenous gammaglobulin was given empirically for severe sepsis. Acyclovir, vancomycin and amphotericin B were added. His condition deteriorated with disseminated intravascular coagulation, liver and renal failure. Continuous veno-venous haemofiltration was commenced and repeated infusions of blood products were given. He finally succumbed on 21<sup>st</sup> May. Paramortem biopsies of liver, kidney, bone marrow were taken. Paramortem lumbar puncture was also performed. His parents refused postmortem examination.

Microbiological investigation showed an elevated influenza A serological titre (18<sup>th</sup> May) of 1 : 40, with no increase in titre of other viruses. Cerebrospinal fluid was clear with a white cell count of 3/mm<sup>3</sup> and was negative on bacterial and viral culture. Bronchoalveolar lavage was negative for *Pneumocystis carinii*. Tracheal aspirate on 19<sup>th</sup> May yielded influenza A virus and was negative for bacterial and fungal culture. Pleural fluid, urine and blood cultures were negative. No acid fast bacilli were detected in pleural fluid, gastric aspirate, urine and sputum.

Paramortem liver biopsy showed microvesicular fatty change. There also were multiple Councilman bodies with scanty inflammatory cells that suggested viral infection. However, no viral inclusions were seen. Renal biopsy revealed vacuolation and vesicular change of proximal tubules which were consistent with the microvesicular fatty changes of Reye's syndrome. No abnormal inflammatory infiltration or viral inclusions were seen. Bone marrow examination showed reactive changes including active granulopoiesis with left shift, active erythropoiesis and increase in reactive histiocytes with occasional haemophagocytic activity.

The initial culture of the tracheal aspirate grew atypical influenza A virus. The isolates were then sent to the Center for Disease Control and Prevention, USA; National Institute for Medical Research, London, UK; and National Influenza Center, Rotterdam, The Netherlands for further study. The virus was subsequently confirmed to be H5N1 avian influenza A virus. The virus was designated as A/Hong Kong/156/97.

The kindergarten of this patient kept chickens and ducklings but there was no definite history of contact of this patient with these birds. There was no history of travel either.

## DISCUSSION

Influenza had caused several pandemics in history. Influenza A virus possesses external spikes that comprise two different glycoproteins: the hemagglutinin and neuraminidase. Hemagglutinin subtypes of H1 to H15 and neuraminidase subtypes of N1 to N9 are described. Hemagglutinin is important in determining the virulence of avian influenza A virus.<sup>7</sup> Multiple basic amino acids are found in the cleavage site sequence of hemagglutinin H5.<sup>8</sup> The presence of basic amino acid at the cleavage site is thought to allow activation of hemagglutinin by proteases present in many body tissues.<sup>9</sup> This may account for the virulence of H5 avian influenza virus. Besides the outbreak of H5N1 infection in turkeys in England in 1991, laboratory studies of the H5N1 strain also showed that the virus was highly pathogenic in chickens.<sup>10</sup> The virus also replicated in tissues other than the respiratory tract, as viral antigen could be found in neurons and vascular endothelium.<sup>10</sup>

The effect of H5N1 influenza virus in human is still to be determined, but animal studies showed that H5N1 influenza virus could suppress the T-cell function and enhance macrophage phagocytic activity in mallard ducks.<sup>11</sup> This patient had a 1 week history of fever (up to 39–40°C) with throat inflammation. He also had abdominal pain on admission without any evidence for a surgical cause. He then deteriorated quickly 1 week after the onset of disease with development of bilateral pneumonia with respiratory failure. A major concern was the leukopenia on admission. His total white cell count was  $2.0 \times 10^9/L$  with a lymphocyte count of  $0.84 \times 10^9/L$ . Whether there was an underlying primary immune problem that predisposed to the extraordinary severity of disease or whether this was a secondary effect due to viral infection is unknown. Extra pulmonary complications of influenza including carditis, encephalopathy, myopathy, and renal failure have been described.<sup>12,13</sup>

One week after the onset of disease, he developed acute encephalopathy and impaired liver function with grossly elevated liver enzymes including AST and ALT. His bilirubin level was not raised. The cerebrospinal fluid was clear with a WCC of 3/mm<sup>3</sup>. The findings on paramortem liver and renal biopsy together with a history of aspirin ingestion are suggestive of complications of Reye's syndrome. This patient fulfilled both the British Reye's syndrome Surveillance Scheme Criteria and the CDC criteria for Reye's syndrome including influenza illness, acute non-inflammatory encephalopathy with normal CSF findings, hepatic dysfunction with greater than three fold rise in AST and ALT with normal bilirubin, and microvesicular fatty infiltration of liver and kidneys. However, in the liver biopsy specimen, besides the microvesicular fatty change, there were also some changes suggestive of viral infection. Although no viral inclusions were detected, the possibility of extrapulmonary spread with multi-organ involvement could not be excluded. As postmortem examination was refused, detailed histological evaluation for probable additive pathogenic effects by H5N1 virus was not possible. Nonetheless, since this patient developed adult respiratory distress syndrome (ARDS) and multiple organ system failure that could not be explained by Reye's syndrome alone, it is possible that this virus may be highly pathogenic in humans.

Adult respiratory distress syndrome is the pulmonary manifestation of asystemic inflammatory response syndrome. There is vascular endothelial damage leading to pulmonary edema in lungs. The mechanisms leading to tissue damage are complicated and include release of various mediators. The role of surfactant replacement therapy in ARDS is controversial. Problems of dosage, preparation and method of delivery are still to be solved. One of the authors (ASWK) previously treated two children with ARDS with endotracheal instillation of surfactant with survival in both cases (unpublished data). Endotracheal surfactant instillation was given empirically to this patient. However, he developed repeated pneumothoraces and continued to deteriorate. As disturbance in alveolar surfactant function is only one of the events that occurred in ARDS, failure of surfactant therapy in this patient may reflect the multiplicity of pathology that occurred in the lungs and in other organs that could not be dealt with by surfactant alone.

As early antiviral treatment may improve the outcome of influenza infection, rapid viral diagnosis is extremely helpful. Investigation in Hong Kong in H5N1 avian influenza patients revealed that direct immunofluorescence with influenza A type specific reagents had suboptimal sensitivity in the rapid diagnosis of H5N1 directly from clinical specimens, while reverse transcription polymerase chain reaction assay was a

sensitive and reliable investigation for the rapid diagnosis of the presence of H5N1 virus. In specimens strongly positive for influenza A antigen by direct immunofluorescence test, the negative reaction with H5 monoclonal antibody could rapidly exclude H5N1 virus infection.<sup>14</sup> This can facilitate earlier decision making in management. Amantidine and rimantidine are known to be effective antiviral agents for influenza A virus. Amantidine 100 mg twice a day for 5 days is the recommended adult dose, while for children aged 1–9 years, the dosage is 5 mg/kg/day in two divided doses up to 150 mg/day. The dose of rimantidine is 100 mg twice daily and needs to be decreased in patients with liver or renal insufficiency. The H5N1 influenza isolates from Hong Kong that had been tested are sensitive to both amantidine and rimantidine.<sup>15</sup> Amantidine prophylaxis can be considered in persons who develop symptoms compatible with influenza after having close contact with patients.

At the time of submission of this report (May 1998), there were 18 confirmed cases of H5N1 avian influenza with 6 fatalities in Hong Kong. The 33.3% mortality is unusual and is of concern. The source of infection, the mode of transmission and the degree of infectivity in human to human transmission of this virus remain to be determined.

In conclusion, this report describes the first patient with systemic infection by H5N1 avian influenza. We hope that by providing this clinical information, clinicians will be alert to the importance of this new strain of human influenza virus. We also advise avoiding aspirin in children with an influenza-like illness.

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#### REFERENCES

- 1 Kilbourne ED. Animal Influenza: Ecology and Disease. In Kilbourne ED, ed. *Influenza*. Plenum Medical, New York, 1987: 229–251.
- 2 Webster RG. Predictions for future human influenza pandemics. *J. Infect. Dis.* 1997; **176** (Suppl. 1): S14–9.
- 3 Kawaoka Y, Naeve CW, Webster RG. Is virulence of H5N2 influenza virus in chicken associated with loss of carbohydrate from the hemagglutinin? *Virology* 1984; **139**: 303–16.
- 4 Alexander DJ, Lister SA, Johnson MJ, Randall CJ, Thomas PJ. An outbreak of highly pathogenic influenza in turkeys in Great Britain in 1991. *Vet. Rec.* 1993; **132**: 535–6.
- 5 Webster RG, Geraci J, Petursson G, Skirnisson K. Conjunctivitis in human beings caused by influenza A virus of seals [letter]. *N. Engl. J. Med.* 1981; **304**: 911.
- 6 Kurtz J, Manvell RJ, Banks J. Avian influenza virus isolated from a woman with conjunctivitis. *Lancet* 1996; **348**: 901–2.
- 7 Horimoto T, Kawaoka Y. Reverse genetics provides direct evidence for a correlation of hemagglutinin cleavability and virulence of an avian influenza A virus. *J. Virol.* 1994; **68**: 3120–8.
- 8 Wood GW, Banks J, McCauley JW, Alexander DJ. Deduced amino acid sequences of the haemagglutinin of H5N1 avian influenza virus isolates from an outbreak in turkeys in Norfolk, England. *Arch. Virol.* 1994; **134**: 185–94.
- 9 Rott R. Molecular basis of infectivity and pathogenicity of myxovirus. *Arch. Virol.* 1979; **59**: 285–98.
- 10 Kobayashi Y, Horimoto T, Kawaoka Y, Alexander DJ, Itakura C. Neuropathological studies of chickens infected with highly pathogenic avian influenza viruses. *J. Comp. Path.* 1996; **114**: 131–47.
- 11 Laudert E, Sivanandan V, Halvorson D. Effects of an H5N1 avian influenza virus infection on the immune system of mallard ducks. *Avian Dis.* 1993; **37**: 845–53.
- 12 Kilbourne ED. Influenza in man. In Kilbourne ED, ed. Plenum Medical, New York, 1987: 157–218.
- 13 Shenouda A, Hatch FE. Influenza A viral infection associated with acute renal failure. *Am. J. Med.* 1976; **61**: 697–702.
- 14 Yuen KY, Chan PKS, Peiris M, Tsang DNC, Que TL, *et al.* Human disease associated with avian influenza A virus subtype H5N1—clinical features and rapid viral diagnosis. *Lancet* 1998; **351**: 467–71.
- 15 CDC. Isolation of avian influenza A (H5N1) viruses from human – Hong Kong, May–December 1997. *MMWR* 1997; **46**(50): 1204–7.