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Review

Borna disease virus – Fact and fantasy

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ABSTRACT

The occasion of Brian Mahy's retirement as editor of *Virus Research* provides an opportunity to reflect on the work that led one of the authors (Lipkin) to meet him shortly after the molecular discovery and characterization of Borna disease virus in the late 1980s, and work with authors Briese and Hornig to investigate mechanisms of pathogenesis and its potential role in human disease. This article reviews the history, molecular biology, epidemiology, and pathobiology of bornaviruses.

Contents

1. A brief history of the field

Borna disease (BD), 'Borna'sche Krankheit' in German (Gensert, 1896; Kohl, 1896; Schumm, 1896; Dexler, 1900) was first described as a meningoencephalitis of horses (Trichtern, 1716; von Sind, 1767; Abildgaard, 1795; Veith, 1822; Autenrieth, 1823; Wörz, 1858). The name Borna reflects outbreaks in the vicinity of the town Borna, in Saxony, wherein large numbers of animals died in the late 1800s (Königliche, 1896; Siedamgrotzky and Schlegel, 1896; Königliche, 1897, 1898, 1900; Schmidt, 1912; Zwick et al., 1926).

In the 1920s, transmission experiments between naturally infected horses and sheep, and rabbits, guinea pigs, rats, chickens, and monkeys, established the infectious nature of BD (Zwick and Seifried, 1925; Beck and Frohböse, 1926; Zwick et al., 1926, 1929; Nicolau and Galloway, 1928; Pette and Környey, 1935). Joest and Degen (1909) identified characteristic intra-nuclear inclusion bodies in the brains of animals with BD that provided the first diagnostic marker for disease and first clues to the unusual nuclear localization of the agent (Briese et al., 1992).

Interest in BD and its causative agent lapsed until the early 1970s when Rott, Ludwig and colleagues resurrected research on BD in Giessen and began to focus on identification of the agent and mechanisms of pathogenesis in rabbit, rat and tree shrew models (Ludwig et al., 1977; Sprankel et al., 1978; Narayan et al., 1983). In the early 1980s, Narayan's observations of a biphasic disease in adult-infected rats, characterized by initial hypermotility and excitability followed by depressed locomotion, led some investigators to suggest an analogy to bipolar disorder in humans (Narayan et al., 1983). This in turn prompted efforts to determine whether humans were infected with a related agent. Although Borna disease virus (BDV) was still uncharacterized, it had been propagated in primary tissue culture and transferred to permanent cell lines through co-cultivation (Mayr and Danner, 1972, 1974; Ludwig et al., 1973; Danner et al., 1978; Herzog and Rott, 1980),

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enabling the development of an immunofluorescence assay for serology (Wagner et al., 1968; Danner and Mayr, 1973; Ludwig et al., 1973). After a prominent publication from Rott and Koprowski in 1985 (Rott et al., 1985) reported that sera from patients with bipolar disorder were immunoreactive with infected cell lines, the authors of the present publication and others devoted themselves to identifying and characterizing the BD agent. Efforts to isolate virus for biochemical characterization or visualize particles by electron microscopy were unsuccessful in several laboratories. In the first application of purely genetic methods in pathogen discovery, cDNAs were obtained via subtractive hybridization and used to demonstrate relationship to disease through *in situ* hybridization experiments with rat brain (Lipkin et al., 1990). Thereafter, demonstration of the nuclear localization of transcription, RNA splicing and determination of the complete genomic sequence led to classification of BDV in 1996 (Pringle, 1996) as the first member of a new family *Bornaviridae* in the order *Mononegavirales* (Lipkin et al., 1990; Briese et al., 1992, 1994; Cubitt et al., 1994; de la Torre, 1994; Schneemann et al., 1994; Schneider et al., 1994). The identification of BDV sequences dovetailed temporally with the development of PCR as a tool for molecular epidemiology. Application of PCR, as well as serologic surveys, led to reports of BDV infection in association with a wide range of neuropsychiatric diseases. However, at the time of this writing, the question of human infection remains controversial. Molecular investigation of proventricular dilatation disease (PDD), a disease recognized primarily in psittacine species since the 1970s (Gregory et al., 1994), led in 2008 to the recognition of a virus that is genetically related to BDV, avian bornavirus (ABV) (Kistler et al., 2008; Honkavuori et al., 2008). ABV appears to be globally distributed (Rinder et al., 2009; Lierz et al., 2009; Weissenbock et al., 2009; Ogawa et al., 2011; Heffels-Redmann et al., 2011). The recent discovery of sequences distantly related to BDV L, M and N genes in the genomes of bats, elephants, fish, lemurs, rodents, squirrels, primates and humans (Horie et al., 2010; Belyi et al., 2010) indicates that at least historically, bornaviruses infected a wide range of vertebrate species.

2. Virion properties and molecular biology

2.1. Virion morphology

Spherical, enveloped particles ranging in diameter from 40 to 190 nm have been identified by electron microscopy in extracts from infected cultured cells (Zimmermann et al., 1994; Kohno et al., 1999). Particles of 90–100 nm or more contain a 50–60 nm electron-dense core and are presumed to represent infectious virions. Smaller particles are proposed to be defective. Spikes of 7 nm have been visualized on the larger particles that may represent the viral glycoprotein; however, this has not been confirmed by immunoelectron microscopy. To date, particles consistent with virions have not been identified in tissues or fluids from infected animals (Anzil and Blinzinger, 1972; Sasaki and Ludwig, 1993; Compans et al., 1994).

2.2. Genome organization

Complete genomic sequence has been reported for four equine isolates, strain V, HE/80, H1766, and No/98 (Briese et al., 1994; Cubitt et al., 1994; Nowotny et al., 2000; Pleschka et al., 2001); whereas strain V, HE/80, and H1766 sequences are 95% identical at the nucleotide (nt) level, No/98 sequence differs by more than 15% from the other three. The BDV genome is a linear, negative-stranded, nonpolyadenylated RNA comprising approximately 8900 nt. The genome is compact; 99.4% of its nt are transcribed into subgenomic RNAs. Only 55 of 8910 nt (strain V) are not found in primary viral transcripts. These nt represent the trailer region at the 5′-end of the genome (Fig. 1). The region between the 3′-end of the genome and the first base of the first transcriptional unit is 42 nt long and has a high adenosine/uridine content of 67%, similar to 3′-leader sequences of other non-segmented, negative strand (NNS) RNA viruses. Extracistronic sequences are found at the 3′ (leader) and 5′ (trailer) termini of the BDV genome that are complementary and have the potential to align to form a terminal panhandle. The genomic organization of avian bornavirus (ABV) is similar to that of BDV; however, homology between any ABV isolate and any BDV isolate is <70% at the nt level and <80% at the amino acid (aa) level (Honkavuori et al., 2008; Kistler et al., 2008). These differences notwithstanding, polyclonal antisera to the nucleoprotein and phosphoprotein of BDV are immunoreactive with ABV.

BDV has six major open reading frames (ORFs) (Briese et al., 1994; Cubitt et al., 1994) (Fig. 1) that code for polypeptides with predicted M_r of 40 kDa (p40), 23 kDa (p23), 10 kDa (p10), 16 kDa (p16), 57 kDa (p57) and 180 kDa (p190). Based on the positions of gene sequences in the viral genome, relative abundance in infected cells, and biochemical and sequence features, these polypeptides correspond to the nucleoprotein (N, p40), phosphoprotein (P, p23), matrix protein (M, p16), glycoprotein (G, p57) and L-polymerase (L, p190) found in other *Mononegavirales*. The p10 (X protein) does not have a clear homologue in other nonsegmented negative strand (NNS) RNA viruses (Wehner et al., 1997). It has been postulated to mediate nuclear shuttling of viral gene products such as unspliced RNAs and/or ribonucleoprotein particles (Wolff et al., 2002). It also is involved in the regulation of the viral polymerase (Schneider et al., 2003; Poenisch et al., 2004; Perez and de la Torre, 2005), appears to inhibit apoptosis (Poenisch et al., 2009), and the regulation of its expression may involve interaction of cellular proteins with its messenger RNA (Watanabe et al., 2009). The N protein contains a nuclear localization signal (NLS) as well as a nuclear export signal (NES), and is present in BDV in two isoforms (p40 and p38) that differ in length by 13 aa at the *N*-terminus; the NLS is located at the *N*-terminus of the p40 isoform. The P protein is acidic (predicted p*I* of 4.8), and has a high serine–threonine content (16%). Its phosphorylation at serine residues is mediated by both protein kinase C-ε and casein kinase II (Schwemmle et al., 1997; Prat et al., 2009). As with phosphoproteins of other *Mononegavirales*, P forms a central structural unit in the assembly of the active polymerase complex. P contains two NLS, binds to N, L and X, and may contribute through protein-protein interactions to nuclear localization of X and the 38-kDa isoform of N. The 16-kDa polypeptide is a putative matrix protein (Kraus et al., 2001). The ORF for p57 directs the synthesis of a glycoprotein of 94-kDa, a polypeptide that can be processed by the subtilisin-like endoprotease furin (Richt et al., 1998). Both GP-94 and its *C*-terminal cleavage product GP-43 are associated with infectious particles and are proposed to function in early events in infection (Gonzalez-Dunia et al., 1997, 1998). Incorporation of the *N*-terminal cleavage product GP-51 may also occur (Kiermayer et al., 2002; Eickmann et al., 2005). The ORF of BDV complementary to the 5′ half of the genome (L, p190) is fused to a small upstream ORF by RNA splicing to generate a continuous ORF with a coding capacity of 190 kDa in the 6.1 and 6.0 kb transcripts (Fig. 1). The deduced aa sequence of this ORF includes motifs that are conserved among NNS RNA virus L-polymerases.

2.3. Replication and transcription

Replication and transcription occur in the nucleus (Briese et al., 1992). Although this strategy is also found in some plant rhabdoviruses, it is a unique feature among animal NNS RNA viruses. In influenza virus, a segmented negative-strand RNA virus, the

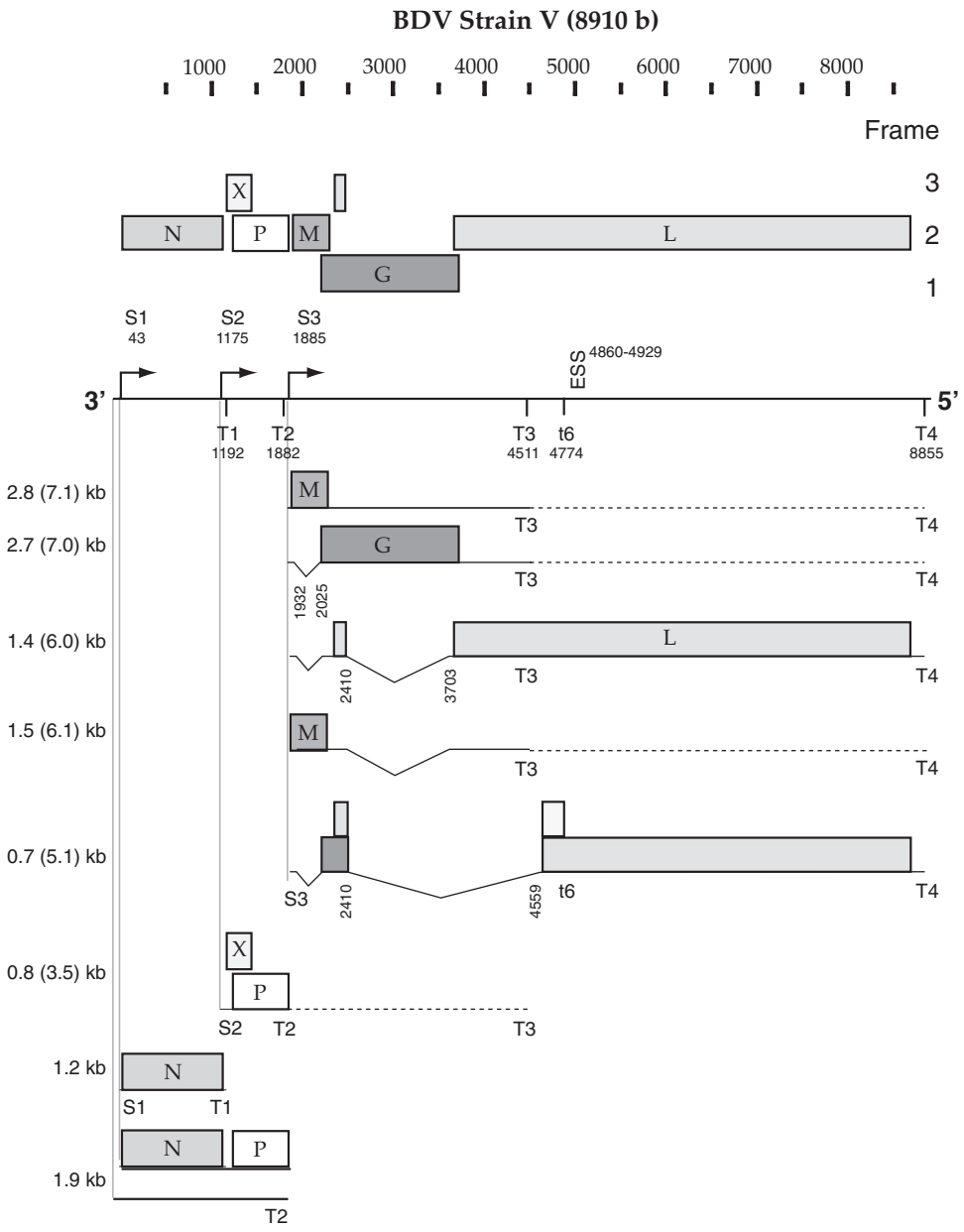

Fig. 1. BDV genomic map and transcripts. *Abbreviations*: S1–S3 initiation sites of transcription; T1–T4 and t6 termination sites of transcription. Read-through at termination signals T2 and T3 is indicated by dashed lines; ESS exon splicing suppressor.

nuclear localization of transcription has been linked to a cap-snatching mechanism whereby cellular RNAs are used to prime viral transcription. This is not the case with BDV, as sequences at the 5′-end of the BDV mRNAs are homogeneous and genome-encoded (Schneemann et al., 1994). Instead, nuclear localization of transcription in BDV appears to reflect a requirement for the cellular splicing machinery to process some of its primary subgenomic RNA transcripts. Replication of its negative-strand RNA genome is facilitated, as in other NNS RNA viruses, by the synthesis of a full-length positive-strand copy of the viral genome (antigenome) that serves as a template for new negative-strand progeny genomes. It has recently been suggested that BDV employs an unusual strategy for copying its genomic termini that results in non-triphosphorylated 5′-termini; these termini variants appear to escape detection by pattern recognition receptors responsible for triggering innate immune responses (Schneider et al., 2005; Habjan et al., 2008). The four terminal bases of genome and antigenome appear to be copied from internal template motifs through a realignment mechanism, allowing later cleavage of 5′-triphosphorylated terminal bases from progeny strands without loss of genetic information (Martin et al., 2011).

Recombinant virus systems have confirmed that BDV N, P and L are essential, and sufficient, for transcription and replication of the viral genome (Perez et al., 2003; Schneider et al., 2003, 2005; Perez and de la Torre, 2005; Martin et al., 2006; Yanai et al., 2006). As with other negative strand RNA viruses, genomic RNA packaged by N constitutes the ribonucleocapsid that serves as template for the associated polymerase complex components L and P (Mayer et al., 2005; Hock et al., 2010). The BDV X protein, although not part of the incoming RNP complex (Mayer et al., 2005; Schwardt et al., 2005), appears to modulate later in infection the formation and activity of functional polymerase complexes by buffering the

crucial N-to-P ratio, and likely attenuating the enzymatic activity of the polymerase (Watanabe et al., 2000; Perez and de la Torre, 2005; Poenisch et al., 2008a).

Transcription of the BDV genome results in the synthesis of four essential primary, 5′-capped and 3′-polyadenylated RNAs with apparent chain lengths of 0.8 kb, 1.2 kb, 2.8 kb and 7.1 kb (Fig. 1). Similar to other *Mononegavirales*, sequential and polar transcription results in a transcriptional gradient; however, levels of individual transcripts are also modified through alternative splicing and incorporation of stability-modulating sequences in spliced introns (Siemetzki et al., 2009). The six major ORFs (N, X, P, M, G and L) are expressed from only three transcription units. The first transcription unit (1.2 kb) is monocistronic and encodes the N protein. The second transcription unit (0.8 kb) is bicistronic and encodes the X and P proteins. The third transcription unit (2.8 or 7.1 kb RNA) is tricistronic and encodes the M, G and L proteins. The transcription start signals (S) are comprised of a semiconserved uridine-rich motif that is partially copied into the respective transcripts (Schneemann et al., 1994). This motif appears to be specific for bornaviruses, in that different sequence motifs are present at the gene start sites of previously described *Mononegavirales*. Each termination site consists of 6–7 uridine residues preceded by an adenosine residue. This consensus sequence is similar to the transcriptional termination–polyadenylation signals in other NNS RNA viruses, and by analogy, suggests that polyadenylation of BDV transcripts also occurs by polymerase stuttering on the repetitive uridine residues.

An unusual feature of the bornaviral genome organization is the positioning of transcriptional termination and initiation signals at gene junctions (Briese et al., 1994; Schneemann et al., 1994; Honkavuori et al., 2008; Kistler et al., 2008). In contrast to filo-, rhabdo- and paramyxoviruses, where transcriptional termination–polyadenylation sites are usually separated from the next transcription initiation site by an intergenic region, the BDV transcriptional initiation site for the 0.8 kb RNA (S2 in Fig. 1) is located 18 nt upstream of the termination site of the 1.2 kb RNA (T1 in Fig. 1). A similar organization has been observed in the respiratory syncytial virus (RSV), where the transcriptional initiation site for the polymerase gene is located 68 nt upstream of the transcription termination site of the preceding 22 K gene. This arrangement has been proposed to serve as a mechanism for attenuation of transcription of the RSV polymerase gene (Collins et al., 1987). However, the 1.2 kb and the 0.8 kb RNAs are the most abundant RNAs in BDV-infected cells, implying that the overlap does not significantly affect transcription of the 0.8 kb RNA. It is possible that the degree of attenuation is a function of the length by which the two transcriptional signals are separated. If so, a stretch of 18 nt may not be sufficient to cause a noticeable decrease in transcription of the 0.8 kb RNA. Two nt separate the second from the third transcription unit of BDV. However, the transcriptional initiation signal for the 2.8/7.1 kb RNAs (S3 in Fig. 1) extends upstream across these two bases into the termination signal of the 0.8 kb RNA (T2 in Fig. 1), such that T2 is part of S3. The overlap of these domains does not appear to interfere with their recognition by the BDV polymerase, because termination and initiation occur efficiently at this gene junction. It is not clear how the BDV polymerase recognizes the overlapping transcription signals as separate functional entities.

BDV termination signals are frequently read-through. Read-through at T1 generates transcripts of approximately 1.9 kb that appear to include a species of capped, polyadenylated transcripts capable of supporting translation of N and P (Poenisch et al., 2008b), and a non-capped, non-polyadenylated species that starts at the genomic terminus rather than S1. The latter may represent abortive replication intermediates or subgenomic RNAs, analogous to leader RNAs found in other mononegaviruses (Schneemann et al., 1994). Several other polycistronic BDV RNAs arise by read-through at termination site T3 (Fig. 1). Although transcriptional read-through is observed in other NNS RNA viruses, it is usually considered to be aberrant. In contrast, transcriptional read-through is an essential feature of the molecular biology of bornaviruses. Only RNA transcripts resulting from read-through at termination site T3 are capable of directing expression of the L protein (Fig. 1).

RNA splicing is another aspect of bornavirus molecular biology that is unique in NNS RNA viruses. Two primary RNA transcripts of 2.8 kb and 7.1 kb originate at the third transcriptional start site of BDV that differ at their 3′-end due to use of alternative transcriptional termination sites (T3 or T4, Fig. 1). Whereas the 2.8 kb transcript contains only the M and G ORFs, the 7.1 kb transcript contains in addition the L ORF. These primary transcripts are post-transcriptionally modified by differential splicing of two introns, intron 1 (94 nt, 1932–2025 nt, located within M ORF) and intron 2 (1.3 kb, 2410–3703 nt, located within G ORF) (Fig. 1), to generate six additional RNAs (Schneider et al., 1994; Cubitt et al., 1994). Differential splicing of the two introns regulates expression of the M, G and L proteins. Splicing of intron 1 places the 13th amino acid (aa) residue of the M ORF in frame with a stop codon. While this abrogates M expression, the resulting 13-aa minicistron facilitates G expression by ribosomal reinitiation. Splicing of intron 2 fuses 17 nt of upstream sequence (2393–2410 nt) containing an AUG to a continuous ORF comprising the remainder of the L coding sequence (nt 3703–8819). Whether splicing of intron 1 in the 6.0 kb transcript is essential for L expression is uncertain; however, the 13-aa minicistron that facilitates G expression by ribosomal reinitiation may also facilitate the expression of L.

2.4. Infectivity

BDV is sensitive to heat, organic solvents, detergents, exposure to a pH below 4, and to UV-light (Nicolau and Galloway, 1928; Zwick, 1939; Heinig, 1955, 1969; Danner and Mayr, 1979; Narayan et al., 1983; Duchala et al., 1989). Dried preparations can be viable for up to eight years (Zwick et al., 1926; Nicolau and Galloway, 1928; Ludwig et al., 1973, 1988; Danner and Mayr, 1979; Pauli and Ludwig, 1985).

BDV adsorption and entry appear to occur analogous to the pH-dependent entry via intracellular vesicles described for rhabdo- and filoviruses, as opposed to the pH-independent surface fusion mechanism used by paramyxoviruses (Smith et al., 2009; Lamb and Parks, 2007; Sanchez, 2007; Roche et al., 2008). BDV G has been implicated in binding to one or more still unidentified cellular surface receptor(s) through reduction of neutralizing activity of immune sera following adsorption with gp94, blockade of infection after preincubation of host cells with gp94, and neutralization of BDV by sera raised against a recombinant G fragment starting at M150 (Gonzalez-Dunia et al., 1997; Schneider et al., 1997). Receptor interaction of G triggers BDV internalization through energy dependent clathrin-mediated endocytosis, and subsequent pH-dependent membrane fusion leads to release of the RNP from intracellular vesicles into the cytosol (Gonzalez-Dunia et al., 1998; Clemente and de la Torre, 2009). Protease inhibitor studies indicated that cleavage of the precursor gp94 is essential for infectivity (Richt et al., 1998), and pseudotyping experiments showed that the amino-terminal 244 aa of gp94 and/or GP-N are involved in receptor binding, while the hydrophobic amino-terminus of GP-C is hypothesized to initiate membrane fusion upon a conformational change induced by acidification in the early to intermediate endosome (Schneider et al., 1997; Gonzalez-Dunia et al., 1998; Perez et al., 2001; Eickmann et al., 2005; Clemente and de la Torre, 2009). Recent studies with furin protease-deficient CHO cells indicate that BDV can disseminate by G-receptor independent pathways (Clemente and de la Torre, 2007); however, correct G maturation

Table 1
Immunoreactivity to BDV in serum of subjects with various diseases or exposures.

Disorder or exposure	Prevalence in patients/exposed individuals	Prevalence in controls	Assay type	References
Psychiatric (various)	0.6% (4/694)	0% (0/200)	IFA	Rott et al. (1985)
	2% (13/642)	2% (11/540)	IFA	Bode et al. (1988)
	4–7% (200–350/5000)	1% (10/1000)	WB/IFA	Rott et al. (1991)
	12% (6/49) IFA		IFA	Bode et al. (1993)
	30% (18/60) WB		WB	Kishi et al. (1995b)
	14% (18/132)	1.5% (3/203)	WB	Sauder et al. (1996)
	24% (13/55)	11% (4/36)	IFA	Igata-Yi et al. (1996)
	0% (0/44)	0% (0/70)	IFA/WB	Kubo et al. (1997)
	2.8% (35/1260)	1.1% (10/917)	ECLIA	Yamaguchi et al. (1999)
	9.8% (4/41)		IFA	Bachmann et al. (1999)
	14.8% (4/27)	0% (0/13)	IFA	Vahlenkamp et al. (2000)
	0% (0/89)	0% (0/210)	WB/IFA	Tsuji et al. (2000)
	1.1–5.5% (1 or 5/90)	0% (0/45)	WB (N or P)	Fukuda et al. (2001)
	2.1% (17/816)		ECLIA	Rybakowski et al. (2001a)
	2.4% (23/946)	1.0% (4/412)	ECLIA	Rybakowski et al. (2001b, 2002)
	12.6% (11/87)	15.5% (45/290)	IFA	Lebain et al. (2002)
	15% (26/171)	2% (1/50)	RLA	Matsunaga et al. (2005)
	23% (39/171)	0% (0/9)	WB	Matsunaga et al. (2005)
	29% (24/84)	20% (77/378)	RLA	Matsunaga et al. (2008)
	67% (26/39)	22% (28/126)	CIC	Rackova et al. (2009)
	54.3% (25/46 positive × 36+ month follow up)		IFA	Heinrich and Adamaszek (2010)
Affective disorders	4.5% (12/265)	0% (0/105)	IFA	Amsterdam et al. (1985)
	4% (12/285)	0% (0/200)	IFA	Rott et al. (1985)
	38 or 12% (53 or 17/138)	16 or 4% (19 or 5/117)	WB (N or P)	Fu et al. (1993)
	37% (10/27)		IFA	Bode et al. (1993)
	12% (6/52)	1.5% (3/203)	WB	Sauder et al. (1996)
	0–0.8% (0–1/122)	0% (0/70)	IFA/WB	Kubo et al. (1997)
	5% (3/65)	0% (0/69)	ELISA (antigen)(CSF)	Deuschle et al. (1998)
	2% (1/45)	0% (0/45)	WB	Fukuda et al. (2001)
	92.6% (26/28)	32.3% (21/65)	CIC	Bode et al. (2001)
	27% (9/33)	4% (1/25)	WB	Terayama et al. (2003)
	19% (25/129)	20% (77/378)	RLA	Matsunaga et al. (2008)
	4.8% (5/104)	0% (0/42)	ELISA	Flower et al. (2008)
	0% (0/138)	0% (0/60)	IFA	Na et al. (2009)
Schizophrenia	25% (1/4) IFA		IFA	Bode et al. (1993)
	9–28% (8 or 25/90)	0–20% (0 or 4/20)	WB (N or P)	Waltrip et al. (1995)
	17% (15/90)	15% (3/20)	IFA	Waltrip et al. (1995)
	14% (16/114)	1.5% (3/203)	WB	Sauder et al. (1996)
	20% (2/10)		WB	Richt et al. (1997)
	0–1% (0–2/167)	0% (0/70)	IFA/WB	Kubo et al. (1997)
	14% (9/64)	0% (0/20)	WB	Waltrip et al. (1997)
	17.9 or 35.8% (12 or 24/67)	0% (0/26)	WB (N or P)	Iwahashi et al. (1997)
	12.1% (38/276)		WB	Chen et al. (1999a)
	10.3% (3/29)	23.1% (6/26)	IFA	Selten et al. (2000)
	9% (4/45)	0% (0/45)	WB	Fukuda et al. (2001)
	12.6% (11/87)	15.5% (45/290)	IFA	Lebain et al. (2002)
	8.6% (10/116)	0% (0/54)	WB	Yang et al. (2003)
	22% (7/32)	4% (1/25)	WB	Terayama et al. (2003)
	23% (21/91)	20% (77/378)	RLA	Matsunaga et al. (2008)
	0% (0/60)	0% (0/60)	IFA	Na et al. (2009)
Childhood neuropsychiatric disorder	56% (93/166)	51% (50/98)	CIC	Donfrancesco et al. (2008)
Alcohol and drug addiction	37% (15/41)	37% (47/126)	CIC	Rackova et al. (2010)
Chronic fatigue syndrome	24% (6/25)		WB	Nakaya et al. (1996)
	34% (30/89)		WB	Kitani et al. (1996), Nakaya et al. (1997)
	0% (0/69)	0% (0/62)	WB	Evengard et al. (1999)
	100% (7/7)	33% (1/3)	WB	Nakaya et al. (1999)
	11% (7/61)	0% (0/73)	WB	Li et al. (2003)
	21% (17/82)	0% (0/73)	WB	Li et al. (2005)
Multiple sclerosis	13% (15/114)	2.3% (11/483)	IP/IFA	Bode et al. (1992)
	0% (0/50)		IFA	Kitze et al. (1996)
	11% (2/19)	0% (0/69)	ELISA (antigen)(CSF)	Deuschle et al. (1998)
Mental health care workers	9.8% (8/82)	2.9% (8/277)	WB	Chen et al. (1999a)
Family of patients with schizophrenia	12.1% (16/132)	2.9% (8/277)	WB	Chen et al. (1999a)
HIV-positive	7.8% (36/460)	2.0% (11/540)	IFA	Bode et al. (1988)
HIV-early	8.1% (61/751)	2.3% (11/483)	IP/IFA	Bode et al. (1992)
HIV-lymphadenopathy	14% (34/244)	2.3% (11/483)	IP/IFA	Bode et al. (1992)
Schistosomiasis/malaria	9.8% (19/193)	2.3% (11/483)	IP/IFA	Bode et al. (1992)

Table 1 (*Continued*)

Disorder or exposure	Prevalence in patients/exposed individuals	Prevalence in controls	Assay type	References
SSPE-associated anti-BDV antibody	22% (39/174)	23% (39/173[a])	ELISA	Güngör et al. (2005)
Suspected hantavirus infection	0.2% (1/361)		IFA	Kinnunen et al. (2007)
Veterinarians	0.7% (1/138)		IFA	Kinnunen et al. (2007)
Race horse exposure (jockeys)	0% (0/48)		IFA	Song et al. (2011)
Living near horse farms	2.6–14.8% (2/78–16/108)	1% (1/100)	ELISA	Takahashi et al. (1997)
Ostrich exposure	46% (19/41)	10% (4/41)	ELISA	Weisman et al. (1994)
Multi-transfused	8.3% (14/168)	0% (0/42)	ELISA	Flower et al. (2008)
Blood donors		2.3% (5/219)	ELISA	Flower et al. (2008)
Pregnant women		0.9% (2/214)	ELISA	Flower et al. (2008)
Normal population		59% (1204/2101)	TELISA	Patti et al. (2008a)
		37% (591/1588)	TELISA	Patti et al. (2008b)
		50% (130/258)	TELISA	Patti et al. (2008c)

Abbreviations: CIC, circulating immune complexes; ECLIA, electrochemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus; IFA, immunofluorescence assay; IP, immunoprecipitation; MS, multiple sclerosis; N, nucleoprotein; P, phosphoprotein; RLA, radioligand assay; SSPE, subacute sclerosing panencephalitis; TELISA, triple ELISA (CIC, antibody, antigen); WB, western immunoblot.

[a] Epilepsy, headache, and cerebral palsy.

enhances the efficiency of cell-to-cell spread, and is required for the formation of infectious progeny virions.

3. Tropism and pathogenesis

Although cells of many lineages and species can be experimentally infected, virus production is more efficient in neural than nonneural cells. Infection *in vitro* is not associated with cytopathic effect. BDV is also neurotropic *in vivo*, with a particular predilection for neurons of the limbic system (Ludwig et al., 1988). The virus ultimately spreads throughout the central, peripheral and autonomic nervous systems infecting astrocytes, Schwann cells and ependymal cells in the central nervous system (CNS); sensory and autonomic ganglia; and nerves to organs. Viral transport is presumably axonal and transsynaptic. Following intranasal infection, viral antigen is detected sequentially in olfactory receptor cells, olfactory nerve fibres, cells of the olfactory bulb and olfactory. In the hippocampus, viral antigen is localized in axon terminals which form synaptic contacts with CA1 pyramidal cell dendrites, prior to appearing in pyramidal cell bodies. Similar to rabies virus infection, it is likely that the spread of BDV infection within the CNS is mediated by ribonucleoprotein particles rather than enveloped virions (Gosztonyi et al., 1993; Ludwig et al., 1993; Clemente and de la Torre, 2007). The regional distribution or activity of host phosphorylating kinases such as PKC may also influence tropism for the limbic system: early in the viral life cycle, BDV proteins are phosphorylated by PKCε, an isoform of the host enzyme that is highly expressed in limbic areas (Schwemmle et al., 1997).

Depending on the integrity and intensity of the host immune response, clinical signs of BDV infection may be dramatic, subtle or inapparent. The most common model system for BDV pathobiology is the Lewis rat. In adult immunocompetent animals infection results in an immune-mediated multiphasic syndrome that may include stereotyped motor behaviours, dyskinesias, dystonias, ataxia and paresis (Narayan et al., 1983). These rats have disturbances in brain levels of catecholamine neurotransmitters, sensitivity to dopamine agonists and altered levels of dopamine receptors in caudate-putamen and nucleus (Solbrig et al., 1996). In contrast to the robust disease observed in adult-infected rats, rats infected as neonates do not mount a cellular immune response to the virus and have a different syndrome, characterized by stunted growth, hyperactivity, subtle learning disturbances, altered taste preferences and abnormal responses to novel environments (ranging from excessive inhibition to excessive exploratory behaviour). CNS dysfunction in neonatally infected animals may reflect direct viral effects on morphogenesis of the hippocampus and cerebellum, two structures in rodents that continue to mature postnatally. Although overall architecture is maintained, granule cells of dentate gyrus and Purkinje cells of cerebellum are lost through apoptosis.

Accumulating evidence suggests that these disturbances in cytoarchitecture are linked to alterations in expression of tissue factors, cytokines, neurotrophins and apoptosis-related products during critical periods of neural development (Hornig et al., 1999). *In vitro* studies may also provide insights into the pathogenesis of neonatal infection. Inhibition of cell-to-cell spread of BDV by a MAPK/ERK kinase (MEK) inhibitor in cell culture (Planz et al., 2001) and analyses of neuronal differentiation of PC12 cells (Hans et al., 2001) indicate an interaction of BDV with cellular MAP kinase signaling pathways. Infected PC12 cells demonstrate constitutive phosphorylation of MEK, ERK, and the transcriptional activator, Elk-1, but fail to differentiate with NGF treatment. Inhibition of neurite outgrowth is also reported in other infected cell lines, and has been ascribed to interference by P protein with the normal interaction between the neurite outgrowth factor, amphoterin, and its receptor, RAGE (*R*eceptor for *A*dvanced *G*lycation *E*nd-products) (Zhang et al., 2003). Infected cells have altered intracellular distribution of amphoterin, with reduced levels of amphoterin and of RAGE activation at growth cones of extending cells (Kamitani et al., 2001). PKC-dependent phosphorylation of P protein plays a key role in inhibition of neuronal plasticity by BDV: introduction of a mutation at the PKC phosphorylation site of P protein abolishes the capacity of BDV to interfere with phosphorylation of endogenous substrates of PKC (MARCKS, SNAP-25) and reverses its downregulatory effects on activity-dependent synaptic modulation (Prat et al., 2009). These results suggest that neuronal dysfunction may arise as a result of competition for components of the PKC signaling pathway during phosphorylation of BDV P protein.

Although we and others have focused on mechanisms of disease due to infection of neurons, BDV also infects astrocytes. Behavioural abnormalities reminiscent of neonate rat infection have been found in a transgenic mouse model in which the BDV P protein was expressed in glial cells (Kamitani et al., 2003). Animals expressing high brain levels of P were characterized by reduced levels of brain-derived neurotropic factor (BDNF), serotonin (5-HT) receptors and decreased synaptic density in the absence of astrocytosis. These findings demonstrate that BDV gene products can directly interfere with neuronal function without inducing gross degenerative processes (Volmer et al., 2006; Prat et al., 2009). Interactions of neurons with other resident CNS cell subsets are likely to play an important role in BDV pathogenesis. Astrocytes, reportedly required for activation of microglia early in the course of BDV infection, may also be activated by BDV-infected neurons without becoming infected; the appearance of activated microglial cells precedes the onset of neuronal losses through apoptosis in the dentate gyrus of the hippocampus (Ovanesov et al., 2008). Clinical features of ABV infection

Table 2
BDV RNA, virus or protein in subjects with various disorders or exposures.

Disorder or exposure	Sample type	Prevalence in patients/exposed individuals	Prevalence in controls	Divergence[a]	References
Psychiatric (various)	PBMC	67% (4/6)	0% (0/10)	0–3.6%	Bode et al. (1995)
	PBMC	37% (22/60)			Kishi et al. (1995b)
	PBMC	42% (5/12)	0% (0/23)	0–4.0%	Sauder et al. (1996)
	PBMC-coculture	9% (3/33)	0% (0/5)	0.07–0.83%	Bode et al. (1996), de la Torre et al. (1996)
	PBMC	2% (2/106)	0% (0/12)		Kubo et al. (1997)
	PBMC	0% (0/24)	0% (0/4)		Richt et al. (1997)
	PB	0% (0/159)			Lieb et al. (1997)
	Blood	100% (1/1)			Planz et al. (1998)
	PBMC	4% (5/126)	2.4% (2/84)		Iwata et al. (1998)
	PBMC	20% (3/15)	0% (0/3)		Planz et al. (1999)
	PBMC	0% (0/81)			Kim et al. (1999)
	PBMC	0% (0/27)			Bachmann et al. (1999)
	CSF	0% (0/27)			Bachmann et al. (1999)
	PBMC	1.8% (1/56)	0.6% (1/173)		Tsuji et al. (2000)
	PBMC	37% (10/27)	15.4% (2/13)		Vahlenkamp et al. (2000)
	PBMC	1.1% (1/90)	0% (0/45)		Fukuda et al. (2001)
	PBMC	33% (10/30)	13% (4/30)		Miranda et al. (2006)
Affective disorders	PBMC	33% (1/3)	0% (0/23)		Sauder et al. (1996)
	PBMC	17% (1/6)	0% (0/36)		Igata-Yi et al. (1996)
	PBMC	0% (0/9)			Richt et al. (1997)
	Brain	40% (2/5)	0% (0/10)		Salvatore et al. (1997)
	PBMC	4% (2/49)	2% (2/84)	0–5.1%	Iwata et al. (1998)
	PBMC	2% (1/45)	0% (0/45)		Fukuda et al. (2001)
	PBMC	11.3% (6/53)	0% (0/32)		Wang et al. (2006)
	PBMC	0% (0/138)	0% (0/60)		Na et al. (2009)
Schizophrenia	Brain	0% (0/3)	0% (0/3)		Sierra-Honigmann et al. (1995)
	CSF	0% (0/8)	0% (0/8)		Sierra-Honigmann et al. (1995)
	PBMC	0% (0/7)	0% (0/7)		Sierra-Honigmann et al. (1995)
	PBMC	64% (7/11)	0% (0/23)		Sauder et al. (1996)
	PBMC	10% (5/49)	0% (0/36)		Igata-Yi et al. (1996)
	PBMC	100% (3/3)		4.2–9.3%	Kishi et al. (1996)
	PBMC	0% (0/10)	0% (0/10)		Richt et al. (1997)
	Brain	53% (9/17)	0% (0/10)		Salvatore et al. (1997)
	PBMC	9.8% (6/61)	0% (0/26)		Iwahashi et al. (1997)
	PBMC	4% (3/77)	2% (2/84)	0–5.1%	Iwata et al. (1998)
	PBMC	14% (10/74)	1.4% (1/69)		Chen et al. (1999b)
	Brain	25% (1/4)		[RNA, virus, protein]	Nakamura et al. (2000)
	PBMC	13.8% (4/29)	34.6% (9/26)		Selten et al. (2000)
	PBMC	0% (0/45)	0% (0/45)		Fukuda et al. (2001)
	PBMC	12% (7/57)	4.9% (8/172)		Kitani et al. (1996), Nakaya et al. (1997)
	PBMC	0% (0/18)			Evengard et al. (1999)
	PBMC	0% (0/60)	0% (0/60)		Na et al. (2009)
Schizoaffective	PBMC	44% (12/27)	15% (4/27)		Nunes et al. (2008)
Fibromyalgia	CSF	0% (0/18)	0% (0/6)		Wittrup et al. (2000)
Chronic fatigue syndrome	PBMC	12% (3/25)		6.0–14%	Nakaya et al. (1996)
Viral encephalitis	CSF-MC	11.5% (6/52)	0% (0/32)		Wang et al. (2006)
	PBMC	13.9% (6/43)	0% (0/98)	2.3–4.5%	Wang et al. (2008)
	PBMC	15% (6/40)	0% (0/46)		Li et al. (2009)
	PBMC	10% (6/59)	0% (0/60)	4.70%	Ma et al. (2009)
Parkinson disease	PBMC	0% (0/5)	0% (0/98)		Wang et al. (2008)
Guillain-Barre syndrome	PBMC	0% (0/7)	0% (0/98)		Wang et al. (2008)
Epilepsy	Brain	0% (0/106)			Hofer et al. (2006)
Hippocampal sclerosis	Brain	80% (4/5)			de la Torre et al. (1996)
	Brain	15% (3/20)	0% (0/85)		Czygan et al. (1999)
Multiple sclerosis	PBMC	0% (0/34)	0% (0/40)		Haase et al. (2001)
	PBMC	22.2% (2/9)	0% (0/98)	2.3–4.5%	Wang et al. (2008)
	PBMC	0% (0/9)	0% (0/46)		Li et al. (2009)
Peripheral neuropathy	PBMC	0% (0/7)	0% (0/98)		Wang et al. (2008)
	PBMC	0% (0/16)	0% (0/46)		Li et al. (2009)
HIV infection	PBMC	13% (11/82)			Cotto et al. (2003)
Immunosuppressive treatment	PBMC	1.3% (1/80)			Cotto et al. (2003)
Multi-transfused	PBMC	0.8% (1/127)	2% (2/200)		Lefrère et al. (2004)
Mental health care workers	PBMC	15% (7/45)	1.4% (1/69)		Chen et al. (1999b)
Race horse exposure (jockeys)	PBMC	0% (0/48)			Song et al. (2011)
Normal controls	PBMC		4.7% (8/172)		Kishi et al. (1995a)
	Brain		6.7% (2/30)		Haga et al. (1997)
	PBMC		0% (0/100)		Davidson et al. (2004)
	Plasma		0% (0/275[b])		Davidson et al. (2004)

Abbreviations: CSF, cerebrospinal fluid; MC, mononuclear cells; PB, peripheral blood; PBMC, peripheral blood mononuclear cells.

[a] Divergence of P-gene nucleotide sequence from common BDV isolates (strain V and He/80); [RNA, virus, protein] indicates virus and antigen analysis.

[b] Plasma minipools of 91 individual samples.

in birds include inflammation of the central, peripheral and autonomic nervous systems, in association with fatal gastrointestinal dysfunction, ataxia and seizures (Gregory et al., 1996).

4. Epidemiology

4.1. Domestic animals and wildlife

Originally described as a fatal encephalitis in horses, BD has also been reported in sheep, cattle, llamas, cats, dogs and ostriches. Because an even larger variety of species has been experimentally infected, including rabbits, birds and primates, the potential host range includes all warm-blooded animals. Natural BDV infection has been reported primarily in Europe; however, more recent reports also include North America and parts of Asia (Japan, China, Israel and Iran), although classical Borna disease remains to be confirmed outside of central Europe (Lipkin and Briese, 2007). Infections of birds with ABV are reported from North America, Israel, Europe and Australia. Reports of asymptomatic, naturally infected animals suggest that bornaviruses may be more widespread than previously appreciated. Neither the reservoir nor the mode of transmission for natural infection is known for BDV. An olfactory route for transmission has been proposed because intranasal infection is efficient and the olfactory bulbs of naturally infected horses show inflammation and oedema early in the course of disease (Ludwig et al., 1988). Reports of BDV nucleic acid and proteins in peripheral blood mononuclear cells also indicate a potential for haematogenous transmission. Experimental infection of neonatal rats results in virus persistence and is associated with the presence of viral gene products in saliva, urine and feces. Thus, rats or other rodents have potential roles as natural reservoirs or vectors. Potential reservoirs for BDV in avians (Berg et al., 2001) or in the white-toothed shrew, Crocidura leucodon (Hilbe et al., 2006) have been suggested. The potential role of Crocidura leucodon as a reservoir host species is supported by recent field studies (Puorger et al., 2010). Vertical transmission of BDV has also been reported (Hagiwara et al., 2000). ABV is almost certainly transmitted via the fecal–oral route. Virus is present in high levels in cloacal swabs and guano of infected birds (Lierz et al., 2009; Rinder et al., 2009).

4.2. Humans

The epidemiology and clinical consequences of human BDV infection remain controversial. Although most reports of an association between infection and disease have focused on unipolar depression, bipolar disorder or schizophrenia, BDV has also been implicated in an improbably wide range of disorders, including chronic fatigue syndrome, acquired immune deficiency syndrome (AIDS) encephalopathy, multiple sclerosis, motor neuron disease and aggressive brain tumors (Tables 1 and 2) (Hatalski et al., 1997). The vast majority of reports of human infection are based on PCR or serology. Isolation of infectious virus from humans has been infrequently reported. Most investigators with results indicating infection of blood or brain have used nested reverse transcription–polymerase chain reaction, a method prone to artefacts due to inadvertent introduction of template from laboratory isolates or cross-contamination of samples. BDV is characterized by extraordinary sequence conservation, unlike other NNS RNA viruses where the inherent low fidelity of viral RNA-dependent RNA polymerases results in sequence divergence of 10^3–10^4 per site per round of replication. Thus, sequencing cannot readily distinguish products representing *bona fide* isolates from those due to amplification of low level contaminants. Methods used for serological diagnosis of infection include indirect immunofluorescence with infected cells, Western immunoblot or enzyme-linked immunosorbent assays (ELISAs) with extracts of infected cells or recombinant proteins. An immune complex assay has been described as more sensitive and specific than other immunoassays (Bode et al., 2001); however, its performance has not been independently validated (Wolff et al., 2006).

In an effort to definitively address the question of whether BDV infection is associated with neuropsychiatric disease, the authors of this paper and international colleagues incorporated tight environmental and study design controls into a large, multi-center epidemiologic study design. Unlike prior studies, rigorous clinical characterization was carried out using standardized instruments in all patient groups (schizophrenia, bipolar disorder, and major depressive disorder) as well as for their matched controls. Controls were individually matched to patients within each diagnostic group on the basis of age, sex, geographic residence, socioeconomic status, and calendar timing of sample collection. To maximize the possibility of detection of evidence of current or past BDV infection, sensitive molecular (real time RT-PCR) and serologic (ELISA, IFA) measures were applied to serum, plasma, and WBC samples collected at the time of acute onset or exacerbation of illness, and also 6 weeks later, to allow for capture of a potential anamnestic response to BDV. To guard against laboratory contamination, samples were processed in a setting with no known exposure to BDV. Strict blinding was maintained throughout the study at all laboratory sites, with specific, predetermined criteria for designating samples as positive or negative. No evidence of infection was found in any sample at either sampling time point using real time RT-PCR or ELISA (Hornig, Briese and Lipkin, unpublished data). Although IFA results revealed four samples containing high avidity antibodies targeting BDV, we found no relationship to psychiatric diagnosis (2 positive samples were from subjects with bipolar disorder, 1 was from a bipolar disorder group control, and the fourth was from a schizophrenia group control).

The recent findings that BDV sequences are incorporated into the genome of humans and other mammals (Horie et al., 2010; Belyi et al., 2010) indicate that bornaviruses infected primates more than 40 million years ago. Whether BDV has ever contributed to clinically significant alterations in CNS function, or to other aspects of pathogenesis, remains unsolved.

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