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Highly pathogenic avian influenza H5N1 virus in cats and other carnivores

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Abstract

The Asian lineage highly pathogenic avian influenza (HPAI) H5N1 virus is a known pathogen of birds. Only recently, the virus has been reported to cause sporadic fatal disease in carnivores, and its zoonotic potential has been dominating the popular media. Attention to felids was drawn by two outbreaks with high mortality in tigers, leopards and other exotic felids in Thailand. Subsequently, domestic cats were found naturally infected and experimentally susceptible to H5N1 virus. A high susceptibility of the dog to H3N8 equine influenza A virus had been reported earlier, and recently also HPAI H5N1 virus has been identified as a canine pathogen. The ferret, hamster and mouse are suitable as experimental animals; importantly, these species are also kept as pets. Experimental intratracheal and oral infection of cats with an HPAI H5N1 virus isolate from a human case resulted in lethal disease; furthermore, cats have been infected by the feeding of infected chickens. Spread of the infection from experimentally infected to in-contact cats has been reported. The epidemiological role of the cat and other pet animal species in transmitting HPAI H5N1 virus to humans needs continuous consideration and attention.

Keywords: Cat; Feline; Avian influenza; H5N1

1. Introduction

In 1997, the Asian lineage highly pathogenic avian influenza (HPAI) H5N1 virus spread among poultry in Hong Kong and was directly transmitted to humans

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(Claas et al., 1998; Webster et al., 2006). Then, after several years of silence, the virus re-emerged in Asia, causing high-mortality outbreaks in poultry; in addition, it was responsible for acute respiratory infection in human with lethality rates approaching 50% (Li et al., 2004). The property of this virus to infect and kill mammals in addition to birds (Govorkova et al., 2005) became particularly conspicuous during outbreaks in Thailand with many fatalities amongst tigers, domestic cats and other felids (Kuiken et al., 2006a). This information did not immediately alert the scientific community, and caused a stir only after decisive experiments had proven the susceptibility of cats to a H5N1 virus isolated from a human case (Kuiken et al., 2004; Rimmelzwaan et al., 2006). Earlier experiments with other human or avian influenza (AI) A viruses had shown that the cat can be infected, but without clinical signs (Hinshaw et al., 1981; Vahlenkamp and Harder, 2006). After the Asian endemics, two outbreaks of AI in cats occurred in Europe in February/March 2006, on the Rügen isle, Germany, involving three cats (Editorial team, 2006; Thomas Mettenleiter, personal communication). In Graz, Austria, three cats were found infected in a rescue shelter by demonstration of virus followed by seroconversion (Leschnik et al., in press). These recent data substantiate earlier reports (2004) of experimental HPAI H5N1 virus infection in household cats in Thailand (Kuiken et al., 2006a; World Health Organisation, 2004). At least two outbreaks of fatal disease in large felids, tigers and leopards, have occurred in Thailand (Keawcharoen et al., 2004; Thanawongnuwech et al., 2005). Experimental infection with a HPAI H5N1 virus isolated from a human case produced a highly lethal disease in cats (Kuiken et al., 2004; Rimmelzwaan et al., 2006).

The current HPAI H5N1 viruses emerged from the Gs/Gd lineage isolated in China in 1996, from which derived the virus that caused the first cases of human AI in Hong Kong in 1997 (Li et al., 2004). The continuous evolution of H5N1 virus through mutations, including deletions and reassortment, gave rise to the dominant genotype Z in 2003 (Li et al., 2004; Chen et al., 2006). Phylogenetic analyses of the haemagglutinin H5 gene revealed two different lineages, also termed clades 1 and 2 (World Health Organization global influenza program surveillance network, 2005). Clade 1 viruses were responsible for the regional outbreak in Thailand, Vietnam, Cambodia and Malaysia where fatal human cases were observed, and clade 2 spread in Indonesia and China, where several sublineages cocirculated. One of those originated from lake Qinghai in China and spread in Asia and over Siberia to Europe in 2005 (Chen et al., 2006). Reported mammalian (human and felid) cases of HPAI H5N1 virus have been caused by clade 1 viruses in Vietnam (Amonsin et al., 2006) but recently clade 2 virus infection was also demonstrated in a cat (Yingst et al., 2006). It is likely that the 2006 European cat cases were also due to clade 2 viruses.

The recent emphasis on cat infections is understandable from the zoonotic perspective, but other susceptible carnivores, like the ferret (Govorkova et al., 2005), have recently gained popularity and become companion animals; the role of other household pets, like mice and hamsters has been reviewed by Vahlenkamp and Harder (2006). Some thirty years ago, the dog was recognized as infectable by H3N2 influenza A virus (Kilbourne and Kehoe, 1975–1976), but without clinical significance. This changed only in recent years, when reports of fatal cases due to H3N8 equine influenza A virus (Crawford et al., 2005) and HPAI H5N1 virus were published (Songserm et al., 2006b).

2. Epidemiology

At present, transmission of HPAI H5N1 virus to mammals only sporadically results in disease. However, these infections are important because of their high morbidity and lethality rates and zoonotic potential. The mammalian species shown to be naturally or experimentally susceptible include man, non-human primates like the cynomolgus macaque, mouse, hamster, pig, ferret, stone marten, dog, domestic cat, tiger, leopard and the civet (Choi et al., 2005; Gao et al., 1999; Govorkova et al., 2005; Keawcharoen et al., 2004; Kuiken et al., 2004, 2006a; Maines et al., 2005; Rimmelzwaan et al., 2001; Songserm et al., 2006b; Vahlenkamp and Harder, 2006; Zitzow et al., 2002).

Apart from the cat, only ferrets transmit HPAI H5N1 virus within their own populations and, as pets, could possibly also infect humans; upon experimental

infection, these animals excrete large amounts of virus (Govorkova et al., 2005; Vahlenkamp and Harder, 2006). In Asia, HPAI H5N1 virus has been occasionally transmitted from birds to pigs, but this species seems to be a dead-end host experiencing only subclinical infections (Choi et al., 2005).

Most prominently, felids suffer from H5N1 virus infections under natural conditions, and their susceptibility has been confirmed in laboratory experiments. Chronologically and geographically, AI in felids was correlated with outbreaks in poultry in Asia (Keawcharoen et al., 2004; Songserm et al., 2006a) and with diseased aquatic wild birds in Europe (Editorial team, 2006; Thomas Mettenleiter, personal communication; Leschnik et al., in press). Sometimes they led to small endemics, as observed in household cats and tigers in Thailand (Kuiken et al., 2006a; Thanawongnuwech et al., 2005). Horizontal transmission is likely to occur in such situations, but most affected animals are infected by direct or indirect contact from a common source, namely infected birds. Cats, tigers and leopards can be infected by eating infected birds, swans, goose, chicken or pigeons (Editorial team, 2006; Keawcharoen et al., 2004; Rimmelzwaan et al., 2006; Songserm et al., 2006a). Indirect transmission could also occur by passive virus carriage in the fur of a cat that had been in contact with infected birds' faeces (Leschnik et al., in press). Furthermore, infection can be transmitted from infected to in-contact cats or tigers through contaminated saliva, urine and faeces (Kuiken et al., 2004; Thanawongnuwech et al., 2005). Cat-to-cat transmission may depend on the level of virus excretion: it is assumed to be higher in Thai tigers and in experimentally infected cats, both having been exposed to high infectious doses (Kuiken et al., 2004; Thanawongnuwech et al., 2005) than under the conditions in Europe (Leschnik et al., in press).

3. Pathogenesis

It is still unknown which is the most efficient route of infection. Oral infection can be suspected after feeding infected raw chicken but respiratory infection cannot be completely ruled out by this way. Both routes can be suspected upon cat-to-cat virus transmission. Virus has repeatedly been isolated from saliva, the trachea and intestinal contents as well as from urine and faeces of infected cats (Rimmelzwaan et al., 2006; Songserm et al., 2006a; Yingst et al., 2006). It is therefore assumed that first replication takes place in the upper respiratory and digestive tracts. The virus is propagated in the lower respiratory tract after infection of type II pneumocytes that line the alveoli (van Riel et al., 2006); replication in the lung leads to foci of alveolar damage. The virus eventually reaches the liver, heart, brain, renal glomeruli, adrenal gland and sometimes the spleen and pancreas (Rimmelzwaan et al., 2006; Songserm et al., 2006a); it has also been found in the large intestine (Yingst et al., 2006). Infection of internal organs suggests systemic spread through viraemia, but so far no virus has been isolated from blood (Rimmelzwaan et al., 2006). Multifocal haemorrhages and necroses are found in different infected organs, which – together with the extended pulmonary damage – are responsible for acute death (Keawcharoen et al., 2004).

A peculiar feature is a ganglio-neuritis of the intestinal plexus nervosus that could be explained by infection of submucosal tissues from the intestinal lumen (Rimmelzwaan et al., 2006). A non-suppurative encephalitis is observed in infected cats, which explains the neurological signs observed in natural cases (Keawcharoen et al., 2004; Rimmelzwaan et al., 2006).

Clinical signs appear after a short incubation period, when the virus had multiplied in the primary and secondary replication sites. In clinically affected cats, virus excretion starts by day 3 after infection and persists until day 7 after infection or longer (Rimmelzwaan et al., 2006).

Subclinical infections have been identified in cats after contact with a dead swan, probably after exposure to a low infectious dose of virus. These cats, in a shelter in Graz, Austria, experienced a limited upper respiratory infection, as pharyngeal swabs were virus-positive whereas rectal samples remained negative (Leschnik et al., in press).

4. Clinical signs

The incubation period ranges from 2 days (as assessed in experimentally infected cats) to 3 days in large felids. In cats and tigers, the clinical signs are fever, decreased activity, protrusion of the nictitating membrane, conjunctivitis and laboured breathing

(Kuiken et al., 2004). Serosanguinuous nasal discharge and icterus in case of diffuse haemorrhagic lesions can be observed (Thanawongnuwech et al., 2005; Rimmelzwaan et al., 2006). In severely affected cats, sudden deaths may occur as soon as 2 days after the onset of illness (Songserm et al., 2006a). Nervous signs including convulsions and ataxia are consistent with the brain lesions (Songserm et al., 2006a). Subclinical infections also occur, as evidenced by the cases in the animal shelter in Graz, Austria.

5. Diagnosis

A HPAI H5N1 virus infection can be suspected when high fever and acute respiratory distress is seen in cats that have access to outdoors, and when this virus had affected poultry and/or aquatic wild birds in the region. The clinical signs are not pathognomonic and may be taken for the feline upper respiratory disease syndrome, caused by feline herpesvirus and calicivirus, or for a bacterial pneumonia (due to *Bordetella bronchiseptica*, *Chlamydophila felis*, *Mycoplasma*). Feline infectious peritonitis may also lead to respiratory signs but the disease course is rather subacute. Immunodeficiency caused by feline immunodeficiency virus and immunodepression provoked by feline leukaemia virus also facilitate secondary respiratory infections. It is therefore important to correlate the clinical signs observed in cats with the epidemiological situation of HPAI H5N1 virus infection in birds in the region.

At necropsy, multifocal lung lesions and petechial haemorrhages in the lungs, heart, thymus, stomach, intestine, tonsils, mandibular and retropharyngeal lymph nodes and liver, as well as a haemorrhagic pancreatitis are seen macroscopically (Keawcharoen et al., 2004; Yingst et al., 2006). Microscopically, the lesions are characterized by inflammation and necrosis. In large felids, thrombocytopenia, haemorrhagic lesions in the lung and encephalitis characterised by multifocal infiltration by neutrophils and macrophages have been reported (Keawcharoen et al., 2004).

The virological diagnosis *in vivo* is made on oropharyngeal, nasal and rectal swabs or faecal samples. At necropsy, affected organs, intestinal content and pleural fluid are sampled. After nucleic acid extraction, a RT-PCR is performed using primers designed to identify the haemagglutinin and neuraminidase genes (Keawcharoen et al., 2004) as well as the nucleocapsid gene (Amonsin et al., 2006). H5N1 virus antigens are identified by immunohistochemistry on sections of affected organs, using a monoclonal antibody specific for the nucleocapsid of influenza A virus (Keawcharoen et al., 2004; Rimmelzwaan et al., 2006); a polyclonal goat antiserum against H5N1 virus has also been used (Songserm et al., 2006a). Virus isolation follows the influenza virus protocol of inoculating tissue homogenates into the allantoic sac of embryonated chicken eggs (Keawcharoen et al., 2004; Songserm et al., 2006a). For identification, RT-PCR can be applied on the isolated virus. In subclinical cases, serological diagnosis is performed using the haemagglutination inhibition assay (World Organisation for Animal Health, 2005).

6. Control and vaccination

Highly pathogenic avian influenza H5N1 virus infection of the cat and other pet carnivores could be controlled by preventing any contact with affected poultry or wild birds. The European Commission has therefore recommended to keep cats indoor in the areas where cases of HPAI H5N1 virus were recorded in poultry or wild birds (Anonymous, 2006; Council of the European Union, 2006).

When HPAI H5N1 virus infection is suspected in a cat, the veterinary practitioner must take measures to minimise the risk of transmission, like avoiding direct physical contact with the cat by wearing gloves, mask and goggles. The suspected cat is kept in isolation in a cage. Surfaces are decontaminated using a household detergent or standard medical disinfectant. The owner and his relatives are instructed to minimise contacts with the cat and about the disinfection of litter trays, drinking bowls, etc. Detailed measured have been published by the European Advisory Board on Cat Diseases (2006) and can be consulted at http://www.abcd-vets.org/guidelines/.

Antiviral treatment with Oseltamivir (Tamiflu Roche, Basel, Switzerland) has been tried at a dose of 75 mg/60 kg, twice daily in healthy tigers (Thanawongnuwech et al., 2005). The dosage was obtained by extrapolating from human use, but

evidence of protection was not obtained. The bioavailability of Oseltamivir may vary with the animal species: indeed, the effective dose in mice is 5× that of that in humans (Ward et al., 2005).

It can be debated whether there is a place for the vaccination of cats against HPAI H5N1 virus. An experimental challenge protocol has been established, and the safety and efficacy of such vaccines could be tested in cats (Kuiken et al., 2004; Rimmelzwaan et al., 2006). In a pilot experiment, the fowlpox virus vector Trovac expressing the H5 gene of AI virus induced high levels of antibodies to the homologous haemagglutinin. The serological response rose as early as one week after one vaccination, and a booster allowed cats to develop antibodies cross-reacting with a recent, HPAI H5N1 Asian isolate (Karaca et al., 2005). Another vector, based on canine adenovirus 2 expressing the H5 haemagglutinin of a tiger isolate, was able to induce an antibody response in a cat (Gao et al., 2006).

7. Conclusions

Acute AI in cats is the consequence of an efficient crossing of the host barrier to infect a susceptible species (Kuiken et al., 2006b). Contacts between birds and cats are a precondition for transmission and have occurred on different continents. Although the epidemiological situations are quite different in Asia and Europe, the same pattern was observed, the incidence in cats being indeed proportional to the prevalence of infected birds. The sporadic cat-to-cat transmission of HPAI H5N1 virus allowed some prediction to be made. In the putative case of a human epidemic, the cat could play a role in virus transmission to other cats, other pet animals, like ferrets, mice and hamsters, and to their owners (Kuiken et al., 2006a). In such an epidemiological situation, infections of exotic felids in zoological gardens, safari parks and circuses can also be expected. It is obviously unknown to what extent felids will play a role in the epidemiology of the infection.

The high susceptibility of cats must be balanced against the discovery of subclinical infections in the Austrian cases (Leschnik et al., in press). These could be related to low infectious doses that are insufficient to reach the lower airways and cause an acute illness. The lower respiratory infection induced by HPAI H5N1 virus in cats could serve as an experimental model to investigate the human infection, which appears to have a similar pathogenesis (van Riel et al., 2006).

Other susceptible carnivores should not be disregarded in epidemiological considerations, especially the ferret, which is becoming increasingly popular as a companion animal species. More information will certainly become available about the infection of dogs with HPAI H5N1 virus; recently a fatal canine disease case has been reported from Thailand (Songserm et al., 2006b).

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