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Avian influenza virus and human: pandemic concern and threat?

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ABSTRACT

Type A influenza viruses causes infections in human and animals, especially in birds. Wild aquatic birds are the natural hosts for all known influenza type A viruses. Avian type viruses are divided into two groups: highly pathogenic avian influenza (HPAI) and low pathogenic avian influenza (LPAI). HPAI virus is very dangerous, but LPAI virus is much weaker. Two forms of mutations including drift and shift have been recognized for antigenic changes in influenza viruses. Antigenic shift is responsible for producing re-assortment viruses with a potentiality to be transmissible to human and possibly resulting in pandemic. Emerging new species of viruses, the loss of previous immunity in human population and the transmission from human to human are the three major conditions that result in the occurrence of influenza pandemic in human. When pandemic happens, public health is a major concern due to probability of high fatality rate and other socioeconomic consequences.

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Introduction

Influenza A virus (IAV) has a membrane and consists of 8 pieces of RNA. The virus is a member of the Orthomyxoviridae family. Type A influenza virus is responsible for recurrent epidemics almost every year, and also is responsible for pandemics, which have high mortality in human. Spanish flu in 1918, Asian flu in 1957 and Hong Kong flu in 1968 are examples of such pandemics. It is told that Spanish flu in 1918 has killed nearly 40 million, and the pandemic between 1957 and 1968 is also responsible for respectively 4 and 1 million deaths (1,2). Eight RNA segments produce about 10 proteins including neuramynidaze (NA), hemagglutinin (HA), matrix protein M1 and M2, non-structural protein NS2 and NS1, nucleocapsid protein and three polymerases of PB1, PB2 and PA. Lately, PB1 gene of some influenza virus encodes protein known as PB1-F2 (3). Type A influenza virus contains HA and NA antigens. Mutation in the viral antigens leads to regular changes over time that is called antigenic drift. In this circumstance, only minor antigenic changes will occur, but antigenic shift may be responsible for rapid and dangerous variation of the virus (recombinant or reassortment), and if the antigenic changes occur, it may be the major cause of epidemics and pandemics. This phenomenon occurs when two (or more) influenza viruses infect the same cell (1) .Currently 16 H and 9 N types have been identified. Clinical and pathogenic H5N1 human infections differ from seasonal influenza (4). H5N1 influenza infection may clinically cause diarrhea, liver and kidney failure and severe pneumonia. All of these effects are related to systemic conditions (sepsis like syndrome). For example, in some cases after being infected with the virus, no viruses directly enter into the liver cells and liver inflammation can be caused by inflammatory response by kupffer cells (4-6). Based on some postmortem examinations, evidence of viral

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response in organs outside the lungs or intestines has been reported. For verifying that other organs are also involved in infection, more investigations are needed. In some patients with H5N1 virus that cause CSF inflammation and no other complications, the virus has been isolated from the cerebrospinal fluid (4,6,7). The range of age for the H5N1 disease has been classified between 3 months to 75 years with an average of 18 years. The first signs of the disease appears after 2 to 4 days from the last contact with infected poultry. The majority of patients with H5N1 influenza have symptoms such as fever, cough, shortness of breath and signs of pneumonia (1,8-11). Infection is limited to the lungs and no evidence of bacterial infection is found. Non-respiratory symptoms often include diarrhea, vomiting and abdominal pain. H5N1 virus can also enter into the cerebrospinal fluid and infect the central nervous system (CNS). Although the norotropic tendency of H5N1 virus in many mammals such as rats and cats have been observed, the involvement of CNS in human is very rare. The important point is that seasonal influenza virus may rarely lead to diseases of the CNS. Diseases related to the deadly H5N1 virus during pregnancy have been reported, but the possibility of infection of the fetus is not yet certain. Mild cases of H5N1 will appear as flu like syndrome as reported in Hong Kong in 1997. The clinical course of human H5N1 virus is often started with rapid progression of infection to respiratory disease in the lower respiratory tract (LRT). Ordinary course for transmission of virus to patients in hospital is 4 days and the time for probable death is 9 days. Acute Respiratory Disease Syndrome (ARDS) is the outcome of nosocomial infection. Failure of many organs, especially kidneys and heart, Reye's syndrome, pneumothorax and pulmonary hemorrhage should be considered as its complications. Also the virus infected cells may undergo energy depletion. It is shown that IAV can reduce cell respiration in human mitochondria(19). In most cases, sudden death due to acute respiratory failure has been reported. Approximately more than half of patients are under 20 years and 89% of patients are under 40 years. The mortality rate of H5N1 in age from 10 to 19 years old is reached to highest level (76%) (4,12-14). A complete list of all suspected factors (which are interfering in the test results) and using very sensitive methods including viral culture, revealing the antigens, nucleic acid detection by RT-PCR, and detection of antibodies is required for diagnosis of avian influenza virus. As a matter of principle in areas where the flu virus is active, patients with severe pneumonia should be evaluated in terms of virological assay for detection of influenza virus, and in case of positive result other species of H5 should be studied and appropriate treatment, care and epidemiological control measures should be considered (14,15). In severe cases, lymphopenia, thrombocytopenia, and in some cases increasing the amount of albumin, lactate dehydrogenase and creatine kinase will also be occurred. In acute cases, cytokines and chemokines are also increased. Rapid culture may decrease the time of diagnosis, but has low sensitivity. Serological diagnostic tests for severe cases of the disease are not useful for rapid diagnosis (15,16). RT-PCR testing is very reassuring and studies in Hong Kong have shown a sensitivity of 100%. Rapid antigen tests for the detection of H5N1 virus do not have much credibility (positive 33% in Vietnam and 86% in Hong Kong) (15). Invitro experiments of virus culture and consequently measurement of cellular respiration showed that mitochondrial respiration was reduced by many diverse viruses such as influenza virus; perhaps this could explain the fatigue symptom in infected individual (17,18). Similar to H1N1 virus, the cytopathic effect (CPE) of H5N1 virus is detectable easily after 4 or 5 days of viral culture using madin-darby canine kidney cell (MDCK) (16,19).

Literature review

In most rural areas of Asia, domestic birds are kept in unsanitary conditions. This and other health problems make it difficult to know the prevalence of the disease. In some places, stores that sell live chickens are opened overnight, and are suitable places for the progress and development of avian influenza virus. However, these places also help the virus survival. This virus enters from an infected chicken into the store, where they spread in the environment. The transmission can be reached to zero in rest-day (the day when the store is completely empty of birds) (20-24). In dead-up day (the day that chickens are killed) all birds are killed, but the virus can still be transmitted. Personnel that have direct contact with birds or infected poultry materials are in danger (22,23,25). Studies in Hong Kong and South Asia have shown that chicken shops can be considered as a key factor in the survival of the virus. In countries such as Indonesia and Vietnam, there is weak evidence of the role of the shops in transmission of the virus. But if so, the health intervention can prevent effective transmission (26-28). After infection with H5N1 HPAI up to 17 days, birds may show no symptoms to transfer it to others (29-31). Following entry into the host cells, the virus can undergo antigenic variation even in the first turn of replication (29). The virus can also be transmitted from infected birds to other birds, and other domestic animals living in a farmland (32,33). According to studies con-

ducted in Thailand, it can be concluded that the increase number of chickens may be considered as potential risk factors for the spread of HPAI virus (20,32,34). Local or cross-border transport and mobility in increasing of transmission and spread of the virus cannot also be ignored. A standard principle for business related to birds and their products can also help for more prevention of viral transmission. Birds and fowls to be exported in bulk in international trading may be typically a major case for transmitting HPAI H5N1 virus. The use of chicken feces is also an important route for transmitting the virus (26,35). Even with the wide range of genetic differences of H5N1 virus in Asia, only a small spectrum of the disease can spread to Europe and the South West towards India (36). While the displacement of birds and their products cannot be fully contributed to the spread of H5N1 virus, and epidemic; biological and genetic evidences show that the geographical spread of the virus in 2005 has increased because of the migrating birds and movement of poultry in local or regional area or their products. It is estimated that the displacement of birds and their products is a major factor in the H5N1 outbreaks, although this has certainly not been established (37). It is claimed that non-domesticated birds are also the source of HPAI H5N1 virus (35,38). Tiger, leopard, cats and birds can also be infected by feeding of infected birds or infected carcasses. On the basis of serological evidence, pigs are accidently infected. Although it seems that this virus will not become epidemic among pigs, but what is empirically proven is that the vaccination of pigs results in infection of the pigs, but no pig to pig transmission is observed so far. Taken as a whole, the probable role of mammals is their potentiality as an intermediate host in the transmission of H5N1 to humans. The importance of this transmission would be more clear when a person without having a history of contact with infected birds becomes ill (10,14,34,39,40). In 1997, the first report of human infection of H5N1 virus in Hong Kong was reported, with 18 cases and 6 deaths. The source and origin of the disease was in poultry where chickens, ducks, geese and other species of small birds are kept alive, and they sold for human consumption (8,39,41,42). In February 2003, when the world was faced with the disease so called SARS, Hong Kong H5N1 virus was detected in a father and son (13,43). However, at that time there was no clear data for ability of virus for human to human transmission (44). Spring and winter are the seasons for outbreak of human cases. Many organs of infected birds with HPAI H5N1 virus are the source of virus. Consumption of raw poultry or poultry products including blood is dangerous. Because the symptoms of infection in many cases are not detected (especially ducks), the birds infected without symptoms are important factors for the spread of infection. Climatic factors such as wet environment and geographical conditions can be an important cause for rapid transmission. Contaminated things such as water and chicken compost are the sources for the release of H5N1 virus among people who apparently have no direct contact with birds (9,39). The virus is imported through the respiratory, gastrointestinal tract or conjunctiva of the birds and is transmitted to humans. There are reports of diarrhea in patients with H5N1 that results in intestinal infection in humans (4,10,23,31). Despite high prevalence of the virus in birds in populated areas and high chance of exposure to humans, H5N1 has only been reported in a few populations (26). Influenza pandemics occurred in 1889, 1918, 1957, 1968, and 1977 are noticeable examples of pandemics in the past (45). Also, recently the world faced with another influenza pandemic so called swine flu. For occurrence of a pandemic, 3 conditions would be needed: 1) a new species of HA (and probably NA), 2) the loss of previous immunity in the human population, and 3) the viral ability for easily transmission from human to human (46). Fortunately, the virus has not yet shown this ability. Ecological factors affect the probability of pandemic. Of course, an increase in mobility (travel) and international trading play an important role in acceleration of the pandemics. It is not certainly clear whether access to anti-viral and health care in particular, can play a role in reducing the possibility of pandemics (23,44). It is very difficult to predict what type of virus would be responsible for the pandemic (40,47). In fact, the H5N1 virus is always modified genetically among birds and the causative virus is endemic among them. The H5N1 may appear in an intermediate host such as pigs, but cannot leads to epidemic among them. However interaction between pigs and birds can result in transmission of the virus from pigs to poultry and from poultry to humans (48,49). Pandemics of 1957 and 1968 were related to HPAI viruses. Probably the next pandemic may occur by an LPAI virus that is already circulating among poultry or other domesticated birds without symptoms, for example H9N2, which also has the ability to infect pigs. Furthermore, human cells may have susceptible receptors for the virus and thus as a matter the H9N2 virus could perhaps be considered for the next pandemic (43,48).

Conclusion

The logical explanation for fearing of H5N1 virus is not only the probability of pandemic but what is

certain is the severe impact on humans. Virus transmission to human directly or through genetic changes can cause a hazard to humans. Although there is low probability of outbreak of H5N1, but serious risks occur in human societies. The effects on food supplies, economic losses and killing animals, especially birds are the serious outcome and impact of the virus on human populations. Despite all studies, what is clear so far is that the causes of prevalence of the disease in birds are still unclear. For more clarifications, further studies needs to be performed.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Webster RG, Bean WJ, Gorman OT, et al. Evolution and ecology of influenza A viruses. Microbiol Rev. 1992;56:152-179.
2. Johnson NP, Mueller J. Updating the accounts: global mortality of the 1918-1920 "Spanish" influenza pandemic. Bull Hist Med. 2002;76:105-115.
3. Chen W, Calvo PA, Malide D, et al. A novel influenza A virus mitochondrial protein that induces cell death. Nat Med. 2001;7:1306-1312.
4. de Jong MD, Bach VC, Phan TQ, et al. Fatal Avian Influenza A (H5N1) in a Child Presenting with Diarrhea Followed by Coma. N Engl J Med. 2005; 352:686-691.
5. de Jong MD, Simmons CP, Thanh TT, et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. Nat Med. 2006;12:1203-1207.
6. Polakos NK, Cornejo JC, Murray DA, et al. Kupffer cell-dependent hepatitis occurs during influenza infection. 2006. Am J Pathol. 2006;168:1169-1178.
7. van Riel D, Munster VJ, de Wit E, et al. H5N1 Virus Attachment to Lower Respiratory Tract. Science. Science. 2006;312:399.
8. Yuen KY, Chan PK, Peiris M, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. Lancet. 1998 14;351467-471.
9. Tran TH, Nguyen TL, Nguyen TD, et al. Avian influenza A (H5N1) in 10 patients in Vietnam. N Engl J Med. 2004;350:1179-1188.
10. Kandun IN, Wibisono H, Sedyaningsih ER, et al. Three Indonesian clusters of H5N1 virus infection in 2005. N Engl J Med. 2006;355:2186-2194.
11. Chotpitayasunondh T, Ungchusak K, Hanshaoworakul W, et al. Human disease from influenza A (H5N1), Thailand, 2004. Emerg Infect Dis. 2005;11:201-209.
12. Smallman-Raynor M, Cliff AD. Avian influenza A (H5N1) age distribution in humans. Emerg Infect Dis. 2007;13:510-512.
13. Peiris JS, Yu WC, Leung CW, et al. Re-emergence of fatal human influenza A subtype H5N1 disease. Lancet. 2004;363:617-619.
14. Roberton SI, Bell DJ, Smith GJD, et al. Avian influenza H5N1 in viverrids: implications for wildlife health and conservation. Proc Biol Sci. 2006;273:1729-1732.
15. Yuen KY, Wong SS. Human infection by avian influenza A H5N1. Hong Kong Med J. 2005;11:189-199.
16. Yuen KY, Chan PK, Peiris M, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. Lancet. 1998;351:467-471.
17. Derakhshan M, Willcocks MM, Salako MA, et al. Human herpesvirus 1 protein US3 induces an inhibition of mitochondrial electron transport. J Gen Virol. 2006;87:2155-2159.
18. Derakhshan M. Viral infection, a suggestive hypothesis for aetiology of chronic fatigue syndrome. Irn J Med Hypotheses Ideas. 2008;2:10-14.
19. Derakhshan M, Kass GEN, Carter MJ. Human Influenza A Virus (IAV) Decreases Mitochondrial Respiration of Infected MDCK Cell. Iran J Public Health. 2005;34:44-45.
20. Ly S, Van Kerkhove MD, Holl D, et al. Interaction Between Humans and Poultry, Rural Cambodia. Emerg Infect Dis. 2007;13:130–132.
21. Kung NY, Guan Y, Perkins NR, et al. The impact of a monthly rest day on avian influenza virus isolation rates in retail live poultry markets in Hong Kong. Avian Dis. 2003;47:1037-1041.
22. Chen H, Smith GJ, Li KS, et al. Establishment of multiple sublineages of H5N1 influenza virus in Asia: implications for pandemic control. Proc Natl Acad Sci U S A. 2006;103:2845-2450.
23. Li KS, Guan Y, Wang J, et al. Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. Nature. 2004;430:209-213.
24. Weber S, Harder T, Starick E, et al. Molecular analysis of highly pathogenic avian influenza virus of subtype H5N1 isolated from wild birds and mammals in northern Germany. J Gen Virol. 2007;88:554-558.
25. Kung NY, Morris RS, Perkins NR, et al. Risk for infection with highly pathogenic influenza A virus (H5N1) in chickens, Hong Kong, 2002. Emerg Infect Dis. 2007;13:412-418.
26. Vong S, Coghlan B, Mardy S, et al. Low frequency of poultry-to-human H5NI virus transmission, southern Cambodia, 2005. Emerg Infect Dis. 2006;12:1542-1547.
27. Smith GJ, Fan XH, Wang J, et al. Emergence and predominance of an H5N1 influenza variant in China. Proc Natl Acad Sci U S A. 2006;103:16936-16941.
28. Ducatez MF, Olinger CM, Owoade AA, et al. Avian flu: multiple introductions of H5N1 in Nigeria. Nature. 2006;442:37.
29. Hulse-Post DJ, Sturm-Ramirez KM, Humberd J, et al. Role of domestic ducks in the propagation and biological evolution of highly pathogenic H5N1 influenza viruses in Asia. Proc Natl Acad Sci U S A. 2005;102:10682-10687.
30. Sturm-Ramirez KM, Ellis T, Bousfield B, et al. Reemerging H5N1 influenza viruses in Hong Kong in 2002 are highly pathogenic to ducks. J Virol. 2004;78:4892-4901.
31. Sturm-Ramirez KM, Hulse-Post DJ, Govorkova EA,et al. Are ducks contributing to the endemicity of highly pathogenic H5N1 influenza virus in Asia?J Virol. 2005;79:11269-11279.
32. Gilbert M, Chaitaweesub P, Parakamawongsa T, et al. Free-grazing ducks and highly pathogenic avian influenza, Thailand. Emerg Infect Dis. 2006;12:227-234.
33. Isoda, N, Sakoda Y, Kishida N, et al. Pathogenicity of a highly pathogenic avian influenza virus,A/chicken/Yamaguchi/7/04 (H5N1) in different species of birds and mammals. Arch Virol. 2006;151:1267–1279.
34. Kuiken T, Fouchier R, Rimmelzwaan G, et al. Feline friend or potential foe? Nature. 2006;440:741-742.
35. Sims LD, Domenech J, Benigno C, et al. Origin and evolution of highly pathogenic H5N1 avian influenza in Asia. Vet Rec. 2005;157:159-164.
36. Keawcharoen J, Oraveerakul K, Kuiken T, et al. Avian influenza H5N1 in tigers and leopards. Emerg Infect Dis. 2004;10:2189-2191.
37. Kilpatrick AM, Chmura AA, Gibbons DW, et al. Predicting the global spread of H5N1 avian influenza. Proc Natl Acad Sci U S A. 2006;103:19368-19373.
38. Chen H, Smith GJ, Zhang SY, et al. Avian flu: H5N1 virus outbreak in migratory waterfowl. Nature. 2005;436:191-192.
39. Mounts AW, Kwong H, Izurieta HS, et al. Case-control study of risk factors for avian influenza A (H5N1) disease, Hong Kong, 1997. J Infect Dis. 1999;180:505-508.
40. Choi YK, Nguyen TD, Ozaki H, et al. Studies of H5N1 influenza virus infection of pigs by using viruses isolated in Vietnam and Thailand in 2004. J Virol. 2005;79:10821-10825.
41. Shortridge KF. Poultry and the influenza H5N1 outbreak in Hong Kong, 1997: abridged chronology and virus isolation. Vaccine. 1999;17:S26-29.

42. Claas EC, Osterhaus AD, van Beek R, et al. Human influenza A H5N1 virus related to a highly pathogenic avian influenza virus. Lancet. 1998;351:472-477.
43. Peiris M, Yuen KY, Leung CW, et al. Human infection with influenza H9N2. Lancet. 1999;354:916-917.
44. Zhu QY, Qin ED, Wang W, et al. Fatal infection with influenza A (H5N1) virus in China. 2006. N Engl J Med. 354:2731–2732.
45. Taubenberger JK, Morens DM. Pandemic influenza--including a risk assessment of H5N1. Rev Sci Tech. 2009;28:187-202.
46. Ungchusak K, Auewarakul P, Dowell SF, et al. Probable person-to-person transmission of avian influenza A (H5N1). N Engl J Med. 2005;352:333-340.
47. Taubenberger JK, Morens DM. 1918 Influenza: the mother of all pandemics. Emerg Infect Dis. 2006;12:15-22.
48. Matrosovich MN, Krauss S, Webster RG. H9N2 influenza A viruses from poultry in Asia have human virus-like receptor specificity. Virology. 2001;281:156-162.
49. Cameron KR, Gregory V, Banks J, et al. H9N2 subtype influenza A viruses in poultry in pakistan are closely related to the H9N2 viruses responsible for human infection in Hong Kong. Virology. 2000;278:36-41.