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Review

Borna disease virus infection in cats

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ABSTRACT

Bornaviruses are known to cause neurological disorders in a number of animal species. Avian Bornavirus (ABV) causes proventricular dilatation disease (PDD) in birds and Borna disease virus (BDV) causes Borna disease in horses and sheep. BDV also causes staggering disease in cats, characterised by ataxia, behavioural changes and loss of postural reactions. BDV-infection markers in cats have been reported throughout the world. This review summarizes the current knowledge of Borna disease viruses in cats, including etiological agent, clinical signs, pathogenesis, epidemiology and diagnostics, with comparisons to Bornavirus infections in other species.

Introduction

In the 1970s, a neurological disorder of unknown aetiology in cats was described for the first time (Kronevi et al., 1974). Affected cats usually presented with ataxia and behavioural changes, and the disease was later named 'staggering disease' ('vingelsjuka' in Swedish; Ström et al., 1992). On histopathology, there was prominent lymphoplasmacytic or lymphohistiocytic inflammation of the central nervous system (CNS; Kronevi et al., 1974; Lundgren, 1992). Initial attempts to determine the aetiology failed, even though a viral agent was suspected (Kronevi et al., 1974). Twenty years later, the first evidence of a virus was reported when antibodies to Borna disease virus (BDV) were detected in sera from affected cats (Lundgren and Ludwig, 1993). BDV antigens and nucleic acids were found in brain tissue (Lundgren et al., 1995a; Berg and Berg, 1998) and feline BDV was isolated (Lundgren et al., 1995b). The feline isolate of BDV was inoculated into healthy cats, resulting in clinical signs and histopathology similar to natural infection (Lundgren et al., 1997), hence proving that BDV was the cause of staggering disease.

Before these findings in cats, Borna disease (BD) was a well-known neurological disease in horses and sheep in Central Europe. The first description of clinical signs dates from 1660 (Heinig, 1969), and since the 1920s clinical signs of neurological disease have been attributed to BDV (Zwick and Seifried, 1925; Zwick et al., 1928). Interest in BDV increased enormously in the 1980s, due to serological findings in American human patients with neuropsychiatric illnesses (Rott et al., 1985), followed by the detection of antigens and viral nucleic acids in German psychiatric patients (Bode et al., 1995).

Reports of BDV infection markers from several species and parts of the world indicated that BDV was more widespread than previously considered (Ludwig and Bode, 2000), but some of these findings are still controversial (Kinnunen et al., 2013). One concern is the highly stable nature of the BDV genome (around 95% similarity), which is unusual for an RNA-virus; only one more divergent strain of BDV has so far been identified (Nowotny et al., 2000). Recent findings of several lineages of genetically distinct avian Bornaviruses (ABV) in psittacine birds (Honkavuori et al., 2008; Kistler et al., 2008) and other avian species with proventricular dilatation disease (PDD; Delnatte et al., 2013; Rubbenstroth et al., 2013), have raised questions about ABV-like viruses in mammals and the role of birds in virus transmission (Payne et al., 2012). So far, ABV has not been detected in mammals, but BDV RNA has been detected in wild birds (Berg et al., 2001), suggesting their potential role in the spread of BDV.

Interestingly, it has been reported that Bornavirus-like elements are incorporated into the genome of humans and other mammalian species, through events that occurred about 40 million years ago (Belyi et al., 2010; Horie et al., 2010), indicating that Bornaviruses are evolutionarily mature viruses living in stable co-existence with mammals. This review provides current information on the aetiology, clinical signs, pathogenesis, epidemiology and diagnostics of BDV in cats, with comparisons to Bornavirus infection in other species.

Borna disease virus

BDV is an enveloped, non-segmented virus with a genome consisting of a single-stranded, negative-sense RNA of approximately

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8900 nucleotides (Fig. 1; Lipkin and Briese, 2006). However, it is noteworthy that classical virus particles are uncommon and that there are extremely few electron micrographs of the virus (Ludwig and Becht, 1977; Zimmermann et al., 1994; Kohno et al., 1999). BDV belongs to the order Mononegavirales and since it is the only animal virus of this order that uses the host cell nucleus as the site of replication (Briese et al., 1992), it constitutes the family Bornaviridae, together with ABV. The genome encodes for six proteins: the nucleoprotein (N), the phosphoprotein (P), a non-structural protein (X), the matrix protein (M), the glycoprotein (G) and the large protein (L), which is an RNA-dependent RNA-polymerase (Tomonaga et al., 2002). During transcription, the virus employs the host cell splicing machinery to use its comparatively short genome to maximum effect (Cubitt et al., 1994; Schneider et al., 1994).

BDV seems to have a highly conserved genome, since most isolates have >95% genetic similarity (Kinnunen et al., 2013). No feline BDV isolate has been fully sequenced and most molecular epidemiology, regardless of species, is based on partial gene sequences of conserved regions. Hence, there might be more genetic divergence in BDV than currently observed. ABV has a higher degree of genetic variation, and several genotypes have been described (Hoppes et al., 2013). Whether cats or other mammals can be infected by ABV or ABV-like viruses is still unknown.

BDV-like elements in mammalian genomes

It was an unexpected finding that parts of the BDV genome were identified integrated into the genome of various animal species (Belyi et al., 2010; Horie et al., 2010), although numerous copies of retroviral sequences were discovered in the genome of several animal species many years ago. It has been theorised that BDV integration was an accidental occurrence millions of years ago, via co-infection of a retrovirus and an ancient BD-like virus. Nevertheless, it seems implausible that the evolution of BDV has been so slow that it is still recognizable millions of years later. The relevance of this finding in diagnostics and for the biology of BDV is not understood, although the enzymatic activity responsible for this endogenization is highly active in the brain (Feschotte, 2010), leaving any clues to psychiatric diseases wide open for speculation.

Clinical signs in cats

Cats with staggering disease associated with BDV infection, as described by Lundgren (1995) and Wensman et al. (2012), typically display a distinctive combination of clinical signs. Predominating signs are neurological in nature, including gait disturbances and behaviour alterations. In addition, general signs of disease, such as fever, reduced appetite and constipation, are noted in some cats (Kronevi et al., 1974; Lundgren, 1992; Wensman et al., 2012). Common neurological findings include abnormally stiff muscles in the limbs and tail and a stiff ataxic gait in a more or less obtunded cat, with absent or decreased postural reactions and menace responses (Appendix A. Supplementary File 1; Wensman et al., 2012). Clinical findings also include protracted claws, vocalization and increasingly affectionate behaviour. Pain on lumbar palpation is also commonly noted. During the nociception test, dilated pupils and tense muscles indicate that the cat perceives the painful stimulus, but minimal effort is made to escape from it (Appendix A. Supplementary File 1, Sequence 4). Spinal reflexes are normal to exaggerated. The neuroanatomical diagnosis refers to the CNS, particularly the forebrain.

The clinical picture is not pathognomonic for feline BDV infection, since neurological signs do not reflect disease aetiology, but the localisation and spatial distribution of lesions in the CNS. However, cats with ataxia and gait abnormalities not associated with BDV often have other neurological signs such as compulsive walking, generalized epileptic seizures, facial paresis or vestibular signs (Penderis, 2009). Such signs are generally not seen in cats with staggering disease. Totally asymmetric neurological signs are also not seen in BDV. The appearance of such findings on a neurological examination should direct attention to other diseases affecting the feline CNS.

In studies from Austria, the UK, Turkey, and Japan, specimens from cats with a diversity of neurological signs have been tested for BDV-specific antibodies or BDV-nucleic acids and some were found to be positive (Weissenböck et al., 1994; Reeves et al., 1998; Nakamura et al., 1999; Helps et al., 2001; Ouchi et al., 2001). Even though many of these cats were reported to be ataxic, the case presentations often lacked details of thorough clinical and neurological examinations. In addition, in the majority of the reported cats, no post-mortem examination was performed; hence histopathological confirmation was not obtained. The most uniform clinical signs were seen in Austrian cats (Weissenböck et al., 1994). Brain suspensions from these cats were inoculated into rabbits, which developed antibodies to BDV but no clinical signs of BDV infection (Nowotny and Weissenböck, 1995). BDV RNA was later detected in one of these cats (Berg and Berg, 1998). Brain suspensions from Swedish cats with staggering disease were inoculated into neonatal rats, sometimes resulting in characteristic degeneration of the dentate gyrus granule neurons of the hippocampus, typical of BDV-infection (Ludwig et al., 1988; Lundgren et al., 1995b).

The clinical signs of naturally occurring BD in other animal species are well-described only for horses and sheep, and resemble those of staggering disease in cats. Horses and sheep diagnosed with BD are ataxic and display changes in behaviour and mentation (Mayhew, 2008). However, they also develop asymmetric vestibular signs and various functional cranial nerve deficits (Mayhew, 2008), signs not commonly recognized in cats with staggering disease. BDV infection markers have been detected in humans with neuropsychiatric illnesses (Rott et al., 1985; Bode et al., 1995; de la Torre et al., 1996), such as major depression and schizophrenia, although the contribution of BDV to the development of these disease entities is not yet clear and it is not known if there is virus spread between animals and humans (Thakur et al., 2009; Lipkin et al., 2011). ABV infection in psittacine birds leads to PDD and affected birds show neurological and/or gastro-intestinal signs (Gregory et al., 1994). The most common clinical signs are depression, weight loss, passage of undigested feed in the faeces, gait disturbances and abnormal postural reactions.

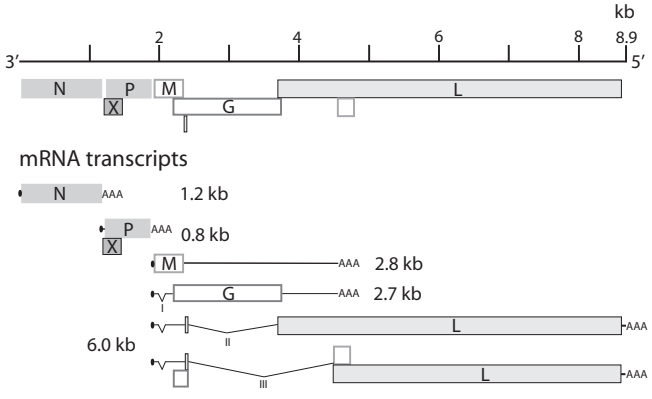

Fig. 1. Genome organization and protein-coding mRNA transcripts of Borna disease virus (BDV). Due to its comparatively short genome, BDV uses alternative transcription strategies, such as overlapping ORFs and usage of host cellular splicing mechanisms.

Pathogenesis

The knowledge of BDV pathogenesis is mostly based on experimental infections of rodents and cell cultures. In addition, careful studies from the early 20th century in horses (Joest and Degen, 1911), and more recent studies in horses (Gosztonyi and Ludwig, 1984; Ludwig et al., 1988) and cats (Lundgren, 1992), give important insights into the mechanisms of BDV infection (Fig. 2).

BDV probably enters the host via nerve cells in the olfactory epithelium and the oro-pharyngeal mucosa (Morales et al., 1988; Sauder and Staeheli, 2003), as originally proposed by Joest and Degen (1911). At the host cell surface, the BDV genome binds to a yet unknown receptor, leading to viral uptake by endocytosis and the release of naked nucleocapsids from the early endosome to the cytoplasm (Gonzalez-Dunia et al., 1998; Perez et al., 2001; Clemente and de la Torre, 2009). The nucleocapsids are transported into the nucleus, where replication and transcription take place in virus replication factories (Matsumoto et al., 2012).

From the initial replication site in the olfactory epithelium, the nucleocapsids are then transported via the olfactory nerve to the olfactory pathways of the CNS, probably using intra-axonal transport systems (Gosztonyi and Ludwig, 1995; Gosztonyi, 2008). The spread of BDV within the CNS most likely occurs via nucleocapsids, since enveloped virus particles have not been found (Gosztonyi et al., 1993). Later in infection, BDV spreads to the spinal cord, cranial and peripheral nerves, resulting in blindness and the infection of visceral organs (Krey et al., 1979; Gosztonyi and Ludwig, 1995; Dietzel et al., 2007; Gosztonyi, 2008). From these organs, infectious enveloped virus particles are released in various secretions, such as lacrimal fluid, saliva, urine and faeces (Zwick, 1939; Richt et al., 2000; Sauder and Staeheli, 2003; Gosztonyi, 2008). There are sometimes inflammatory changes in the intra-abdominal ganglia and in the adrenal medulla in BDV-infected cats, indicating infection of the visceral organs; BDV RNA has also been detected in urine and faeces (Wensman et al., 2012).

BDV triggers an intense T cell-mediated immune reaction in the CNS (Lundgren et al., 1995a; Stitz et al., 1995; Berg et al., 1999), which is responsible for the clinical signs of disease. However, cats with severe inflammatory changes do not always present with severe clinical signs (Wensman et al., 2012), indicating that other factors modulate clinical severity. Several direct virus–host protein–protein interactions have been identified that could contribute to the development of clinical signs (Wensman, 2012, 2013). For example, transgenic mice expressing BDV P in glial cells develop similar neurological signs to those observed in natural infection (Kamitani et al., 2003), possibly due to an interference of γ-aminobutyric acid (GABA) receptor trafficking (Crestani et al., 1999; Peng et al., 2008).

BDV infection occurs in the absence of inflammation when neonatal rats are infected (Gosztonyi and Ludwig, 1995). In these cases, the disease appears to be more subtle, producing learning deficiencies and behavioural changes due to the degeneration of hippocampal neurons (Dittrich et al., 1989; Gosztonyi and Ludwig, 1995). In cats there are also cases without inflammation, suggesting that viral or other host-related factors influence pathogenesis (Berg and Berg, 1998).

Interestingly, some rats that survive acute BDV infection develop aggressive behaviour and obesity syndrome (Hirano et al., 1983; Ludwig et al., 1985; Carbone et al., 1987). The exact mechanism is unclear, but is likely due to uncontrolled appetite, possibly via a neurological disturbance. There are a few rare anecdotal reports of cats with staggering disease surviving the initial acute stage and later developing extreme obesity. Although uncommonly recognized, an obesity syndrome could possibly be a sequel of BDV-infection in cats.

Immune evasion mechanisms of Bornaviruses

Despite the intense host immune reaction, Bornaviruses can establish persistent infections because of several viral immune evasion

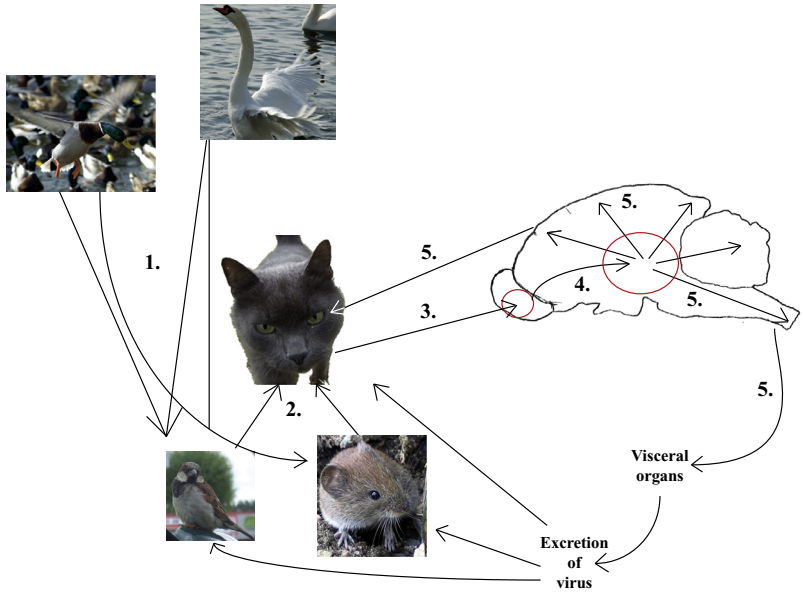

Fig. 2. Proposed virus transmission and pathogenesis of Borna disease virus (BDV) infection in cats. 1. Wild waterfowls can carry BDV over long distances from endemic to non-endemic areas. Stationary birds and rodents are infected and the virus persists in their populations. 2. Cats are infected when they prey upon infected animals. The virus enters the olfactory epithelium where initial replication takes place. 3. The nucleocapsid of BDV is transported to the olfactory bulb through the olfactory nerves by the intra-axonal transport system. 4. Transneural spread in the CNS occurs via nucleocapsids to the higher olfactory pathways. 5. Later, almost the whole cortical area, the brain stem, the meninges of the cerebellum, and the spinal cord are involved. Spread of BDV via peripheral nerves transports the virus to visceral organs, and BDV is transported to the eye through cranial nerves. In these organs, infectious enveloped particles are excreted and can potentially infect other cats and reservoirs. Encircled areas are regions of the brain where most severe inflammatory changes are seen. Photos: Bengt Ekberg, SVA (wild waterfowls); Jonas Wensman (stationary bird); Wikimedia Commons (bank vole); Helena Wensman (cat).

mechanisms. These mechanisms mainly target pathogen recognition systems and the type I interferon (IFN) system of the host, which are key antiviral mechanisms (Garcia-Sastre and Biron, 2006; Baum and Garcia-Sastre, 2010).

One pathogen recognition receptor (PRR) which targets RNA-viruses is retinoid inducible gene I (RIG-I), an important intracellular viral sensor and inducer of type I IFN (Baum and Garcia-Sastre, 2011). At replication, Bornaviruses exchange the triphosphate at the 5′-end to a monophosphate, thereby avoiding recognition by RIG-I (Schneider et al., 2005; Habjan et al., 2008; Reuter et al., 2010).

There are other PRRs that recognize RNA-viruses, thus it is important for viruses to develop several alternative strategies to evade the host immune response. For example, BDV and ABV proteins target different levels of the type I IFN signalling pathway. BDV N inhibits type I IFN expression by interfering nuclear localisation of the interferon regulatory factor 7 (IRF7; Song et al., 2013), whereas BDV P acts as a decoy substrate for phosphorylation of TBK-1 (Unterstab et al., 2005), a cellular kinase activating transcription factors enhancing type I IFN expression. Additionally, the X proteins of BDV and ABV interfere with type I IFN signalling by an unknown mechanism (Wensman et al., 2013). All of these findings are based on in vitro experiments in different cell lines, and there are discrepancies between the reports. For instance, BDV N and X did not inhibit type I IFN in one of the studies (Unterstab et al., 2005), while BDV P did not inhibit type I IFN in another (Wensman et al., 2013). It is possible that different experimental design elements, such as cell line and which type I IFN inducing stimuli were used, are also important factors.

Non-cytolytic mechanisms, such as IFN-γ, antibodies and T-cells, are important for viral clearance in the CNS, but type I IFNs are neurotoxic (Griffin, 2003). BDV infection triggers such an immune reaction and IFN-γ mRNA is expressed in BDV-infected cats (Wensman et al., 2011b). One antiviral effect of IFN-γ is the production of free oxygen radicals by the induction of inducible nitric oxide synthase (iNOS), and BDV P is able to inhibit the expression of iNOS (Peng et al., 2007).

Apoptosis is a response to type I IFN signalling and is an important antiviral activity (Chawla-Sarkar et al., 2003). Thus, it is crucial for BDV to avoid apoptosis so that persistent infection can be established. BDV X is responsible for the resistance to apoptosis observed in some, but not all, cell lines (Poenisch et al., 2009; Wensman, 2012), and the proposed mechanism involves viral interaction with a mitochondrial antiviral signalling protein (MAVS; Li et al., 2013b). Moreover, viral strain differences in the resistance to apoptosis have been reported. BDV laboratory strain V, of equine origin, inhibits apoptosis, whereas one human BDV strain (Hu-H1) promotes apoptosis in human oligodendrocytes (Li et al., 2013a). Whether this finding is due to differences in the X protein, or other factors, is not yet known.

Yet another immune evasion mechanism has been ascribed to BDV. The P protein is tightly connected to the host cell chromosomes, and in dividing cells nucleocapsids are spread to daughter cells through these connections, thereby maintaining a persistent nuclear infection (Matsumoto et al., 2012).

Epidemiology

Since the first descriptions of staggering disease and BDV infection in cats from Sweden and Austria (Kronevi et al., 1974; Lundgren, 1992; Weissenböck et al., 1994; Lundgren et al., 1995b), reports of BDV infection markers in cats have been reported from several other countries, namely, Japan (Nakamura et al., 1996, 1999; Nishino et al., 1999; Ouchi et al., 2001), the United Kingdom (Reeves et al., 1998), Germany (Huebner et al., 2001), Indonesia and Philippines (Horii et al., 2001), Turkey (Helps et al., 2001; Yesilbag et al., 2012), Finland (Kinnunen et al., 2007) and Australia (Kamhieh et al., 2008).

Similar to conditions for horses and sheep in Central Europe, parts of Sweden are considered endemic, even though the disease is seen throughout the country (Richt et al., 2000; Wensman, 2012). Affected cats are most commonly presented with clinical signs from December to May (Lundgren, 1992; Wensman et al., 2012), and there seem to be annual differences in the number of cases (Wensman et al., 2008). These epidemiological features are also similar to BD in horses and sheep (Ludwig et al., 1985; Richt et al., 2000). Hence, different vectors or reservoirs responsible for the spread of BDV have been suggested, such as insectivores (Hilbe et al., 2006), birds (Berg et al., 2001; Payne et al., 2012) and rodents (Sauder and Staeheli, 2003; Kinnunen et al., 2007; Kinnunen et al., 2011). Ticks have also been proposed because of the overlapping endemic regions with tick-borne encephalitis, but if they contribute to spread of BDV they are merely mechanical vectors, since BDV does not replicate in ticks (Schindler, 2004).

For cats, the probable reservoirs are birds and rodents as they are common prey, and cats with outdoor access are at increased risk of developing staggering disease (Berg et al., 1998; Wensman et al., 2012). BDV RNA has been detected in the urine and faeces of bank voles with experimental BDV infections, potentially reflecting virus shedding (Kinnunen et al., 2011). Most infected bank voles did not show any clinical signs or pathological changes, but some were hyperactive and showed behavioural alterations, similar to BDV-infected rats. BDV infection could potentially be maintained within the wild bank vole population. The virus is most likely transmitted to cats as a result of consuming infected prey (Fig. 2). It is known that behavioural changes in the prey caused by *Toxoplasma gondii* facilitate the spread of disease, as infected rodents are more susceptible to feline predation (Webster, 2007). It is unknown if BDV causes behavioural changes in prey that facilitate virus transmission.

Mallard ducks and Canada geese have been reported to have subclinical Bornavirus infection (Hoppes et al., 2010; Payne et al., 2011), and these waterfowl could potentially spread Bornaviruses over long distances from endemic regions to previously non-endemic areas during migration (Payne et al., 2012; Wensman, 2012). Small mammals or stationary birds susceptible to BDV infection, such as rodents, insectivores or stationary birds carrying markers of BDV infection, could maintain the infection along migratory routes (Berg et al., 2001; Hilbe et al., 2006; Kinnunen et al., 2007). Interestingly, an Israeli study showed that BDV-specific antibodies were more prevalent in horses living along the pathways of migratory birds than in areas where migratory birds were absent (Teplitsky et al., 2003).

Our group has recently identified BDV-specific antibodies in Icelandic horses in Iceland (Björnsdóttir et al., 2013), a country with highly restricted animal import regulations. We also found high BDV-antibody titres in Icelandic horses in the most northern parts of Sweden, where few cases of BDV-infection in cats are reported (Wensman et al., unpublished data). Both these regions are along migratory pathways of waterfowl, supporting the possible role of birds in Bornavirus transmission, although it should be emphasized that it is not known to what extent birds are infected with BDV.

Diagnostics

An ante-mortem diagnosis of staggering disease might be suspected based on history (including geographical location, outdoor access, etc.), clinical and neurological signs and the clinical course of the disease. Low to low normal total white blood cell (WBC) counts in routine blood samples could also raise the clinical index

Table 1
Mean leukocyte, neutrophil and lymphocyte counts in cats with staggering disease (Wensman et al., 2012).

	Leucocytes (10^9/L)	Neutrophils (10^9/L)	Lymphocytes (10^9/L)
Reference values	5.5–17.5	2.5–12.5	1.5–7.0
Cats with staggering disease	5.0 ± 1.4	3.1 ± 1.0	1.5 ± 0.84

of suspicion (Table 1; Wensman et al., 2012). No significant changes are found on serum biochemical analysis. In the cerebrospinal fluid (CSF), infected cats often have increased protein content (>0.36 g/L in 8/17 infected cats, Wensman et al., 2012; >0.36 g/L in 5/7 infected cats, Lundgren, 1992; reference values, Rand et al., 1990), and a mononuclear pleocytosis (4/18 infected cats, Wensman et al., 2012; 4/7 infected cats, Lundgren, 1992).

Serology by an indirect immunofluorescence assay (IFA) detected BDV-specific antibodies in serum from 81% (13/16) of cats with staggering disease, whereas a comparison group of cats without neurological signs from the same geographical area had a seroprevalence of 16% (Wensman et al., 2012). This agrees with previous serological studies in healthy cats, which have reported seroprevalences of 16% in Turkey and 24% in Japan (Helps et al., 2001; Ouchi et al., 2001), suggesting the existence of subclinical BDV-infection in cats. Apart from IFA, several different serological assays have been developed, and one ELISA detecting circulating immune-complexes (CIC) has high sensitivity (Bode et al., 2001; Bode, 2008). Sera from six of the neurologically affected cats studied by Wensman et al. (2012) were analysed using this CIC-ELISA and all were positive. Additionally, 5/16 diseased cats (31%) tested positive for BDV-RNA in blood (Wensman et al., 2012). The combination of serology and real-time RT-PCR (rRT-PCR) detected BDV infection markers in 89% (17/19) of cats with clinical and histopathological evidence of staggering disease. When staggering disease is suspected, these tests might be helpful diagnostic aids (Wensman et al., 2012).

In two studies of CSF in cats with staggering disease, 21% (3/14) were seropositive by IFA (Wensman et al., 2012) and 38% (3/8) by ELISA (Johansson et al., 2002). Although not a very sensitive diagnostic method, the presence of antibodies in the CSF of cats is probably highly specific for BDV-infection, as it is in horses (Ludwig and Thein, 1977; Richt et al., 2000).

At post-mortem examination, meningoencephalomyelitis with extensive lymphohistiocytic or lymphoplasmacytic perivascular cuffing and inflammatory nodules has been reported (Lundgren, 1992; Wensman et al., 2012). Perivascular aggregates infiltrate the surrounding parenchyma and neuronophagia and neuronal degeneration are sometimes observed. Axonal degeneration and myelin deterioration can be seen in the ventrolateral tract of the spinal cord (Lundgren, 1992, 1995). In cats with staggering disease, the inflammation has a characteristic distribution pattern. Inflammation predominates in the grey matter, with a strong predilection for the brain stem, hippocampus, basal nuclei and olfactory bulb (Lundgren, 1992, 1995). In some cats, lymphocytic infiltrates are seen in the optic nerve and around retinal vessels (Lundgren, 1995; Lundgren et al., 1995a); however, retinal degeneration, as seen in BDV-infected rabbits (Krey et al., 1979) and horses (Dietzel et al., 2007), has not been observed in cats. Intra-nuclear inclusion bodies, called Joest–Degen inclusion bodies, which are sometimes found in horses, are not detected in cats (Joest and Degen, 1911; Gosztonyi and Ludwig, 1984). Interestingly, each of 5/19 affected cats in one study also had a lymphohistiocytic or lymphoplasmacytic inflammatory reaction of an intra-abdominal ganglion (Wensman et al., 2012).

The microscopic appearance of the CNS lesions in feline BDV has the same spatial distribution as BD in horses and sheep, suggesting a viral cause (Gosztonyi and Ludwig, 1984). However, from the histopathological view, other viral meningoencephalomyelitides cannot be excluded. Virus detection by immunohistochemistry of paraffin-embedded brain sections and rRT-PCR from fresh frozen brain tissue samples have been used to prove the presence of BDV in affected brains (Lundgren et al., 1995a; Wensman et al., 2007, 2012), but not all clinically affected animals are positive by these tests (Lundgren 1995a; Wensman et al., 2011b, 2012). When positive, these methods are considered confirmatory for diagnosis. In most clinical cases of feline BDV infection, by combining all relevant case information and by ruling out differential diagnoses, it should be possible to reach a diagnosis.

Clinical course, treatment and prognosis

In the first publication by Lundgren (1992) describing 25 affected cats, most were euthanased during the first month of illness; however a few cats survived but recovered incompletely. One cat died naturally from the disease. Wensman et al. (2012) reported 19 cats, and 14 of these were euthanased ≤1 month after the onset of signs. The five remaining cats survived for up to 4 years postonset. These cats improved somewhat after the initial stage, but were euthanased after progression of neurological signs (K. Hultin Jäderlund, unpublished observations).

Cats presented in the acute stage of disease, possibly with fever and reduced appetite, should receive supportive care with IV fluids and other therapies as required. Antibiotics, corticosteroids and/or antiviral drugs have been used in many cats with staggering disease, but controlled trials have not been performed; there are anecdotal reports of the beneficial effects of glucocorticoid therapy (Wensman et al., 2011a). The antiviral drug amantadine hydrochloride has been used in cats, but response to treatment has been inconclusive. Amantadine hydrochloride blocks the cell-penetrating ability of RNA-virus and theoretically could be useful. This drug has been used against BDV-infection in cell cultures, experimental rats, in horses with BD and in seropositive humans with varying results, possibly because of differential sensitivity of viral strains (Bode et al., 1997; Cubitt and de la Torre, 1997; Stitz et al., 1998; Dieckhöfer, 2008; Dietrich and Bode, 2008).

Conclusions

Bornaviruses still intrigue the research community almost 100 years after BDV was first isolated. The persistence of the virus in the CNS poses challenges for viral detection in clinically affected animals and its isolation in cell culture. BDV has unusual genetic stability for an RNA-virus, prompting debate about its molecular characteristics, which in turn has contributed to the complexity of BDV research. The addition of ABV into the Bornaviridae family has increased interest in the field, and future research should include investigations into whether ABV could be transmitted to mammals, or BDV could be transmitted to birds. Such findings would clarify the transmission and epidemiology of Bornaviruses, and could explain some previous controversial results. The role of endogenous Bornavirus-like elements found in the genomes of several species, and how these influence BDV and ABV diagnostics, also needs further elucidation. Future research is critical to advance our understanding of these fascinating viruses.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tvjl.2013.12.012.

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