

BORNA DISEASE VIRUS INFECTION IN CATS

ABCD guidelines on prevention and management



Hans Lutz, Diane D Addie, Corine Boucraut-Baralon, Herman Egberink, Tadeusz Frymus, Tim Gruffydd-Jones, Katrin Hartmann, Marian C Horzinek, Margaret J Hosie, Albert Lloret, Fulvio Marsilio, Maria Grazia Pennisi, Alan D Radford, Etienne Thiry, Uwe Truyen and Karin Möstl

Overview: Borna disease virus (BDV) has a broad host range, affecting primarily horses and sheep, but also cattle, ostriches, cats and dogs.

In cats, BDV may cause a non-suppurative meningoencephalomyelitis ('staggering disease').

Infection: The mode of transmission is not completely elucidated. Direct and indirect virus transmission is postulated, but BDV is not readily transmitted between cats. Vectors such as ticks may play a role and shrews have been identified as a potential reservoir host. Access to forested areas has been reported to be an important risk factor for staggering disease.

Disease signs: It is postulated that BDV may infect nerve endings in the oropharynx and spread via olfactory nerve cells to the central nervous system. A strong T-cell response may contribute to the development of clinical disease. Affected cats develop gait disturbances, ataxia, pain in the lower back and behavioural changes.

Diagnosis: For diagnostic purposes, detection of viral RNA by reverse transcription PCR in samples collected from cats with clinical signs of Borna disease can be considered diagnostic. Serology is of little value; cats without signs of Borna disease may be seropositive and yet not every cat with BDV infection has detectable levels of antibodies.

Human infection: A hypothesis that BDV infection may be involved in the development of selected neurological disorders in man could not be confirmed. A research group within the German Robert Koch Institute studied the potential health threat of BDV to humans and concluded that BDV was not involved in the aetiology of human psychiatric diseases.

Background

Borna disease virus (BDV) historically has affected horses and sheep (for a review see Ludwig and Bode¹). The disease was first described in 1855 in horses which became severely sick, near the German town of Borna (cited in Lundgren et al²). More recently, BDV has been described as the causative agent of a viral meningoencephalitis in cattle, ostriches, cats and dogs.¹ In the mid-1970s, staggering disease – a non-suppurative meningoencephalomyelitis – was described in Swedish cats (cited in Lundgren et al² and Cubitt and de la Torre³). Later, it was found that antibodies recognising BDV were common to these cases.⁴ Finally, in 1995, BDV was confirmed as the aetiological agent of staggering disease.²

Aetiological agent

BDV is an enveloped virus with a helical capsid and a single-stranded RNA genome. The genome comprises 8900 bases and, based on sequence analysis, it was assigned to the order of *Mononegavirales* as the only member of the *Bornaviridae* family.^{3,5} BDV particles are spherical and have an average diameter of approximately 100 nm. The genome encodes six known proteins including an envelope protein of 56 kd. Interestingly, BDV can infect a number of brain-derived cell types, but it does not usually induce any cytopathic effect.

Epidemiology

The mode of transmission of BDV has not been completely elucidated. It is postulated that transmission occurs through direct contact with an infected animal or indirectly by contact with secretions of an infected animal. In addition, the local occurrence of disease in forested areas in Sweden suggests that vectors such as ticks may play a role in transmission. In 2006, a shrew (*Crocidura leucodon*) was identified as the reservoir host in an area of Switzerland where BDV is prevalent in horses and sheep.⁶ Shrews could also serve as reservoirs for BDV infection in cats. BDV infection appears not to be readily transmitted between cats.

Feline BDV infection has been reported in many countries, including Germany, Switzerland, Belgium, the United Kingdom, Japan, the



Philippines, Indonesia, Australia and Finland (cited in Ludwig and Bode¹ and Someya et al⁷). The fact that BDV was also shown to be present in horses in North America and several other species in Western China suggests that cats in the USA and China might also be affected by BDV. Clinical staggering disease has been mainly observed in Sweden, Austria, Germany, Switzerland and Liechtenstein.

The seroprevalence in cats with neurological disease in different countries has been reported to vary widely, between 0 and 67%. In healthy cats, the occurrence of BDV antibodies is much lower, varying between 2% and over 40%.⁸ Access to forested areas was reported to be an important risk factor for staggering disease, since 68% of all clinical cases occurred in cats with access to forests.⁴ Staggering disease shows a clear peak in frequency in the spring.⁹ So far, an association between BDV infection and gender has not been described. The findings on the age distribution of BDV infection are controversial. A recent study in Japan found no age predisposition in BDV infection, although cats younger than 1 year were already found to be affected.⁷

Pathogenesis and clinical signs

It is postulated that BDV may infect nerve endings in the oropharynx, nose and/or intestinal tract. The virus is thought to migrate along the nerves to the central nervous system (CNS),¹⁰ where it leads to lymphocytic inflammation and neuronal degeneration. A strong T-cell response to the virus is believed to be responsible for the development of clinical signs but other factors may also be important for disease development.¹⁰ Affected cats develop gait disturbances, ataxia, pain in the lower back and behavioural changes. In some cases, cats lose the capacity to retract their claws. Clinical signs will usually progress and cats will eventually die after developing severe paralysis of the hind legs. However, some cats will recover partially or even completely. Subclinical infections can also occur.

Immune response

CD8+ lymphocytes stimulated by BDV have been found in peripheral blood, spleen and brain.¹¹ These findings suggest that a successful immune reaction usually allows infected cats to control the infection. A weak innate immune response to BDV infection was recently described in rat brain cell cultures.¹² It is, therefore, expected that a weak innate immune response may likewise contribute to disease development in cats.

European Advisory Board on Cat Diseases
The European Advisory Board on Cat Diseases (ABCD) is a body of experts in immunology, vaccinology and clinical feline medicine that issues guidelines on prevention and management of feline infectious diseases in Europe, for the benefit of the health and welfare of cats. The guidelines are based on current scientific knowledge of the diseases and available vaccines concerned.

The latest version of the Borna disease virus infection in cats guidelines is available at www.abcdcatsvets.org and www.abcd-vets.org



Clinical staggering disease has been mainly observed in Sweden, Austria, Germany, Switzerland and Liechtenstein.

Diagnosis

Diagnosis on the basis of clinical signs alone is not possible as there are several other viral infections (feline immunodeficiency virus, feline leukaemia virus and feline coronavirus) that can lead to similar clinical signs. Detection of antibodies to BDV by ELISA or indirect immunofluorescence in cats exhibiting clinical signs typical of BDV infection permits a tentative diagnosis.¹³

However, the diagnostic sensitivity of the detection of antibodies, at 81%, means that not every cat with BDV infection will have detectable levels of antibodies.¹³ The reason for this is unclear. It is speculated that different strains of BDV exist which are sufficiently different from the antigen used in the assay and therefore remain undetected. Alternatively, some cats may not be capable of mounting an immune response that is serologically detectable.

The diagnostic specificity of antibody detection is also very low, as many seropositive cats may be completely healthy.¹³ In the absence of clinical signs of Borna disease, diagnostic serology is of little value.

Detection of viral RNA by reverse transcription PCR in pooled samples of blood, serum, urine, conjunctival, nasal, oral and anal swabs collected from cats with clinical signs of Borna disease can be considered diagnostic.¹³

Currently, the most reliable means of diagnosis of Borna disease is considered to be pathology and histopathology.

Pathology

In cats with end-stage staggering disease, mild neutropenia is observed in about a third of the affected population. No other changes in clinical or biochemical parameters are observed. The most important histopathological findings include perivascular cuffing in the hippocampus, basal ganglia, cerebellum, cerebrum and grey matter of the brainstem.⁹ In addition, plasma cells have been frequently seen in the close vicinity of neurons,¹⁴ indicative of an inflammatory reaction and thereby explaining the clinical findings in cats with staggering disease.

Prevention

Currently, no vaccine is available for the prevention of staggering disease. As the exact modes of transmission are still not completely clear, it is difficult to make specific recommendations for preventive measures. Cats without access to a rural environment are probably at lower risk of BDV infection compared with those with unlimited access to such areas. In

Zoonotic aspects

As BDV persistently infects the CNS of many animal species, it was postulated that this virus might also infect humans. Indeed, it was shown that humans can be seropositive for BDV and that the frequency of BDV antibodies was increased in human patients with chronic neurological disorders. Specifically, among 70 psychiatric patients, 20% were found to be seropositive, compared with a few percent of the normal population. This led to the hypothesis that BDV infection may be involved in the development of selected neurological disorders,^{15,16} and triggered the creation of a research group within the German Robert Koch Institute in the 1990s to study the potential health threat of BDV to humans.

In 2007, this research group published a statement that (1) the methods providing seropositive results in human blood were not adequate to substantiate the presence of antibodies to BDV; and (2) the RNA sequences found in human blood and tissue were the consequence of BDV contamination in the laboratory of the respective research laboratory. Therefore, it was concluded that BDV was not involved in the aetiology of human psychiatric diseases and after dozens of careful studies the research group ended its activity.

For details see http://www.rki.de/DE/Content/Forsch/Forschungsschwerpunkte/NeueRisiken/NeuartigeErreger/Einstellung_Projekt_Bornavirus.html.

areas where staggering disease is known to occur, it might therefore be recommended that cats should be kept indoors. However, limiting outdoor access should be carefully weighed against the risk of BDV infection. For many cats, outdoor access is an important component of their wellbeing.

Funding

The authors received no specific grant from any funding agency in the public, commercial or not-for-profit sectors for the preparation of this article. The ABCD is supported by Merial, but is a scientifically independent body and its members receive no stipends from Merial.

Conflict of interest

The authors do not have any potential conflicts of interest to declare.

KEY POINTS

- ❖ Borna disease virus (BDV) is the aetiological agent of staggering disease, seen in several animal species, including horses, sheep and cats.
- ❖ Transmission probably occurs through direct contact or indirectly via the secretions of an infected animal.
- ❖ Ticks may play a role in transmission.
- ❖ Infection starts in the olfactory nerve cells and then spreads to the central nervous system.
- ❖ Signs include an abnormal gait, ataxia progressing to paralysis, lower back pain and behavioural changes.
- ❖ Serological tests are of little diagnostic value.
- ❖ Detection of viral RNA by reverse transcription PCR in pooled samples of body secretions is diagnostic.
- ❖ Pathology and histopathology are considered the most reliable diagnostic methods.
- ❖ BDV is not involved in the aetiology of psychiatric disease in humans.



References

- 1 Ludwig H and Bode L. Borna disease virus: new aspects on infection, disease, diagnosis and epidemiology. *Rev Sci Tech* 2000; 19: 259–288.
- 2 Lundgren AL, Zimmermann W, Bode L, et al. Staggering disease in cats: isolation and characterization of the feline Borna disease virus. *J Gen Virol* 1995; 76: 2215–2222.
- 3 Cubitt B and de la Torre JC. Borna disease virus (BDV), a non-segmented RNA virus, replicates in the nuclei of infected cells where infectious BDV ribonucleoproteins are present. *J Virol* 1994; 68: 1371–1381.
- 4 Lundgren AL and Ludwig H. Clinically diseased cats with non-suppurative meningoencephalomyelitis have Borna disease virus-specific antibodies. *Acta Vet Scand* 1993; 34: 101–103.
- 5 Cubitt B, Oldstone C and de la Torre JC. Sequence and genome organization of Borna disease virus. *J Virol* 1994; 68: 1382–1396.
- 6 Hilbe M, Herrsche R, Kolodziejek J, et al. Shrews as reservoir hosts of borna disease virus. *Emerg Infect Dis* 2006; 12: 675–677.
- 7 Someya A, Fukushima R, Yoshida M, et al. A study on Borna disease virus infection in domestic cats in Japan. *J Vet Med Sci* 2014; 76: 1157–1160.
- 8 Reeves NA, Helps CR, Gunn-Moore DA, et al. Natural Borna disease virus infection in cats in the United Kingdom. *Vet Rec* 1998; 143: 523–526.
- 9 Lundgren AL. Feline non-suppurative meningoencephalomyelitis. A clinical and pathological study. *J Comp Pathol* 1992; 107: 411–425.
- 10 Wensman JJ, Jaderlund KH, Holst BS, et al. Borna disease virus infection in cats. *Vet J* 2014; 201: 142–149.
- 11 Johansson M, Berg M and Berg AL. Humoral immune response against Borna disease virus (BDV) in experimentally and naturally infected cats. *Vet Immunol Immunopathol* 2002; 90: 23–33.
- 12 Lin CC, Wu YJ, Heimrich B, et al. Absence of a robust innate immune response in rat neurons facilitates persistent infection of Borna disease virus in neuronal tissue. *Cell Mol Life Sci* 2013; 70: 4399–4410.
- 13 Wensman JJ, Jaderlund KH, Gustavsson MH, et al. Markers of Borna disease virus infection in cats with staggering disease. *J Feline Med Surg* 2012; 14: 573–582.
- 14 Lundgren AL, Johannisson A, Zimmermann W, et al. Neurological disease and encephalitis in cats experimentally infected with Borna disease virus. *Acta Neuropathol* 1997; 93: 391–401.
- 15 Bode L, Ferszt R and Czech G. Borna disease virus infection and affective disorders in man. *Arch Virol Suppl* 1993; 7: 159–167.
- 16 Bode L and Ludwig H. Borna disease virus infection, a human mental-health risk. *Clin Microbiol Rev* 2003; 16: 534–545.