Borna disease virus and its host

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Introduction

In the 18th century, a neurological disease in horses, at that time called “Kopfkrankheit der Pferde” (head disease of horses), was described in a German textbook [80]. This disease had been known for a long time in Germany, especially in the southern and southeastern parts, where it occasionally occurred [213]. After severe losses around the city of Borna (Saxony) in the 1890’s, the disease was thereafter known as “Bornasche Krankheit” (Borna disease, BD). In 1907, the Ministry of Home Affairs of the Kingdom of Saxony decided that the disease should be thoroughly investigated, with the aim to characterize its clinical signs, pathology and etiology. The clinical signs and pathology were then well characterized by Schmidt in 1912 and by Joest and Degen in 1911 [10] [22]. Several attempts to establish the etiology behind BD were made. At first, bacterial causes of the disease were proposed; however, based on the lack of presence of a purulent inflammation, the proposed cause was changed to a bacterial toxin [213].

At the end of the 19th century, the first viruses were discovered: Ivanovsky and Beijerinck described the tobacco mosaic virus, and Loeffler and Frosch the first animal virus (foot-and-mouth disease virus) [143]. The first successful attempts to transmit BD from a diseased horse to rabbits were made by Zwick and Seifried in 1924-25 [30], and a few years later Zwick and his co-workers had convincing evidence for a viral etiology of BD. In the early history of BD research, studies of the pathogenesis, viral entry and secretion, as well as epidemiology, clinical signs and treatment, were in focus. This focus of the BD research has not changed dramatically over the last century, but still many questions within these fields have to be answered. This review will give an overview of the current knowledge of BDV and its hosts, and is a part of the doctoral thesis of the author [26].

Borna disease virus

Borna disease virus (BDV) was first considered to be the etiological cause of BD in 1928. Through successful transfer of filtered brain suspensions from a horse with BD to rabbits, and thereafter by several passages in rabbits [30] [31], it was concluded that a virus was the causative agent of BD. However, at that time the characteristics of viruses and the structures of viral particles (virions) were unknown. The characterization of BDV was begun by Zwick and others, especially regarding physical properties, and how the virus could be inactivated [31] [148] [213]. The size was established to be around 85-125 µm, values that are still valid today [69] [213]. In the late 1960’s, viral antigens could be visualized by immunofluorescence [200], and a few years later successful cultivation of BDV in tissue culture was performed [130] [136]. It was suggested that BDV was an RNA-virus [67] [129], mainly associated with the infected cells and only to a minor extent released from the cells [129]. The first electron micrographs showed spherical particles [129], which was later confirmed [119] [211]. For a long time, the sequence and organization of the virus genome was unknown. It was not until the 1990’s that the first full-genome sequences, and the organization of the BDV genome, were established [3] [4].

Genome organization

BDV is an enveloped virus with a non-segmented genome of single-stranded negative sense RNA of around 8900 nucleotides in length [3] [4] [125]. On the basis of its unique nuclear site of replication, compared to other animal viruses within the order of Mononegavirales [2], BDV is the sole member of the Bornaviridae family. The genome is organized in a similar manner to other members of the order of Mononegavirales, i.e. N, P, M, G and L (Figure 1). In addition, like most members of the Paramyxoviridae family, BDV has a small non-structural gene, designated X, which is located as an over-lapping open reading frame (ORF) together with the P gene [112] [167].

BDV has three transcription units that encode six ORFs [112], and exploits the cellular splicing mechanisms to efficiently use its comparatively short genome (Figure 1) [5] [181]. The first ORF in the

first transcription unit results in the nucleoprotein (N), whereas the second transcription unit contains two overlapping ORFs for the phosphoprotein (P), and the p10 or X protein [25] [112]. The third transcription unit is spliced differently, and also has different transcription initiation and termination signals, enabling polymerase read-through during transcription, which results in expression of the matrix protein (M), the glycoprotein (G), and the large protein or RNA-dependent RNA-polymerase (L) [25] [112].

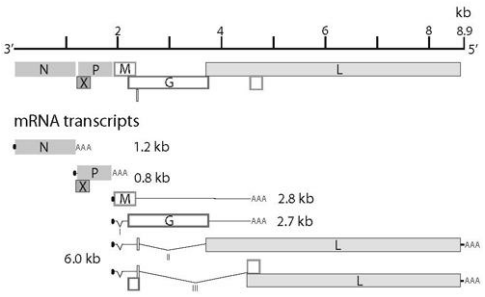

Figure 1. Map of genome organization and protein-coding mRNA transcripts of BDV. The BDV genome is comparatively short, and therefore BDV uses alternative transcription strategies, like over-lapping ORFs and usage of host cellular splicing mechanisms. Modified from Tomonaga et al., [25].

The genome of BDV is highly conserved, and so far two genotypes have been observed with approximately 15% differences at the nucleotide level [19]. Some observations indicate that BDV isolates cluster into separate geographical regions based on their genetic composition [120], though other studies have not confirmed this [27] [44]. The conserved genome has led to the conclusion that BDV is an evolutionarily old virus, which has further been supported by recent findings of BDV-like elements in the genome of different mammals including the human genome [1] [9]. Recently, a more divergent Bornavirus with similar genome organization has been detected in psittacine birds, designated Avian Bornavirus (ABV) [8] [12].

Viral proteins

The six polypeptides encoded in the BDV genome each have important functions in the viral life cycle.

Nucleoprotein

The nucleoprotein (N) is the most abundant viral protein, and is mainly located inside the nucleus [69]. Besides the genomic RNA, N is the main component of the nucleocapsid or ribonucleoprotein (RNP) complex. BDV N and the BDV-RNA form polymers [106], together forming the backbone of the RNP. BDV N also interacts with P [41], and has an important role, together with P, in the intracellular transport of the RNPs to and from the nucleus [118].

Phosphoprotein

In other negative-stranded non-segmented RNA-viruses, the phosphoprotein (P) is an important co-factor to the polymerase complex in the processes of transcription and replication. However, unlike these other viral phosphoproteins, BDV P down-regulates the activity of the viral polymerase upon phosphorylation [178]. The phosphorylation of P is still needed for efficient viral spread in infected cells [179], indicating important functions of P in viral transmission. BDV P is phosphorylated at serine residues mainly by protein kinase Cε (PKCε), but to a lesser extent also by casein kinase II (CKII) [186]. In infected cells, P forms homomers, either as tri- or tetramers [106] [183]. The phosphorylated P multimer can interact with L [201]; however, N not bound to the RNP complex can block this interaction [182].

BDV P can also interact with X [187], and does so preferably as a monomer, which indicates that X plays a role in multimerization of P [182].

Matrix protein

The matrix protein (M) of BDV composes a shell or an outer layer of the RNP, likely protecting the genomic RNA and the other nucleocapsid proteins. BDV M forms tetra- or octamers [122] [194], which are a part of the RNP complex by interaction with P without inhibitory effects of the polymerase activity [57]. Moreover, M binds to single-stranded RNA and interacts with lipid membranes [147], suggesting

a key role in assembly of RNPs and viral particles similar to other negative-stranded RNA-viruses. Antibodies towards M neutralize BDV infectivity [99] [193], indicating that M is present on the surface of the infectious virus particle. However, BDV also spreads as RNPs, from cell to cell inside the CNS as well as in cell culture [60] [69] [86]. Hence, the neutralizing effect of anti-M antibodies most likely is due to neutralization of infectious RNPs.

Glycoprotein

Glycoproteins (G) of viruses are membrane proteins important for viral attachment to cellular receptors and viral entry into the host cell. In BDV, G is a glycosylated protein with a molecular weight of about 94 kDa (gp94) [180], which is a precursor molecule needed to be cleaved by the cellular protease furin into two biologically active proteins, GP-1 and GP-2 [172]. GP-1 is responsible for attachment to the host cell surface by binding of (a) yet unidentified cellular receptor(s) [62] [160]. However, one potential player is BiP (immunoglobulin heavy chain-binding protein), which is an endoplasmic chaperone also expressed on the cell surface [107]. Upon receptor binding, BDV is taken up by the host cell through endocytosis [61] [160]. In the early endosome inside the cytoplasm, GP-2 mediates the pH-dependent fusion of the viral and endosomal membranes to release the RNP [61] [83]. Antibodies against BDV G have neutralizing activity [84] [180].

Large protein or RNA-dependent RNA-polymerase

The large (L) protein of BDV is an RNA-dependent RNA-polymerase of around 190 kDa [201]. L has the possibility to translocate into the nucleus by itself [201] [202], though other viral proteins within the RNP further facilitate this nuclear translocation [69]. Cellular kinases phosphorylate L, which probably is a part of the regulation of the polymerase activity [201].

For successful transcription and replication, several BDV proteins (N, P, and L) are needed to form a polymerase complex [182]. The model for how this complex works, is most likely the same as that proposed for other non-segmented negative-stranded RNA-viruses, like Sendai virus [65] [106] [182]. Phosphorylated BDV P negatively regulates the activity of the polymerase complex [178], which could be contributed by the binding of X to P [164].

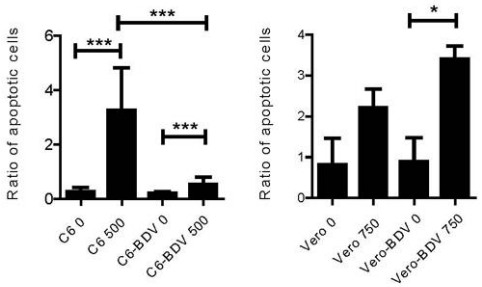

Figure 2. Apoptosis resistance in BDV-infected C6 cells, but not in BDV-infected Vero cells after H2O2 treatment. Cells were either mock-treated (0) or treated with 500 (C6) or 750 (Vero) µM of H2O2 for 48 h, harvested and incubated with Annexin V antibody (apoptotic cell marker) and propidium iodide (necrotic cell marker). Subsequently, fluorescent activated cell sorting (FACS) was performed, and the ratio of apoptotic cells (R) then calculated according to the equation R=([necrotic+apoptotic cells]+apoptotic cells)/living cells. The asterisks indicate statistically significant differences (two-tailed t-test), where * is $p<0.05$, and *** $p<0.001$.

X protein

Like other members of the order of Mononegavirales [167], BDV also expresses a small non-structural or accessory protein [185]. This protein is called X or p10, based on its molecular weight of 10 kDa, and co-localizes in the nucleus together with N and P [204], by interaction with P [187] [208]. BDV X seems to be a multifunctional protein. Besides its involvement in the regulation of the polymerase complex activity [163] [164] [165], X also inhibits apoptosis, thereby promoting a persistent infection [162]. The mechanism for this apoptosis resistance is as yet unknown, though X seems to have to localize to the mitochondrion to exercise this resistance [162]. However, there are cell line differences in the X-induced apoptosis resistance of BDV-infected cells. In a rat astrocytoma (C6) cell line, BDV-infected cells are clearly resistant to apoptosis stimuli (Figure 2, left diagram; [162], whereas a green monkey kidney (Vero) cell line shows no BDV-induced apoptosis resistance (Figure 2, right diagram).

BDV-like elements in mammalian genomes

Some viruses are known to be able to insert parts of their genomes into the genomic DNA of the host. For some viruses, like retroviruses, this strategy is needed for their replication. Other viruses, like herpesviruses and parvoviruses, most likely use this capacity as a means to avoid the host immune response, by establishing a form of latent or persistent infection [126] [142], but it could also be a way to exchange genetic material. The integration of viral genes into the host genome can lead to different pathological changes, such as tumour formation, and possibly even autoimmunity [142]. During the course of evolution, viral hosts likely have gained new genes, beneficial for their survival, through this gene exchange, either by getting novel functional proteins and/or as a way to acquire immunity to these viruses [121].

Until recently, only retroviruses and DNA-viruses were known to have the ability to incorporate into the genome of the host cell. BDV-like elements have now been found integrated into the genome of different mammals, including humans [1] [9]. These integration events happened millions of years ago [1] [9], though they can also occur in acute infection of different animals [9] [117]. Furthermore, elements from other RNA-viruses within the order of Mononegavirales, Ebola and Marburg viruses have also been found incorporated into the genomes of mammalian hosts [1]. Some of these elements result in protein expression [1] [9].These findings have led to renewed discussions about the relationship between BDV and possible human infections [81] [115] [195].

Diseases caused by Bornaviruses

Most mammals and birds seem to be susceptible to BDV infection, although not all experimental infections are followed by disease. Infection occurs naturally in most mammals, as well as in birds. In the following sections, the most common natural host species of BDV leading to disease will be described. Experimental infection in rats will also be discussed briefly.

Borna disease in horses, sheep and cattle

The horse was the first recognized host species of BDV, and it was from brain tissues from horses with BD that Zwick and his co-workers could infer a viral etiology [30] [31] [213]. Around the same time, BDV was found in sheep and cattle [148] [213]. Before the etiology of BD was determined, the clinical signs in horses were carefully characterized [22]. This thorough investigation of over 400 cases, as well as similar recent studies by others [7] [21] [132], have established the following clinical signs: The early signs of BD are disturbances in feed intake, like arrested eating, fever and different degrees of somnolence. Mild colic signs and/or irregular defecation, alternately with constipation and diarrhoea, are commonly seen. In stallions and geldings, a continuously prolapsed penis without urination is common (Figure 3). Hypersensitivity and muscular twitches occur in both the head and extremities, as well as gait disturbances and hesitation when jumping over hurdles. These signs become progressively aggravated over the following days. The sick horse gets more somnolent, with abnormally lowered head most often pressed against the wall or supported by the crib, and its eyes closed (Figure 4, to the right). The gait disturbances get more pronounced, and if the horse is allowed to move at will it frequently moves in circles, always in the same direction (Figure 4, to the left). If the legs are manipulated, horses with BD will sometimes keep standing with over-crossed legs without trying to make corrections, indicating postural deficits. Muscular convulsions are common, for example in the chewing muscles, causing bruxism and problems with feed intake. Involuntary eye movements (nystagmus), different sized pupils and blindness are also common signs [7] [21] [22].

Figure 3. Horse with clinical signs of BD. The horse shows apathy, weight loss, and a continuously prolapsed penis, all typical signs of BD. Received from Hanns Ludwig, Berlin, Germany.

In the end-stage, muscles of the head and extremities get paralyzed. Paralysis is usually the cause of death, by hindering feed and water intake (paralysis of the tongue, chewing, and/or swallowing

muscles), and/or by immobilizing the animal. Fever is also seen frequently in the end-stage of the disease [22]. More atypical and milder clinical signs, like recurrent colic, gait disturbances and behavioural changes, connected to BDV-infection have also been reported [38] [46]. The duration of disease is mostly 1-3 weeks, but longer durations can be seen [7]. In some cases, complete or partial recovery occurs spontaneously, sometimes followed by relapses and death [7] [22]. The prognosis of BD is usually considered to be bad, and a mortality rate of 75-95% has been described [7].

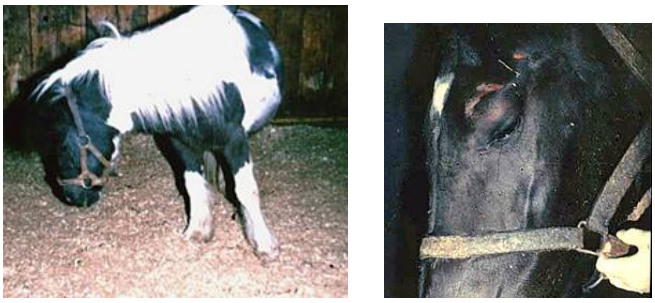

Figure 4. Horses showing typical clinical signs of BD. Left: A pony showing circular movement. Ponies and haflingers seem to be more susceptible to BDV-infection, and show more severe signs with faster progression (Liv Bode and Hanns Ludwig, personal communication). Right: A horse with BD in the end-stage of the disease. This horse is somnolent with lowered head, and head injuries after throwing it against the wall. This horse was positive for BDV by FACS analysis [50]. Received from Hanns Ludwig, Berlin, Germany.

However, reports where novel diagnostic methods have been used for detection of antibodies and/or antigen have questioned the high mortality rate of BD, since many horses seem to have sub-clinical or atypical BDV-infection [14] [38] [44] [74]. In sheep, a similar clinical picture is seen as for horses, although up to 20% of a herd can develop the disease, while only sporadic cases occur in horse stables [131]. Early signs in sheep are social behavioural changes and apathy [7]. Hyperesthesia in the lumbosacral region is also common. As the disease progresses, decreased feed intake, bruxism and circular movement are seen (Figure 5). The incubation time is several weeks, and the duration of disease is around 4-10 days, with around 90% mortality [7] [131]. Besides the initial reports of BD in cattle [148] [213], demonstrated by transmission of the disease to laboratory animals, there seems to be only sporadic occurrence in this species. Hence, BDV-infection of cattle has been considered as a possible event [138]. In more recent cases, similar clinical signs as for horses and sheep have been reported, such as decreased feed intake, gait disturbances including circular movement, and finally in some cases paresis or paralysis [47] [52] [151]. BD has also been observed in other ungulates (donkeys, mules and hinnies), as well as in goats and rabbits, with similar signs as for horses and sheep [7] [51] [139].

Figure 5. Sheep with BD in the end-stage of the disease. This sheep is severely ataxic and paretic. The same sheep is shown from another angle in Figure 5 of [14]. Received from Hanns Ludwig, Berlin, Germany.

Bornavirus infection in birds

Recently, two research groups in the United States independently found a BDV-like virus in psittacine birds suffering from proventricular dilatation disorder (PDD), designated Avian Bornavirus (ABV) [8] [12]. The genome organization of ABV is similar to that of BDV. Recently, successful experimental infection with an ABV isolate of two different bird species has been reported, thereby fulfilling Koch's postulates [89] [157]. PDD is a devastating disease in wild and captive exotic birds, previously known as macaw wasting disease, where the birds show gastrointestinal (GI) and/or neurological signs [90]. The pathology is mainly characterized as a lymphocytic inflammation of the ganglia of the GI tract and/or CNS. The most common clinical signs are depression, weight loss, passage of undigested feed

in the faeces, gait disturbances, seizures, and decreased or absent postural reactions.

Not all birds positive for virus and/or antibodies develop disease, but instead can be healthy carriers and transmitters of ABV [108]. The routes of transmission are likely to be fecal-oral, but air-borne transmission could also occur. ABV-RNA has been found in nasal, choanal, and cloacal swabs, as well as in faeces and in feathers. However, only faeces have been confirmed to contain infectious virus, because mallards that had eaten faecal droppings from infected cockatiels two weeks later shed viral RNA in their faeces [108].

BDV-infection in wildlife

A few wildlife species have been shown to be susceptible to BDV-infection followed by clinical signs, and even more species have been shown to carry virus (viral RNA and/or antigen), or BDV-specific antibodies without obvious clinical signs. The latter group will be discussed more in detail below, in their role as potential BDV reservoirs. The first note of BD or a BD-like disease in wildlife was reported from Germany in the early 20th century [148] [213]. A deer was showing strange behaviour when a hunter was approaching, and was subsequently shot. At necropsy, the typical histological lesions of BD were found, including the presence of intra-nuclear Joest-Degen inclusion bodies. In Sweden, a free-ranging lynx was shot because of its abnormal behaviour [71]. At necropsy, a non-purulent inflammation of the CNS was found. Neurons and glial cells were positive for BDV-RNA and BDV-antigen, using in situ hybridization (ISH) and immunohistochemistry (IHC). Furthermore, BDV-RNA was found by RT-PCR, and partial sequence analysis revealed a close genetic relationship to other Swedish BDV strains (96.2-97.7% amino acid identity), as well as to laboratory strains (98.5% amino acid identity), yet differences were present [27] [71].

Experimental BDV-infection in rats

Depending on the age and immune-competence of the rat, as well as the passage number of the virus, the outcome of BDV-infection is highly variable [6]. In new-born rats, BDV-infection leads either to persistent infection with mild behavioural changes, with or without an inflammatory reaction, or to progressive neurological signs with fatal outcome in the absence of inflammation, depending on the passage number and the species used for virus adaptation. In weanlings and adult rats, acute encephalitis with the classical neurological signs of BD is seen, and the animals die within 1-4 months. However, around 5-10% of these rats survive the acute disease, and develop obesity and aggressive behaviour [55] [105] [128] [132]. Upon intranasal infection, weanlings and adult rats develop an acute or sub-acute disease, with a severe inflammatory infiltration. In natural infection and upon experimental infection of adult rats, BDV shows no or just a few signs of cytopathogenicity; most neurons are intact despite a heavy inflammation. However, in persistent infection BDV causes severe pathological alterations of certain parts of the brain, thereby showing cytopathic effects. Thus, BDV has dual capacities: to induce cell death and neuronal degeneration, and persistence without obvious damage to the host cells.

Borna disease in cats and dogs

In the 1970's, a fatal neurological disorder in cats was reported from certain parts of Sweden [13]. The clinical signs were characterized by gait disturbances (Figure 6), such as ataxia and staggering movement, and by behavioural changes; thereby the disease got known as staggering disease (Sw. vingelsjuka). A viral etiology was suspected, because of the non-purulent inflammation of the CNS, and thus thorough efforts to isolate a virus were made. However, the etiology remained unknown until the 1990's, when antibodies towards BDV were found in diseased cats [17]. This finding pointed towards BDV-infection, which was further supported by the pathological lesions found in the same regions of the CNS as previously found in, for example, horses with BD [15] [87].

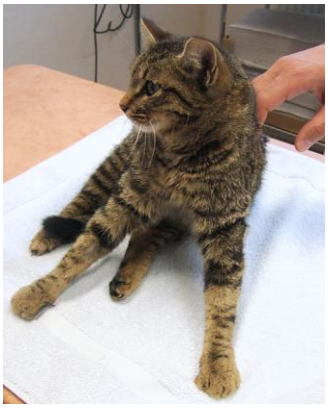

Figure 6. Cat with staggering disease or feline BD. The cat was severely ataxic, and without support it fell over on its side. Photo: Jonas J. Wensman.

MOVIE

Figure 6 Movie. Cat with staggering disease or feline Borna disease. Courtesy of Dr. Karin Hultin Jäderlund DVM, PhD, DiplIECVN; Norwegian School of Veterinary Sciences, Oslo, Norway.

Moreover, clinical signs are strikingly similar to BD in horses and sheep: initially cats have fever, apathy and reduced appetite, followed by staggering and circling movements, behavioural changes, and finally, after a duration of 1-4 weeks, paresis and/or paralysis [13] [15]. Other minor signs in common with horses, like constipation and impaired vision, are also seen. However, a clear etiology was not established until a feline BDV was isolated [18], and used in experimental infection in cats, inducing similar clinical signs and pathological lesions, thereby fulfilling the postulates of Koch [16]. Since then, BDV-RNA, -antigen, and/or BDV-specific antibodies have been found in cats with staggering disease, further strengthening the etiology [27] [28] [29] [37] [110]. Atypical clinical signs have also been reported [37]. In this case, a cat had muscular fasciculation, after a short initial period of reduced appetite and apathy. After a few weeks, the signs progressed and the cat showed decreased postural reactions. Upon histological investigation, no inflammatory reaction was seen inside the CNS, although BDV-RNA was found in situ and by RT-PCR. Cases of full or partial recovery are also seen, mostly followed by relapses [109] [134]. In a few cases, an obesity syndrome in recovered cats has been observed [134], similar to what is seen in experimentally infected rats [132].

Staggering disease or similar neurological disorders have also been reported in other countries [11]. In Austria, cats with staggering disease were sero-positive for BDV [149]. Brain suspensions from those cats were inoculated into rabbits, which sero-converted but did not develop signs of BD. Later, BDV-RNA was also found in an Austrian cat [37]. BDV-infection has been found in dogs showing neurological signs, but only two cases have been scientifically reported [153] [205]. In the Austrian case, the dog was fatigued and had a loss of appetite, followed by severe undefined neurological signs [205]. In the case from Japan, the dog initially showed hypoesthesia and tremor, and after 10 days presented with circling movement, dilated pupils and salivation [153]. In both cases, a non-purulent inflammation of the CNS was seen, and BDV-antigen and –RNA were found in cells. Even though these reports show that dogs can be infected by BDV and develop clinical signs, BDV-infection in dogs needs to be further scrutinized. To my knowledge, at least two dogs have been sero-positive for BDV in Sweden. These dogs were presented with gait disturbances.

Pathogenesis of BDV

Based on the careful characterization of the pathology of BD in horses, Joest and Degen proposed already in the early 20th century that BDV enters the CNS through the olfactory epithelium and olfactory nerve [10]. They also suggested that the virus spreads from neuron to neuron. Some years later, Zwick and his co-workers proposed that BDV is not only taken up by the olfactory epithelium, but also secreted from there [31]. They successfully transmitted BDV from suspensions of olfactory epithelium, taken from experimentally infected rabbits at the end-stage of the disease, to naïve rabbits by intra-cerebral injection. In addition, nasal secretions from an experimentally infected horse were transferred intra-nasally to a rabbit. This rabbit developed mild clinical signs and mild pathological lesions, and brain suspension from this rabbit successfully transmitted the disease to other rabbits in two passages. Taken together, this pioneering work in the first decades of the 20th century, clearly showed that BDV most likely enters into neural cells of the olfactory epithelium, is transported via the

olfactory nerve, and also is transported back to the olfactory epithelium from the CNS and secreted in the nasal secretions of infected animals.

More recent studies confirm that BDV most likely enters the nervous system through the open nerve-endings in the olfactory epithelium and/or oro-pharyngeal mucosa [141] [175]. Viral entry through nerves in the gastrointestinal system has also been discussed [7], based on successful experimental oral infections. Cell entry occurs through the binding of GP1 to a cellular receptor, which guides clathrin-mediated endocytosis [61] [83] [160]. Thereby, BDV is taken up by the cell through encapsulation into endosomes, and can be released as RNPs from the early endosome by a pH-dependent fusion mediated by GP2 [61] [83]. How the RNPs are transported to the replication site inside the nucleus is not known. Even though the exact cellular receptor, to which BDV GP1 binds, has not yet been identified, several host factors important for viral entry have been recognized [62]. Among these are some cell surface proteins, for example a subunit of certain GABA-receptors. Whether these in vitro findings reflect the situation in infected animals needs further elucidation.

BDV probably uses the axonal transport system of macromolecules for transport to the CNS, and reaches the olfactory bulb around 4-6 days after experimental intra-nasal infection [6] [55] [85]. Thereafter, BDV antigen can be detected along the higher olfactory pathways within the limbic system, later disseminating to the entire cortical area [85]. Inside the CNS, the viral spread is trans-neural, most likely through RNPs, and not as whole virus particles [60] [86]. The glutamate kainate 1 (KA-1) receptor has been proposed as the BDV receptor in CNS [85] [88]. Clinical disease appears when viral antigens are expressed in the neurons of the hippocampus, along with an inflammatory reaction [55]. Therefore, the incubation time depends on the route of infection. In an experimental intra-nasal infection of rats, the incubation time was around 20 days [55], whereas it in horses can take up to six months [137]. The infectious dose likely contributes to the incubation time.

One to two months after experimental intra-nasal infection, BDV starts to spread centrifugally to the spinal cord, and to the cranial and peripheral nerves, including nerves of the autonomic nervous system (ANS) [6] [85]. BDV also spreads to retinal neurons, causing neuronal degeneration, which leads to blindness [77]. From the nerves of ANS, more or less every visceral organ gets infected after another one or two months. There, BDV actively replicates, which results in secretion of infectious virus particles [6] [85]. For example, infectious BDV has been detected in lacrimal and nasal secretions of naturally infected horses [21], urine of experimentally infected rabbits [213] and rats [85] [175], in saliva of experimentally infected horses and rabbits [213], and in milk of experimentally infected rabbits [213].

Virus-host interactions

Immune responses of the host

When a virus infects a host cell, a cascade of different actions starts in order to minimize the effects of the intruder. Among these first actions is the shutdown of DNA and RNA synthesis, as well as translation of proteins, thereby obstructing virus replication and production of viral proteins, which the virus uses to interfere with different signalling pathways in the host (see below). The host cell also produces different cytokines (signal molecules), which bind to receptors of neighbouring cells (paracrine) and also to the same cell (autocrine), to induce an antiviral state, thus reducing the possibility for viral infection to spread [82]. Upon infection, the type I interferons, IFN-α and IFN-ß, are important key signal molecules in this first line of defence (the innate immune response), where IFN-ß is the most important in the CNS, because of the neurotoxicity of IFN-α [91]. Type I IFNs induce the expression of hundreds of genes, resulting in different host defence mechanisms to infection. Some of these actions result in death of infected cells (cytolysis), to reduce and control an infection [58]. The CNS is sensitive to cytolytic virus clearance, as many neurons are non-renewable and essential for the organism. Hence, non-cytolytic ways of clearing a viral infection are important within the CNS [59] [91]. Neurons seem to have specific defence mechanisms, driving a viral infection to be non-cytopathic, and stimulating the host immune response to follow non-cytolytic clearance [155]. For example, host neurons reduce or block the budding of viral particles, which can result in cytolysis, and viruses have evolved trans-synaptic, non-cytolytic spread of RNPs to evade this response of the host.

The second line of defence (the adaptive immune response) is composed of two main pathways: the humoral immunity, characterized by antibody production, and cell-mediated immunity, consisting of T cells. The cytokines produced initially by the innate immune response attract cells of the adaptive immunity, such as natural killer (NK) cells, CD4+ and CD8+ T cells, and monocytes/macrophages, first to the perivascular tissues, and then also to the brain parenchyma [91]. These immune cells are important for the non-cytolytic clearance of viruses, although different mechanisms are of varying

importance when clearing viruses from different cells of the CNS. In neurons, virus clearance is mainly carried out by antibodies, locally produced by B cells, and IFN-γ, produced by T cells and neurons. T cells in combination with IFN-γ are responsible for viral clearance of glial cells. Even though virus clearance by these mechanisms can be effective, viruses can still persist. A heavy inflammation with cytokine expression affects the normal functions of the CNS adversely, and can produce different neurological signs, including behavioural changes [53]. Natural BDV infection, and experimental infection of immune-competent animals, leads to the induction of a T cell immune response [24]. Thereby, BD is considered to be an immune-mediated disease, though increasing evidence points towards direct virus-induced clinical signs as well (see below).

In perivascular cuffs of experimentally infected rats, CD4+ T helper cells are the most common cell type, whereas cytotoxic CD8+ T cells are more common in the brain parenchyma [73] [98] [192]. Antibodies, locally produced by plasma cells, can be detected [73], and are probably involved in virus clearance. IFN-γ mRNA is expressed, especially in acute infection [98] but also in the chronic phase [188], and is crucial for CD8+ T cell-mediated clearance of BDV in experimentally infected mice [100].

A similar picture is seen in naturally infected horses and cats, which are the only natural hosts of BDV where the immunological responses have been studied so far. Both in horses and cats, CD4+ T cells dominate the perivascular cuffs, whereas CD8+ T cells are more common in the parenchymal tissues, at least in horses [43] [135]. Overall, CD8+ T cells are less abundant than CD4+ T cells in the brain of BDV-infected cats [39]. BDV infection in cats causes an increase in the peripheral CD8+ T cells. This cell population can be divided into two subpopulations, CD8+low and CD8+high, based on the expression of the ß-chain, and the CD8+low T cells dominate in the brain [39]. The exact difference between these two subpopulations is not entirely known, but it is thought that CD8+low T cells have similar functions to NK cells [39] [189]. Plasma cells are found in the brain parenchyma, next to BDV-infected neurons in cats [135], and IFN-γ mRNA is expressed in brain tissues of cats with feline BD [28], probably facilitating virus clearance. This IFN-γ expression was seen regardless if BDV-RNA could be detected.

Immune evasion mechanisms of BDV

To be able to establish a persistent infection, BDV needs to circumvent the host immune response. Several viruses have evolved type I IFN inhibiting properties, since these cytokines are key players in the innate host immune defence [82]. BDV has also developed several ways to inhibit the expression of type I IFNs. When BDV replicates, the triphosphate group is replaced by a monophosphate at the 5'-end of the genomic RNA [184]. Thereby, BDV, as well as ABV, avoids recognition by retinoid inducible gene I (RIG-I), which is an important cytosolic viral sensor and inducer of type I IFN gene expression [92] [171]. These findings were observed when genomic RNA was transfected into cells. However, it is not known to what extent genomic RNA within the RNP is exposed to RIG-I in natural infections. BDV enters the cell by receptor-mediated endocytosis as an intact viral particle, and is released as RNPs from the early endosome into the cytoplasm, followed by transport to the replication site inside the nucleus [61] [83]. Between cells inside the CNS and in cell culture, BDV spreads as RNPs [60] [86]. Hence, most likely other cellular receptors sensing viral components are important for the recognition of BDV, such as Toll-like receptors (TLRs) 3 or 7/8 inside the endosomes, which recognize double-stranded and single-stranded RNA respectively, or yet unknown viral sensors [33].

Thus, to evade the host immune response and establish a persistent infection, BDV has evolved other IFN-inhibiting strategies as well. BDV P interferes with the IFN-γ mRNA expression by acting as a decoy substrate for phosphorylation by TBK-1 [197], a cellular kinase activating transcription factors that enhance type I IFN expression. One cellular defence mechanism upon type I IFN signal transduction is apoptosis induction [58]. Therefore, it is important to circumvent apoptosis to establish persistent infection. Certain persistently BDV-infected cell lines are resistant to apoptosis (Figure 2) and it is the X protein that is responsible for this resistance [162]. The exact mechanisms by which X interferes with apoptotic pathways are not known. BDV has also developed mechanisms to evade the effects of IFN-γ, a key player within the adaptive immune response to viral infections, facilitating viral clearance by non-cytolytic mechanisms [59]. One such antiviral effect of IFN-y is induction of inducible nitric oxide synthase (iNOS), which results in the production of free oxygen radicals, harmful to viruses. In rat astrocytes, BDV P inhibits the expression of iNOS [159], thereby overcoming this antiviral host response.

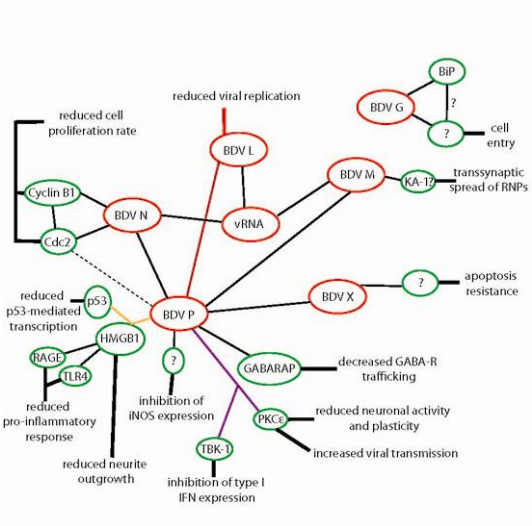

Figure 7. Map of interactions within BDV, between BDV and host cellular proteins, and the biological impact of these interactions. BDV proteins, and viral RNA (vRNA) are marked in red, whereas cellular proteins are in green. Phosphorylated BDV P (i) down-regulates the activity of the viral polymerase (BDV L; connector marked in red), (ii) acts as decoy substrate for TBK-1 and PKCε phosphorylation (purple connector), and (iii) competes with p53 for the same binding site of HMGB1 (yellow connector). The other interactions are described in the text.

Protein-protein interactions

The proteins of BDV interact with each other, and with the genomic RNA, to form the RNP and the virion, as previously discussed. BDV N interacts with P [41] [187], which in turn interacts with L and X [182] [187], as well as with M [57]. Besides these interactions, BDV proteins interact with several host cellular proteins [20], with potential to interfere with important cellular signalling cascades in favour of viral persistence (Figure 7). BDV N and P interact with the Cdc2-Cyclin B1 complex [161], which is a crucial part of the cell cycle [56]. In the G2 phase of the cell cycle, the Cdc2-Cyclin B1 complex is acted on by a series of phosphorylations and de-phosphorylations, resulting in nuclear translocation, which is important for the cells to enter the M phase [56]. BDV N interacts with both phosphorylated and non-phosphorylated Cdc2, as well as with Cyclin B1, whereas BDV P interacts only with non-phosphorylated Cdc2 [161]. Cells transfected with BDV N, had a reduced proliferation rate, indicating an interference of the G2 to M phase transition. This effect was also seen in BDV-infected cells, but not in cells transfected with BDV P. Thus, BDV interferes with cell proliferation to enable a persistent infection.

As previously discussed, BDV P interacts with TBK-1, and competitively interferes with the phosphorylation of endogenous substrates, resulting in decreased type I IFN-expression [197]. Similar interference occurs in PKCε phosphorylation, where BDV P also acts as a decoy substrate, affecting neuronal plasticity [166]. BDV P is also suggested to interfere with the normal transport of γ-aminobutyric acid receptors (GABA-R) to the cell membrane, by interacting with GABA-R associated protein (GABARAP) (Figure 8; [158]). This interference could be responsible for causing some of the behavioral changes seen in BDV-infection, since decreased transport of GABA-R to the cell membrane causes anxiety and other behavioural changes [63]. Transgenic mice expressing BDV P have neurological signs similar to BDV-infection [113], implicating direct disease-causing actions of P, possibly by interfering with the GABAergic neurotransmission.

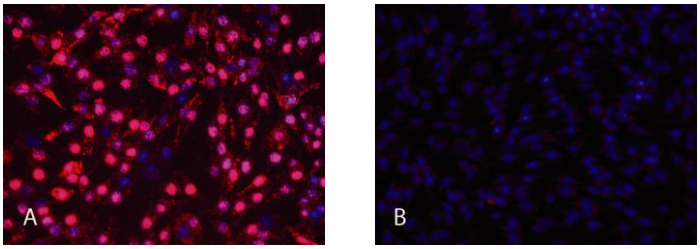

Figure 8. Interaction between BDV P (A) or N (B), and GABARAP in BDV-infected rat astrocytes. To visualize protein-protein interactions, in situ PLA was performed [26]. Red staining indicates BDV-GABARAP interactions, and blue staining is the nuclei. Photos: Karl-Johan Leuchowius & Jonas J. Wensman.

BDV P also interacts with a nuclear protein, called high-mobility group box-1 (HMGB1) [114]. HMGB1 is involved in several cellular functions, such as transcriptional regulation [196], DNA repair [127], cell

migration [170] and neurite outgrowth [169]. In BDV-infected cells and in cells treated with BDV P, neurite outgrowth is impaired, most likely because of decreased secretion of HMGB1, as the result of binding with BDV P [114]. Upon infection or tissue damage, HMGB1 can be released and act as an alarmin, by binding to receptors at the cellular surface (TLR4 and RAGE), inducing a pro-inflammatory response [209]. In BDV-infected cells, RAGE mRNA expression is decreased compared to non-infected cells, further strengthening the data on interference of normal HMGB1 function by BDV P [114]. Moreover, BDV P out-competes the binding between HMGB1 and p53, resulting in impaired p53-mediated transcription (Figure 9) [210]. This interference could be another way for BDV to avoid apoptosis, since p53 is known to induce apoptosis of infected cells [32]. Thus, BDV P interferes with several antiviral, and other, actions of HMGB1 by binding to its p53-binding site, and reducing its release from the cell.

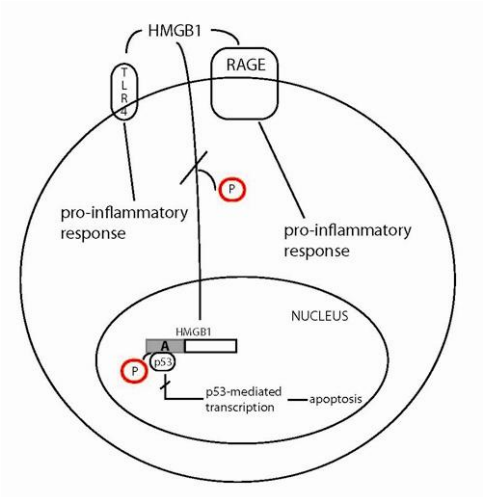

Figure 9. BDV P interferes with the functions of HMGB1. In the nucleus, BDV P out-competes the binding of p53 to the A-box of HMGB1, thereby inhibiting the p53-mediated transcription, which can lead to apoptosis. Upon infection or cell damage, HMGB1 can be released, and bind to the cellular surface receptors TLR4 and RAGE, in turn inducing a pro-inflammatory response. BDV P reduces the release of HMGB1, and hence its pro-inflammatory actions.

Epidemiology of Bornavirus infections

For a long time, BD was considered as a disease of horses and sheep in endemic regions of Germany, Switzerland, Lichtenstein, and Austria [14]. However, in the 1990's several reports of cases outside these endemic regions, as well as in a broader host range, were published. These findings were preceded by the demonstration of BDV-specific antibodies, antigens and RNA in humans from 1985 and onwards [14] [48] [54] [174], which led to an increasing interest in BDV research. This section will focus on the epidemiology of BDV-infection in animals. Horses with BD have been shown to shed infectious viruses in nasal and lacrimal fluids [21]. In addition, sub-clinically infected horses and sheep that are sero-positive can be PCR-positive in these body fluids, as well as in saliva [173] [199], indicating a potential shedding of virus. Hence, BDV could spread between animals either by direct or indirect contact. However, this mode of spread is likely not the most important, because only sporadic cases are shown in the same stable of horses [21] [131]. Similarly, staggering disease in cats is mostly seen in only one cat in households with several cats [40]. Contradictory data concerning vertical transmission of BDV in horses exist [21] [93]. In horses and sheep, cases of BD are observed in a seasonal pattern, where most cases are presented in late spring to early summer [21] [22] [79] [80] [132]. A similar seasonal distribution is also seen in cats [15] [117]. Annual differences in disease incidence are also present in these species [14] [27] [79] [132]. Together with the historically restricted endemic regions in BD of horses and sheep [113], as well as of cats [13] [15] [206] (Figure 10), natural BDV reservoirs have been discussed [23] [79] [134].

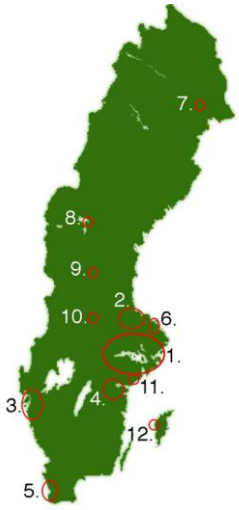

Figure 10. Map of Sweden showing regions where the clinical diagnosis “staggering disease” have been made during the years 1998-2008, based on data from the Agria Animal Insurance Company. The size of the encircled areas is approximately proportional to the number of cases reported. In total, 92 cases were reported, with 65% coming from the previously reported endemic region (1, Areas around Lake Mälaren). In regions previously considered free from disease, cases have also been reported, like the west coast (3) and southern parts (5) of Sweden. Numbers 7-12 represent individual cases, spread over the country. From Wensman [206].

Wildlife reservoirs

Because of the persistent infection in experimentally infected rats and mice, resulting in either mild behavioural changes or in sub-clinical infection only [132], rodents have been proposed as a natural reservoir of BD [23] [79]. Experimentally infected rodents can transmit BDV both by close contact (horizontal transmission) [175] and from mother to foetus (vertical transmission) [152]. Hence, a persistent infection could be maintained within a rodent population in nature, and spread BDV to domestic animals through shedding of infectious viruses. In cats, it is mainly those with outdoor access, hunting rodents, that are at higher risk of BDV-infection [40].

Interestingly, recent studies in Finland have shown the presence of BDV-specific antibodies in wild rodents, namely different kind of voles [116]. Upon experimental BDV-infection, bank voles did not develop pathological alterations in the CNS, despite the fact that BDV-RNA and BDV-antigen were found both in the CNS and in peripheral neural ganglia [117]. Most of the voles did not show any clinical signs, but some of them presented with hyperactivity or other neurological signs. BDV-RNA was detected in the faeces and urine, indicating potential shedding of infectious virus. Thus, voles could be a wildlife reservoir and an infection within the population maintained persistence by viral shedding in faeces and urine. At least in rats, BDV is transmitted only upon close contact for at least 24 hours, most likely by infectious viruses shed in urine [175]. Thereby, if BDV is transmitted to domestic animals, such as horses and sheep, when infected rodents are contaminating their feed, this contamination probably needs to be intensive and repeated. However, in cats the transmission most likely takes place when infected rodents, such as voles, are preyed upon. Whether the behavioural changes that sometimes can be seen in infected voles [117] affect the possibility for these animals to be a prey is not known. However, it is known that the parasite Toxoplasma gondii (Apicomplexa) can change the behaviour of the intermediate host (rodents) to become an easier prey for the main host, the cat [203].

Another proposed reservoir is wild birds. BDV has been reported from wild birds in Sweden, where BDV-RNA was detected in faeces of mallards and jackdaws [42], and from the USA, where clinically healthy Canada geese harboured viral RNA in oropharyngeal/cloacal swabs and brain tissues [156]. Even though the BDV sequences isolated from the Swedish birds were similar to other known reference strains and isolates, some differences were seen [42] [27]. The American isolates clustered together in a distinct group separate from most ABVs and closer to classical BDV strains [156]. Interestingly, experimental ABV infection in mallards does not result in any clinical signs or pathological lesions [108], although faeces from infected animals are intermittently PCR-positive, and antibodies can be found. Furthermore, ABV can be transmitted by the faecal-oral route to mallards, which accidentally happened in non-infected control mallards when they were kept together with a group of sub-clinically infected cockatiels [108]. Most recently, Canada geese and trumpeter swans with non-suppurative CNS inflammation were found to be ABV-positive, carrying a new distinct genotype of ABV [72].

Mallards, as well as other migratory birds, are well-known carriers of other viruses, such as influenza virus, West Nile virus and Newcastle disease virus. The migration route of mallards in Northern Europe goes from parts of Germany, where BD is considered to be endemic, to Northern Siberia, passing over Sweden. Hence, wild birds, such as mallards, could be important for transporting BDV from endemic regions to previously non-endemic areas.

Ticks have also been considered to be a possible reservoir, since approximately the same regions endemic for BDV are endemic for tick-borne encephalitis virus. However, ticks are probably only mechanical or accidental vectors, because BDV does not seem to replicate in ticks [176].

In BDV-endemic regions of Central Europe, bi-coloured white-toothed shrews have been found to carry BDV [104]. These animals do not show any obvious clinical signs. They harbour BDV in many different tissues, indicating a persistent infection as in rodents [104] [168]. Thereby, this insectivore could be another potential reservoir of BDV in certain parts of Europe. However, neither this particular shrew nor any of its closest relatives have their habitat in Sweden. Other species have also been found to carry BDV or BDV-specific antibodies without showing obvious clinical signs, or with unknown clinical status. In Japan, macaques (12%) and raccoons (2%) have been shown to be seropositive [95] [96]. Furthermore, in a few animals of both species BDV-RNA could be found. In France, BDV-RNA has been found in four brain samples from red foxes of unknown clinical status [68]. Whether these findings describe sub-clinical persistent infections or animals with clinical disease, and the potential for these species as reservoirs for BDV, remains unclear.

If there is a wildlife reservoir for BDV, there is obviously not just one, but most likely there are various reservoirs in different parts of the world. Based on the estimated incubation times, from several weeks in sheep [7] [131] up to six months in horses [137], and the reported seasonal distribution of BD cases, natural infection can actually occur all year around in these species. The incubation time in cats is not known, but upon experimental intra-cerebral infection it takes three weeks up to 2.5 months for clinical signs to develop [16]. If these experimental data reflect the true incubation time, natural infection should occur mainly from September to April. The mode of spread of BDV therefore most likely varies between different domesticated species, depending on their feeding preferences and how they are housed.

Diagnostics of BDV-infection

Ante-Mortem diagnostics

Due to the nature of any persistent infection within the CNS, it is difficult to find specific BDV-markers, such as antigens, antibodies or RNA, in a living animal with suspected disease. BD is therefore mainly a tentative diagnosis in different animals, made by ruling out other possible explanations for the clinical signs. Even though the clinical signs are characteristic, they are not specific for BDV-infection.

Serology is potentially an aid for the clinician, but in horses with BD the antibodies are not always found in serum, and clinically healthy horses can carry antibodies [21] [132]. Similar observations have been made in cats. Naturally infected cats developed low or no titers of antibodies, whereas experimentally infected cats developed high titers [110]. Other studies have shown antibodies in clinically healthy cats [101] [154]. Depending on the sensitivity and specificity of the assay used, the sero-prevalence differs even in the same geographical region. The indirect immunofluorescence assay (IFA) is used most commonly [103] [130]. The sero-prevalence of BDV in endemic regions is around 20% using this method [21], and lower in non-endemic areas. In the past decade, enzyme-linked immunosorbent assays (ELISA) detecting antigens, antibodies or circulating immune complexes (CIC) have been developed, which seem to have higher sensitivity [49]. The sero-prevalence of BDV has been reported as high as 60% in endemic regions using these assays [14] [128]. This could indicate that there is no need for reservoirs for the viral spread [44]. There seems to be high cross-reactivity between different viral strains, as IFA using cells infected with an equine BDV strain detected high titers of antibodies in psittacine birds infected with ABV [102], indicating a broad detection range using this classical method for antibody detection.

Antibody detection in cerebrospinal fluid (CSF) is considered to be highly specific for BDV-infection, because antibodies have not been found in healthy horses [21] [133]. Molecular biological assays for detection of viral nucleic acids (RNA) in clinical samples have been widely used, especially for blood samples [38] [94] [144] [145] [198] [199]. Even though viral RNA has been found in PBMCs and in body fluids from horses and sheep with clinical disease [173] [198], this is only for a limited number of cases. Due to the limitations of RT-PCR, only those variants of BDV with sequence similarities to the primers of the assay will be detected. BDV is considered to have a high degree of genetic conservation, but a more divergent strain has been found [19]. The recent findings of the even more

divergent ABV [8] [12] could indicate higher divergence than previously considered. Hence, the different RT-PCR assays developed so far could fail to detect viral RNA in several cases, due to sequence dissimilarities.

Concerns have been raised about the high risk of contamination when using sensitive assays such as RT-PCR and nested RT-PCR [79]. This contamination risk is not unique for BDV, and holds true for all RT-PCR and nested RT-PCR assays, and can be reduced by the use of real-time RT-PCR (rRT-PCR) without losing sensitivity [29] [34] [35] [177].

Post-Mortem diagnostics

BDV-infection is confirmed at necropsy, based on the pathognomonic intra-nuclear inclusion bodies in neurons, named after Joest and Degen who discovered them [10], and/or the presence of a non-purulent inflammation of typical regions of the CNS (Figure 11), olfactory bulb, grey matter of the brain stem, basal ganglia and hippocampus [10] [15] [87]. The presence of BDV-antigen and/or -RNA in situ further confirms the correct diagnosis. However, in some species, such as cats, the viral load seems to be lower compared to horses, since the staining by IHC is commonly weaker [135]. Antigen detection [129] and/or nucleic acid detection [212] in brain homogenates further confirm the infection.

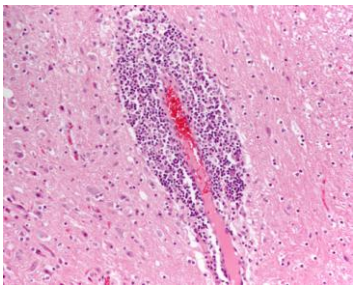

Figure 11. Perivascular cuff consisting of mononuclear cells is one characteristic pathological lesion in BDV-infection. The section comes from a cat suffering from feline BD. Apart from perivascular cuffs, lymphocytic infiltration is also seen in the brain parenchyma. Hematoxylin-Eosin stain. Magnification: lens x20. Photo: Gete Hestvik.

Humans and BDV

The intriguing results of experimental infection in the lower primate tree shrew [181] [191], resulting in different behavioural changes, which were also seen later in rats infected as new-borns, led to the question whether BDV could be involved in human disease. The first serological evidence of human BDV-infection was discovered in patients with affective disorders, whereas the control subjects without signs or history of these disorders were all negative [174].

This finding led to worldwide efforts to study similar and other patient groups, using serological techniques, staining for antigen and RNA in tissues, and molecular methods [48] [54]. By these methods, BDV was detected in brain tissues of humans with hippocampal sclerosis [66] [70]. The first human BDV-variant deriving from brain tissue, isolated in cell cultures and in laboratory animals, was from a patient with schizophrenia, and sequence analysis showed genetic similarities to other isolated BDV-strains [146]. BDV has also been considered a cause of viral encephalitis [124].

Because of the close genetic relationship of most BDV-isolates in humans as well as in animals, false positive results due to laboratory contamination have been discussed [78]. Recent findings show that BDV-like elements have been incorporated into the genome of humans, and other mammals [1] [9]. Whether these data support the reports of BDV-infection in humans, or could influence results based on molecular biological detection methods, is an open question.

Treatment and prophylaxis

During the 19th and early 20th century, several herbal and medical treatments were employed on horses with BD, but none of them seemed to work [22] [148] [213]. More recently, antiviral drugs have been investigated for their potential inhibition of viral replication in infected cell cultures, and in experimentally infected animals. Ribavirin has been promising in cell cultures [111] [140] and in experimentally infected animals [123] [190], partly by facilitating the non-cytolytic viral clearance of the host immune response [190]. However, its use in naturally infected animals remains unknown. In addition to in vitro studies, another drug, amantadine, has been used for treatment of natural infection in animals and humans [45] [74] [75] [76] [150], though its antiviral effects on BDV in cell cultures have been questioned [64] [97].

Cats with feline BD have been commonly treated with corticosteroids, to reduce the inflammatory

response, and the clinical signs this response lead to. This treatment seems to be beneficial when used in the early stage of disease [36] [207], though the use of immunosuppressive treatment could lead to increased virus replication. Early work by Zwick and his co-workers showed that it was possible to immunize horses, preventing clinical disease upon viral challenge [31]. Therefore, vaccination occurred in Germany from the 1920's onwards, though it was recommended only in endemic regions [7]. In the former Federal Republic of Germany (West Germany), the efficacy of the vaccine was questioned, and vaccinations ended in the late 1970's [79]. The vaccinations in the former German Democratic Republic (East Germany) did not come to an end until the reunification of Germany. The spread of BDV due to vaccination with live vaccine strains has been suspected [14], though according to molecular epidemiological data this spread seems to have been limited [79]. Today there is no medical prophylaxis in use to prevent BDV infection, though isolation of sick animals and hygienic safety measures can reduce the spread of disease [14].

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Appendix
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