GUIDELINE for Borna virus infection

Published: 01/01/2015
Last updated: 01/01/2021
Last reviewed: 01/06/2022

These Guidelines were first published by Hans Lutz et al. in Journal of Feline Medicine and Surgery 17 (7), 2015, 614-616, and updated by Hans Lutz in 2017. This update has been compiled by Uwe Truyen.

Key points

- Borna disease virus is the aetiological agent of a central nervous disease (CNS) seen in several animal species, including horses, sheep and cats.
- Borna Disease virus is endemic in certain regions of Europe and can cause severe and fatal encephalitis in humans and certain animal species.
- The mode of transmission is unknown, but may occur through direct contact or indirectly via the secretions of an infected animal.
- Shrews may play a prominent role in the epidemiology of the disease.
- Infection starts in the olfactory nerve cells and then spreads to the CNS.
- Signs include abnormal gait, ataxia progressing to paralysis, lower back pain and behavioural changes.
- Serological tests are of little diagnostic value.
- Detection of viral RNA by RT-PCR in pooled samples of blood, CSF and body secretions (urine, conjunctival, or rectal swabs) are diagnostic for the infection.
- Pathology and histopathology, in conjunction with clinical signs, are considered the most reliable diagnostic methods.
- BoDV-1 is so far not confirmed to be involved in the aetiology of psychiatric disease in humans.
- Other Bornaviruses have been described in rodents (including the variegated squirrel) and birds.
- Other Bornaviruses such as the VSBV-1 may represent a risk for humans.

Introduction

Borna disease virus (BoDV-1) historically affects horses and sheep (for review see Ludwig and Bode, 2000). The disease was first described in 1855 in horses which became severely sick, near the German town of Borna (cited in Lundgren et al., 1995). More recently, BoDV-1 has been described as the causative agent of a viral meningoencephalitis in cattle, ostriches, cats and dogs (Ludwig and Bode, 2000). In the mid-1970s, staggering disease – a non-suppurative meningoencephalomyelitis – was described in cats in Western Sweden (cited in Cubitt and de la Torre, 1994 and Lundgren et al., 1995). Later, it was found that antibodies recognising BoDV-1 were common to these cases (Lundgren and Ludwig, 1993). Finally, in 1995, BoDV-1 was confirmed as the aetiological agent of staggering disease (Lundgren et al., 1995).

A hypothesis that BoDV-1 infection may be involved in the development of selected neurological disorders in man has not been confirmed. A research group within the German Robert Koch Institute studied the potential health threat of BoDV-1 to humans and concluded that BoDV-1 was not involved in the aetiology of human psychiatric diseases. However, the recent detection of cases of fatal encephalitis in humans in Bavaria suggests that the question of BoDV-1 involvement in neurological disorders cannot be clearly answered.
Agent properties

BoDV-1 is an enveloped virus with a helical capsid and a single-stranded RNA genome. The genome comprises 8,900 bases and, based on sequence analysis, it was assigned to the order of Mononegavirales as a member of the Bornaviridae family (Cubitt and de la Torre, 1994; Cubitt et al., 1994). Bornaviruses have been detected in a variety of animal species including mammals and birds (Kuhn et al., 2015). BoDV 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, BoDV-1 can infect a number of brain-derived cell types, but it does not usually induce any cytopathic effect.

Epidemiology

Prevalence

Feline BoDV-1 has been reported in many countries, including Germany, Switzerland, Belgium, United Kingdom, Japan, Philippines, Indonesia, Australia and Finland (cited from Ludwig and Bode, 2000 and Someya et al., 2014). The fact that BoDV-1 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 BoDV-1. Clinical staggering disease has been mainly observed in Sweden, Austria, Germany, Switzerland and Liechtenstein.

The seroprevalence in cats with neurological diseases in different countries has been reported to vary widely between 0 and 67 %. In healthy cats, the occurrence of BoDV-1 antibodies is much lower, varying between 2 and over 40 % (Reeves et al., 1998).

Predisposing factors

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. Staggering disease shows a clear peak in frequency in the spring (Lundgren, 1992). So far, an association between BoDV-1 infection and gender has not been described. The findings on the age distribution of BoDV-1 infection are controversial. A recent study in Japan found no age preference in BoDV-1 infection, although cats younger than one year with infection were reported (Someya et al., 2014).

Transmission

The mode of transmission of BoDV-1 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. Infectious virus and viral RNA can be demonstrated in saliva, urine, skin, tears and faeces (Nobach et al., 2015). In addition, the local occurrence of the disease in forested areas in Sweden suggests that vectors such as ticks may also play a role in transmission. In 2006, a shrew (Crocidura leucodon) was identified as the reservoir host in an area of Switzerland and in Southern Germany where BoDV-1 is prevalent in horses and sheep (Hilbe et al., 2006, Dürrwald et al., 2014). These shrews have recently been shown to shed BoDV-1 over a period of over 200 days in urine, faeces and saliva without showing clinical signs (Nobach et al., 2015). It is therefore clear that shrews can serve as reservoirs for BoDV-1 infection in cats. However, BoDV-1 infection appears not to be readily transmitted between cats.

Pathogenesis

It is postulated that BoDV-1 may infect nerve endings in the oropharynx, the nose and/or the intestinal tract. The virus is thought to migrate along the nerves to the central nervous system (CNS) (Wensman et al., 2014), 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 (Wensman et al., 2014).

Clinical signs

Affected cats develop gait disturbances, ataxia, pain in the lower back and behavioural changes (Fig. 1). In some cases, the affected cats lose the capacity to retract their claws. Clinical signs will usually progress and affected 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. (For review see Tizard et al., 2016).
Immunity

CD8+ lymphocytes stimulated by BoDV-1 have been found in the peripheral blood, spleen and brain (Johansson et al., 2002). These findings suggest that a successful immune reaction usually allows infected cats to control the infection. A weak innate immune response to BoDV-1 infection in rat brain cell cultures was described (Lin et al., 2013). It is therefore to be expected that a weak innate immune response may also contribute to disease development in cats.

Diagnosis

Diagnosis on the basis of clinical signs alone is not possible as there are several other viral infections that can lead to similar clinical signs (Feline Immunodeficiency Virus, Feline Leukaemia Virus and Feline Coronavirus). Detection of antibodies to BoDV-1 by ELISA or indirect immunofluorescence in cats exhibiting clinical signs typical for BoDV-1 infection permit a tentative diagnosis (Wensman et al., 2012).

However, the diagnostic sensitivity of the detection of antibodies, at 81 %, means that not every cat with BoDV-1 infection will have detectable levels of antibodies (Wensman et al., 2012). The reason for this is unclear. It is speculated that different strains of BoDV-1 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 (Wensman et al., 2012). In the absence of clinical signs of Borna disease, diagnostic serology is of little value.

Detection of viral RNA by RT-PCR (reverse transcription PCR) in pooled samples of blood, serum, urine, conjunctival, nasal, oral or rectal swabs and possibly CSF collected from cats with clinical signs of Borna disease can be considered diagnostic (Wensman et al., 2012).

Currently, the most reliable means of diagnosis of Borna disease is considered to be pathology and histopathology of the CNS of affected animals. The most important histopathological findings include perivascular cuffing (Fig. 2) in the hippocampus, basal ganglia, cerebellum, cerebrum and the grey matter of the brain stem (Lundgren, 1992). In addition, plasma cells were frequently seen close to neurons (Lundgren et al., 1997), indicative of an inflammatory reaction and thereby explaining the clinical findings in cats with staggering disease.
Immunohistochemistry or detection of BoDV-RNA are techniques that confirm a tentative diagnosis of BoDV-1 infection. However, they are not used in routine diagnosis as they are expensive and require experience. Antigen and virus specific nucleic acid can be demonstrated in the hippocampus, predominantly in the neuronal nuclei, and, in chronic infections, antigen is also seen in astrocytes. Additionally, not all clinically affected cats are positive by these tests.

In cats with end-stage staggering disease, mild neutropenia is observed in about a third of the affected population. No other changes of clinical or biochemical parameters are observed.

**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 a lower risk of BoDV-1 infection compared to those with unlimited access to such areas. In areas where staggering disease is known to occur, it might therefore be recommended that cats are kept indoors. However, limiting outdoor access should be carefully weighed against the risk of BoDV-1 infection. For many cats, outdoor access is an important component of their well-being.

**Zoonotic risk**

As BoDV-1 persistently infects the CNS of many animal species, it was postulated that this virus might also infect the human CNS. Indeed, it was shown that humans can be seropositive for BoDV-1 and that the frequency of BoDV-1 antibodies was increased in human patients with chronic neurologic disorders. Specifically, among 70 psychiatric patients, 20 % were found to be seropositive, compared to only a few percent of the normal population. This led to the hypothesis that BoDV-1 infection may be involved in the development of selected neurological disorders (Bode et al., 1993; Bode and Ludwig, 2003) and triggered the creation of a research group within the German Robert Koch Institute in the 1990s to study the potential health threat of BoDV-1 to humans. In 2007, the Robert Koch Institute published a statement that:

1) the methods providing seropositive results in human blood were not adequate to support a reliable statement about the presence of antibodies to BoDV-1 and

2) that the RNA sequences found in human blood and tissue were the consequence of BoDV-1 contamination in the laboratory of the respective research lab.

Therefore, it was concluded that BoDV-1 was not involved in the aetiology of human psychiatric diseases and, after dozens of careful studies, the research group ended its activity in 2007.
However, a study published in 2016 demonstrated that patients with primary psychosis showed circulating immunocomplexes and BoDV-1 antigen in their blood significantly more frequently than blood in samples from healthy donors. The authors concluded that surveillance of BoDV-1 should be considered in psychiatric research (Zaliunaite et al., 2016). Furthermore, three human breeders of variegated squirrels (Sciurus variegatoides) in Germany independently developed encephalitis and died within 2 to 4 months after the onset of clinical signs. Using advanced molecular procedures, researchers at the Friedrich-Loeffler-Institute in Greifswald and the Bernhard Nocht Institute for Tropical medicine, Hamburg, detected a previously unknown Bornavirus in brain samples of these three patients and in an in-contact squirrel (Hoffmann et al., 2015). This virus was designated variegated squirrel bornavirus 1 (VSBV-1). A publication in 2017 evaluating more than 450 squirrels from Germany, the Netherlands and the United Kingdom found VSBV-1 RNA in 11 squirrels belonging to 2 squirrel species (Schlottau et al., 2017). These observations suggest that human handling of these animals represents a considerable risk for transmission. Whether or not cats may become infected by VSBV-1 is not clear yet.

A comprehensive epidemiological and virological study on retrospective fatal human encephalitis cases in southern Germany revealed important and surprising insights into classical Borna Disease virus infections (Niller et al., 2020). By screening 56 human encephalitis cases of putative viral origin from 1999-2019 for BoDV-1 RNA, BoDV-1 RNA was detected in eight newly defined cases, and the first human infectious BoDV-1 was isolated. All samples were from endemic regions in southern Germany. Phylogenetic analyses revealed several regional clusters, and epidemiological studies indicated independent spillovers from local wild animal reservoirs, most likely from the bicoloured white toothed shrew (Crocidura leucodon). Virtually all human patients lived in rural areas, and were regularly working in agriculture. Three of them kept dogs, five kept cats, and most of them had regular contact with cats. Some of the cats brought mice and shrews into the patients’ house. However, despite these data, the role of the cat in the transmission of the disease in humans remains unclear. Cats are considered dead-end hosts (Bornand et al., 1998) and hypothetically, may passively pick-up the virus from infected shrews and expose it to humans. In a multicat household in that area, where infected shrews had been brought home by cats, all cats were monitored and none was found to be infected. There is no indication of a cat-to-human or human-to-human transmission.

Acknowledgement

ABCD Europe gratefully acknowledges the support of Boehringer Ingelheim (the founding sponsor of the ABCD), Virbac and IDEXX.

References


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