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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.

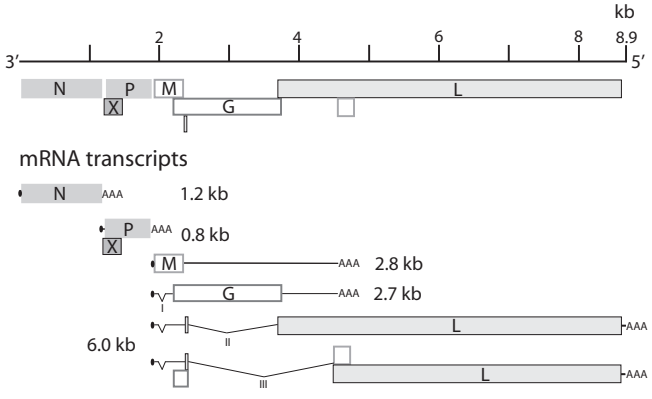

Fig. 1. Genome organization and protein-coding mRNA transcripts of Borna disease virus (BDV). Due to its comparatively short genome, BDV uses alternative transcription strategies, such as overlapping ORFs and usage of host cellular splicing mechanisms.