

## Case Report

# A young girl with suspected encephalitis caused by avian influenza A (H5N1) infection in Indonesia

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## The case

A previously healthy two-year-old girl was admitted to the Emergency Unit of Cipto Mangunkusumo Hospital (CMH) Jakarta, on March 23, 2006 with a deterioration of consciousness since four days before admission. She was referred by a district hospital with a working diagnosis of suspect encephalitis, gastroenteritis, and febrile convulsion. History taken from her parents revealed that since eight days before admission she had a mild fever and cough, without rhinorrhea. Her appetite, defecation and urination were normal. Patient was taken to a clinic, where she was diagnosed as having an upper respiratory tract infection, and was given three kinds of medicine (i.e., antipyretic, expectorant and antibiotic).

Seven days prior to admission the fever increased, cough persisted, along with vomiting five times per day, contained of food about ¼ glass. Patient also had diarrhea once per day (about two spoonfuls), containing fluid and fecal equally, yellow colored, without a trace of blood and/or mucous. Appetite was still normal. Patient was brought to the same clinic, and this time was given symptomatic medicine only. Her condition still had not improved.

Four days before admission, the fever was even higher, cough worsened and the patient began to have shortness of breath. Vomiting was no longer occurred, but patient still had watery diarrhea three times per day. Her appetite decreased and she tended

to sleep longer. Her parents again brought her to the same Clinic. She was given another antibiotic and supportive treatment, and sent back home.

The next day, fever was still high while all other symptoms worsened and small red spots – as small as pinhead needles – appeared on the patient's both hands and forehead. She slept longer than before, but was not brought to a medical facility. One day before admitted to CMH, her consciousness decreased, fever still very high with shortness of breath and persistent diarrhea. She was then brought to a district hospital. On the way to the hospital, the patient had convulsion for about 3 minutes, with her eyes stared above and both arms stiffed. The convulsion stopped spontaneously and afterwards the patient was unconscious. At the district hospital, she received oxygen and parenteral fluid, and was diagnosed as encephalitis. The attending doctor recommended the patient to be referred to another hospital, because the Intensive Care Unit (ICU) of the district hospital was full. The patient's parents refused due to financial constraint and the girl was once again brought home.

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At night of the same day, the patient was again brought to the district hospital, accompanied by the neighbor who was willing to pay for the medication expenses. At that time, the patient was somnolent, GCS (Glasgow Coma Scale) E4V2M5, pulse rate 279 beats/minute, respiratory rate 80 times/minute, and body temperature 40°C. Cyanosis was detected, O<sub>2</sub> saturation 40%, but no neck stiffness. Patient was referred to CMH.

In CMH, patient was somnolent, with shortness of breath, and cyanosis. Her blood pressure was 70/50 mmHg, pulse rate was 140 times/minute, regular but weak, respiratory rate was 74 times/minute, with severe chest indrawing, and the temperature was 35.8°C. From clinical examination and antropometric measurement, the patient was clinically underweight.

No deformity found in the patient's head; head circumference was 47 cm (normal), and major fontanel had closed. No cranial nerve paralysis was found. The eyes were sunken, she was neither pale nor icteric, her pupils were isocor, with 2 mm diameter. Reflex to light and doll's eye movement were found. Ears and pharynx were normal. Mucosal mouth was dry. Heart was within normal condition. In the lung examination, there were weak vesicular breath sound and rales. The turgor of the abdomen was lessen. Liver enlargement was found 2 cm below arcus costae and 2 cm below processus xyphoideus, sharp, with smooth surface, and no tenderness. The extremities were cold, capillary refill >3 seconds and petechiae was found. Physiologic reflexes were weak, while pathological reflexes, meningeal signs and pareses were not found.

Working diagnosis at the time of admission was shock due to diarrhea, metabolic encephalopathy, with differential diagnoses of encephalitis and bronchopneumonia. Oxygen through nasal canule was administered 6 L/minute, and patient was also given fluid resuscitation. After fluid resuscitation, the patient was still somnolent with dyspnea, blood pressure 110/80 mmHg, pulse rate 120 times/minute (regular, normal volume), respiratory rate 48 times/minute with chest retraction, temperature 36.5°C (axilla), and urine output 1 mL/kg/hour. Laboratory findings show hemoglobin 11.5 g/dl, WBC 4,300/ $\mu$ L; platelet 247,000/ $\mu$ L. The blood glucose was 97 mg/dl. Blood gas analysis showed pH 7.232; pCO<sub>2</sub> 35.2 mmHg; pO<sub>2</sub> 43.7 mmHg, HCO<sub>3</sub> 14.9 mEq/L, base excess -12.9 mEq/L, O<sub>2</sub> saturation 71.3%, sodium 134 mEq/L, potassium 4.4

mEq/L, chloride 87 mEq/L. Chest radiographs showed a vast inhomogeneous cloud in both lungs.

Patient was consulted to the Pediatric Tropical Infection Division in CMH with a diagnosis of severe infection, encephalitis or metabolic encephalopathy. The Pediatric Neurological Division had suggested to conduct lumbar puncture if the condition of the patient was stabilized. The patient was also consulted to the Pediatric Respiriology Division. Based on findings of severe respiratory distress, severe pneumonia, and results of laboratory tests (hypoxia and leucopenia), progressive clinical and radiologic deterioration, the patient was suspected as having avian influenza infection. She was immediately intubated and referred to the Sulianti Saroso Infectious Disease Hospital (IDH), one of the referral hospitals for avian influenza cases in Jakarta. However, on the way to IDH, the patient died. Serum, pleura aspirates, nasal and pharyngeal swabs were taken from the body and sent to the avian influenza referral laboratory in the National Institute of Health Research and Development (NIHRD), Jakarta (see results in Table 1).

Results of these tests had been confirmed by the laboratories in the University of Hong Kong and the United States Centre for Diseases Control and Prevention, on March 29<sup>th</sup>, 2006. No autopsy was performed.

From further anamnesis, it was known that the patient had some contacts with sick birds, suspected with AI infection. The patient lived in a slum neighborhood. Within the radius of 50 meters from her house, some neighbors breed poultries. The patient was known to often stroll around the area with her father. It was not known whether there were dead poultries around that time. About one month before the patient's illness, many of the poultries were sold to surrounding neighbors with low prices, suggesting that they were sick poultries. The patient's family denied the possibility of consuming these sick chicken. There were no other people in the surrounding neighborhood who suffered from the same illness as the patient's.

## Discussion

Since 2003 until May 15<sup>th</sup>, 2009, WHO had recorded human avian influenza (AI) cases in 15 countries

**Table 1.** Results of NIHRD laboratory tests

Specimens	rRT-PCR Flu A	RT-PCR H5	rRT-PCR H5	RT-PCR N1	Hemagglutination Inhibition (HI)
Nasal swab	(+)	(+)	(+)	(+)	
Pharyngeal swab	(+)	(+)	(+)	(+)	
Pleural aspiration fluid	(+)	(+)	(+)	(+)	
Endotracheal tube wash	Not performed	(+)	(+)	(+)	
Blood/serum					(-)

including Indonesia. Total 424 cases were recorded, with 261 fatalities.<sup>1</sup> The first AI outbreak in humans occurred in Hong Kong, in 1997. At that time, 18 people were infected (among them 11 were children), six of them died (three children). Epidemiologic investigation suggested that these patients were infected directly from chicken.<sup>3</sup> The next outbreak occurred in Vietnam and Thailand in 2003 to 2004.<sup>4,5</sup> Fatalities often occurred in younger patients. In Thailand, the case fatality proportion (CF) in children under 15 years old was 89%.<sup>6</sup> Fatalities commonly occurred at 9 to 10 days after onset (in 6-30 days observation),<sup>4,6</sup> most of them died due to progressive respiratory failure.<sup>6</sup> In Indonesia, the first AI infected human case was identified in July 2005. Until May 15<sup>th</sup>, 2009, 141 cases were reported as confirmed AI A (H5N1) cases, 115 of them died (CF 82.3%).<sup>7</sup> Data in National Institute of Health Research and Development as national referral laboratory showed that 46 (32.6%) among the 141 cases were children aged 0–14 years old, 34 of them died (CF in children 74%).<sup>8</sup>

Humans can be infected by influenza A (H5N1) virus through sick poultries and their products, and also through environment (air and tools contaminated by the poultry's fecal or secretion). WHO has reported that, most of the confirmed patients had some contact histories with infected poultries, e.g., poultry feather's cutting, product preparation, chicken fight, playing with poultries, especially with asymptomatic infected ducks, consuming uncooked duck or poultry's blood.<sup>4,6</sup> Infection between humans remains ineffective.<sup>4,5</sup> In our case, there had been a suspicious history of poultry or sick/dead poultry (suspected because later on the chicken were sold at very low prices) in the neighborhood. According to the patient's mother, the child often played in those neighborhoods. However, it was not clear whether there had been an actual

contact between the child and the chicken. Hence, the incubation period was also unclear.

The pathogenesis of the influenza A (H5N1) infection in humans is still unclear.<sup>9</sup> The virus infection is suspected to have triggered cytokine storm, an overwhelming immune response through T cell activation or natural killer cell by macrophages infected by this virus. Cytokine storm can cause permanent damage to bronchi, followed by acute respiratory distress syndrome (ARDS) and multiple organ failure.<sup>10</sup> To et al<sup>11</sup> suspected patients with severe AI A (H5N1) infection to have virus replication in the respiratory tract which can trigger hypercytokinemia and hemophagocytic syndrome complications. This syndrome plays an important role on the hematological manifestation of influenza A (H5N1) infection, and can cause multiple organ failure. Kuiken et al<sup>12</sup> described that virus replication occurred in the respiratory tract, causing alveolar diffuse damage. This damage is the trigger of ARDS and can lead to multiple organ failure. This may explain the clinical symptoms and abnormalities in other organs, although virus replication outside the respiratory tract is not detected. Lower respiratory tract manifestation occurs in the disease's early stages, and dyspnea usually occurs in the fifth day (in 1-16 days range) after onset.<sup>6</sup> This patient had an acute onset of fever and started to show shortness of breath at day five after onset. Her latest chest x-ray at day eight showed a bilateral diffuse infiltrate, which related to a progressivity towards respiratory failure.<sup>6</sup>

Encephalitis and encephalopathy are complication from influenza A (H5N1) virus infection in humans which rarely occurs and the pathogenesis is also unclear.<sup>13-16</sup> Cytokine may play a role in encephalopathy related to influenza. High level of interleukin-6 plasma seems to be the indicator of encephalopathy progressivity.<sup>17</sup> Common manifestation of central nerves damage

caused by influenza virus infection are seizure and somnolence.<sup>13</sup> Maricich et al<sup>16</sup> stated that influenza should be considered as a differential diagnosis in patients with seizure and mental disorder, especially if accompanied with respiratory symptoms or during influenza outbreak. The infection of influenza A (H5N1) in our patient was severe and its manifestation was of a systemic illness. The patient had high fever, progressive respiratory failure symptoms (cough, dyspnea on the fifth day of onset), gastrointestinal disorders (vomit and diarrhea), central nervous damage (seizure, somnolence), and shock. Leucopenia without lymphopenia and thrombocytopenia was found, while blood gas analyses showed severe hypoxia and metabolic acidosis. Severe hypoxia was confirmed by chest x-ray showing vast damage throughout bronchi tissues (inhomogeneous cloud in both lungs). Liver and kidney's function test was not performed.

Severe pneumonia in this patient seemed to have developed into ARDS. Pneumonia, diarrhea, encephalopathy, shock, and fatality in this case have supported that ARDS caused by AI infection can progress into multiple organ failure and fatality. Nevertheless, this assumption had not been confirmed because post mortem study was not performed. Ideally, the central nervous system involvement could have been confirmed through isolation of influenza virus in cerebrospinal fluid, brain radiology examination and post mortem histopathology.

The risk factors that may relate to the severity of disease and fatality of this patient were young age, and length of illness previous to hospital admission. Actually, AI infection should be considered in a patient with acute severe respiratory disease in countries where AI infection among animals occurs. The possibility of this viral infection should also be considered in patient with serious unexplained illness (e.g., encephalopathy or diarrhea) in areas where known to have AI A(H5N1) virus on humans or poultry.<sup>6</sup>

This patient showed the complexity of AI case management in Indonesia. The initial and late signs and symptoms of influenza A (H5N1) virus infection were unspecific, they did not arouse alertness towards AI infection. Low socio-economic factor had also prevented the family to take the patient to a more

capable health facility, and/or to get sufficient information about health care and case management. More works have to be conducted to increase the community awareness on health prevention, AI infection, and their rights to health, as well as to increase the health personnels' awareness of where to refer AI patients.

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