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Borna Disease Virus and Psychiatric Disorders: Can Viruses Influence Psychiatric Disorders?

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1. Introduction

1.1 Psychiatric disorders and infectious diseases

Psychiatric disorders are a wide group of diseases with a heterogeneous aetiology (genetic predisposition, environmental factors, exposure to stress, for example). Several infectious agents preferentially affect the central nervous system and these infections are associated with psychic and neurologic symptomatology. It has been suggested that some infectious diseases can influence the development and the course of several psychiatric disorders. Infectious agents of zoonotic diseases with the ability to cause persistent infections of the central nervous system and influence the development and functions of this system include *Toxoplasma gondii*, *Borrelia burgdorferi* and Borna disease virus (BDV). Other neurotropic viruses that affect humans and which are associated with neurologic and psychiatric symptoms include herpes viruses, HIV and rabies virus, among others. *Toxoplasma gondii* is associated with cognitive dysfunctions in infected subjects (human and animals). Studies have shown that there is a direct statistical link between incidences of schizophrenia and toxoplasmosis infection. Several studies reported significantly higher seropositivity of this infection in schizophenic patients (Torrey & Yolken 2003). Lyme borreliosis is caused by the Gram-negative spirochete *Borrelia burgdorferi*, which has a high affinity with the central nervous system. There may be a long latent period between infection and the development of clinical neuropsychiatric symptoms. Several studies associated borreliosis with affective, anxiety (panic) and organic disorders and psychosis. A higher seropositivity was demonstrated in psychiatric patients compared to healthy individuals (Hájek et al., 2002).

1.2 Borna disease virus characteristics and animal infection

Borna disease virus (BDV) is an enveloped non-segmented negative-stranded RNA virus that belongs to the family *Bornaviridae*, order *Mononegavirales*. Examples of other virus families that belong to the order *Mononegavirales* are *Filoviridae*, *Paramyxoviridae* and *Rhabdoviridae*. Borna disease virus is a neurotropic virus that affects the central nervous system, especially limbic structures. Borna disease virus infects warm-blooded animals (birds and mammals, including humans). The clinical symptoms of BDV infection range from asymptomatic or a mild symptomatology to severe neurologic and behaviour disturbances and lethal non-purulent encephalitis.

The BDV genome consists of a linear non-segmented single-stranded RNA with negative polarity. The genome is divided into three main gene blocks: the first codes for nucleoprotein (N) and polymerase cofactors represented by p40 and p24 proteins, the second codes for matrix (M) and virus envelope proteins, represented by p16 and p56 proteins, the third codes for the viral polymerase. The entry of BDV is via receptor-mediated endocytosis; protein p56 is sufficient for receptor recognition and virus entry (Briese et al., 1994; Cubitt et al., 1994). The BDV ribonucleic protein is transported into the cell nucleus where BDV transcription and replication occur. The replication of this virus in host cells is typical of the family *Bornaviridae* (de la Torre et al., 1994).

1.3 History of BDV infection

The first description of Borna disease infection was found in seventeenth century literature that describes this disease as affecting horses; later, behavioural changes in other farm animals were described. By the twentieth century, many cases of this infection in farm animals had been described, especially in horses and later in sheep; this disease causes a high mortality rate in infected animals. Borna disease virus owes its name to the town Borna in Saxony (Germany), where a large number of military horses died during an epidemic of this infection in 1885. It was originally thought that BDV only infected horses and sheep; BDV infection has since been described in other species across the world, including birds, cats, cattle, primates, rats, mice and others.

In the 1920s and 1930s the aetiology of Borna disease was discovered by Zwick and colleagues in Giessen (Germany). They successfully transmitted brain homogenates from naturally infected horses to experimental animals. Borna disease virus was isolated in the following years by Zwick, Siefried, Nicolau and Galoway (Durrwald & Ludwig, 1997).

Borna disease virus antigens were isolated in the 1950s and 1960s (Durrwald & Ludwig, 1997; Ludwid & Bode, 2000) and in 1976 viral antibodies were detected in humans (Ludwig, unpublished data from 1985 in psychiatric patients (Rott et al., 1985). In the 1990s, the structures of BDV and viral RNA were described and isolated, BDV was integrated into the order *Mononegavirales* and the new family *Bornaviridae* (Durrwald & Ludwig 1997, Ludwig & Bode 2000) was created.

1.4 The course of BDV infection in animals

The symptomatology of BDV infection in animals ranges from asymptomatic, to a mild subclinical infection to lethal meningoencephalitis. The majority of infected individuals have subclinical, mild symptoms and BDV infected hosts are generally asymptomatic carriers. Some infected subjects develop relapsing mood disorders and behaviour disturbances (changes in appetite and sleeping, apathy or aggressive behaviour and cognitive impairments such as in memory or learning functions, for example) or neurological symptoms (movement or posture impairments, cramps and motor disturbances). A minority of infected animals have a lethal course of BDV infection and die from non-purulent meningoencephalitis.The course of BDV infection is influenced by several factors, including the age of animal at the time of infection, its immune status, genetic background and the type of animal, among others. This viral infection is associated with neurological, behavioural, mood and cognitive changes. This symptomatology leads to the possible connection with human psychiatric disorders such as affective and psychotic disorders and the possibility that BDV infection could contribute to the aetiology of several psychiatric disorders.

1.5 Epidemiology of Borna disease virus infection

Borna disease virus infection was originally believed to be limited in horses and sheep in endemic areas in Central Europe, especially in Germany. But over the years, the use of new diagnostics methods discovered the presence of natural BDV infections in other regions, such as Australia, the United States of America (Kao et al., 1993; Richt et al., 2000), China (Hagiwara et al., 2001), the United Kingdom (Reeves et al., 1998), Japan (Watanabe et al., 2006), Israel (Teplitski et al., 2003), other European countries (Italy, Poland, Czech Republic, France, Switzerland) (Galabru et al., 2000; Pisoni et al., 2007) and others. Natural BDV infection was detected not only in horses and sheep but also in other animal species: cats (Berg et al., 2001; Reeves et al., 1998), dogs (Weissenbock et al., 1998), cattle (Watanabe et al., 2006), birds (Berg et al., 2001), foxes (Dauphin et al., 2001), and ostriches (Weismann et al., 1994). Borna disease virus infection differs in its course according to the species; the most serious form of Borna disease is described in horses and sheep with severe neurologic symptoms and high mortality rates, in contrast to other species (Ludwig & Bode 2000).

1.6 The transmission of BDV infection

There are several supposed routes of transmission of BDV infection between humans and animals: by direct contact with infectious secretions through the nasal mucosa (Durrwald & Ludwig 1997; Hatalski et al., 1997; Ludwig and Bode 2000; Richt et al., 1993, 2000, 2001), vertically during pregnancy (Hagiwara et al., 2000; Okamoto et al., 2003), and indirectly by infected (contaminated) food or water (Durrwald & Ludwig 1997; Hatalski et al., 1997; Ludwig & Bode 2000; Richt et al., 1993, 2000, 2001). Findings of BDV RNA and proteins in peripheral blood mononuclear cells indicate the possibility of hematogenous transmission (Solbrig et al., 2003; Vahlenkamp et al., 2000). Pisoni and colleagues reported the possible sexual transmission of BDV infection. They detected higher BDV seropositivity in sexually active female horses compared to lower BDV seropositivity in animals that had never had sexual contact (Pisoni et al., 2007). Human-to-human transmission of BDV infection is supported by several studies that described higher BDV positivity in mental health workers and family members who were in contact with BDV-positive psychiatric patients (Chen et al., 1999a). Some studies described higher BDV positivity in humans who were in contact with infected animals; this BDV positivity was positively correlated with the degree of contact with infected animals. These findings proved the animal-to human transmission of BDV infection, which is typical of zoonotic infections (Takahashi et al., 1997; Thomas et al., 2005; Weismann et al., 1994).

Infected rodents and wild birds are considered to be reservoirs of BDV infection (Berg et al., 2001), but pets and farm animals represent a greater risk of human BDV infection because of the closer contact with them. Experimentally infected rodents developed persistent BDV infection, which is associated with the presence of the virus in saliva, urine and faeces. Borna disease virus was also found in the excrement of migrating birds. These reports suggest that wild birds could be a reservoir because of the possibility of water or food contamination by infected secretions.

The most frequent route of BDV infection transmission is probably via contact with infected saliva or other secretions through the nasal mucosa. The olfactory route of BDV transmission is efficient; the olfactory bulbs in naturally infected horses show oedema and inflammation early in the course of infection. After infection, BDV initially replicates in the neuroreceptor cells of the olfactory epithelium; then, BDV spreads intra-axonally and trans-synaptically towards olfactory structures and then preferentially to the limbic system. In the

nuclei of infected neurons, aggregates of virus material form Joest-Degen inclusion bodies that are typical of BDV infection. The spread of this virus is not just restricted to the limbic system; during later stages of infection BDV diffuses though the central nervous system and can be detected in oligodendrocytes, astrocytes, Schwann cells and ependymal cells in the peripheral nervous system. In the late stages of BDV infection the virus spreads centrifugally and virus markers can be detected in the peripheral nerves of all tissues. The spread of BDV infection within the CNS is mediated by ribonucleoprotein particles rather than by the enveloped virus. A minimum incubation period of 3 to 4 weeks is estimated for horses and sheep with nonspecific signs such as hyperthermia, anorexia, colic and constipation in the initial phase (Carbone et al., 1987; Gonzales-Dunia et al., 1997, 2000; Gosztonyi & Ludwig, 1984, 2001).

1.7 Mechanism of action, persistent infection, and the course of infection

Borna disease virus can cause persistent infection in the central nervous system. Persistent viral infection is characterized as circumstances in which the virus is not cleared but remains in the cells of infected individuals. There are three types of persistent viral infection: latent, chronic and slow infection. The latent type of persistent infection is typical of BDV. Latent infection is associated with a lack of demonstrable viral particles. The reactivation of persistent latent BDV infection can be triggered by several stimuli: super-infection by other infectious agents, trauma, stress factors, medication or other diseases that lead to changes in immune system. After reactivation, it is possible to detect viral structural proteins that interfere with neurotransmitter receptors and their functions. During infection, BDV influences the central nervous system in several ways: firstly, there is a direct influence through the binding of viral proteins with neurotransmitter receptors (monoamine, serotonin and dopamine systems), and secondly there is an indirect influence though the immune response and inflammatory reactions. Both types of mechanisms contribute to neurotransmitter changes and lead to mood, emotional or behaviour changes in infected subjects, and they may also be associated with psychiatric disorders. The severity of clinical symptoms and the course of BDV infection depend on several factors: immune status and response of the host, the age at infection, and genetic vulnerability (predisposition) to the development of psychiatric disorders, among others (Dietrich et al., 1998). The third mechanism by which BDV can possibly influence CNS functions is due to the fact that viral infections are able to influence the human genome. Some human genetic material originates from viruses and viral sequences being assimilated into the host genome. After infection, BDV sequences are integrated into the genome of brain cells. These sequences are not heritable but they can cause mutations that interfere with brain functioning and can contribute to the development of psychiatric disorders (Feschotte, 2010).

1.7.1 Borna disease virus and its influence on the central nervous system

Animal models have been used to study and help explain the influence of BDV infection on the central nervous system. Changes in several neurotransmitter receptors have been described. Research on adult experimental rats has shown how BDV infection causes long-term changes in cognition, emotions and behaviour. Research on neonatal animals has explained how BDV infection influences brain development with subsequent changes in behaviour and cognition.

Changes in the dopamine system of infected adult rats were described, where disturbances were found in the levels of dopamine in the caudate-putamen (D2 receptors) and the nucleus accumbens (D2 and D3 receptors): pre- and postsynaptic sites of dopamine receptors were damaged in the striatum, dopamine reuptake sites were reduced in the caudate-putamen and nucleus accumbens, postsynaptic D2 receptors were reduced in the caudate-putamen and D2 and D3 receptor binding was decreased in the nucleus accumbens. Postsynaptic dopamine receptors (D1 and D2) remain intact in the prefrontal cortex; this imbalance leads to D1 hypersensitivity and neurobehavioural disturbances in BDV-infected animals. Partial dopamine deafferentation and compensatory hyperactivity of the remaining striatal nerve terminals in the nigrostriatal projections are associated with locomotor activity and stimulant sensitivity. Decreased numbers of dopamine D2 and D3 receptors and the remaining numbers of D1 receptors in the striatum are associated with dyskinesias and dystonia (Solbrig et al., 1994, 1996, 2000, 2010). These changes in dopamine neurotransmission support a connection between BDV and neuropsychiatric disorders such as schizophrenia and addiction and extrapyramidal disorders.

In addition to the altered dopamine system the dysfunction of serotonin and noradrenergic systems is present and is associated with other symptoms. There is evidence of a serotonin system dysfunction in the striatum and norepinephrine dysregulation in the prefrontal and anterior cingulate cortex. Changes caused by BDV infection include reduced serotonin transmission, which is associated with autistic disorders and depression.

The course of BDV infection in adult rats is more severe in comparison to infected neonate rats, which have a milder symptomatology in BDV infection. These animals developed behaviour and cognitive changes, learning difficulties, increased motor activity, abnormal anxiety responses, deficits in motor coordination and postural stability and impairments in social behaviour, and they also showed abnormally early locomotor development. They also showed altered circadian rhythms and appetite changes. Damage to or dysfunction in the CNS of these animals is associated with direct viral effects on the morphogenesis of the hippocampus and cerebellum (Dietz et al., 2004; Pletnikov et al., 2000, 2001, 2002; Solbrig et al., 2010). Borna disease virus infection impairs synaptic plasticity, which is important for learning and memory (Volmer et al., 2007).

Behaviour disturbances were reported in other experimentally infected animals: altered social and sexual behaviours such as abnormal dominance relationships and a failure to mate were described in primates (tree shrews and rhesus monkeys). Rhesus monkeys were initially hyperactive and later became apathetic (Sprankel et al., 1978; Stitz et al., 1980).

Neonatal Borna disease virus infection in rats is associated with the activation of microglia and astrocytes and the loss of neurons in the dentate gyrus in the hippocampus, cortex and cerebellum (Gonzales-Dunia et al., 2000; Pletnikov et al., 2002; de la Torre, 2002). Ovanesov and colleagues were the first to find a significant increase in microglial activation and secondary neuronal loss (Ovanesov et al., 2008). Borna disease virus infection also affects astrocytes, which play an essential role in the maintenance of homeostasis in the CNS. Borna disease virus infection is also associated with impairment in the ability of astrocytes to take up glutamate; this impairment leads to increased levels of extracellular glutamate, the activation of NMDA receptors and an increased calcium influx, and results in neurotoxicity and cell death (Billaud et al., 2000).

In the pathogenesis of Borna disease, Borna disease virus infection also plays an important role in the inflammatory reaction (the BDV-specific T-cell response and the activity of CD8+

T-cells cause the destruction of virus-infected neurons). The inflammatory reaction is associated with the symptomatology of infection (Stitz et al., 1995).

1.7.2 Viro-psycho-immunological disease model and schematic (in connection with psychiatric disorders)

The connections between viral infections, stress and immune functions are described and explained by the viro-psycho-immunological disease model. Acute or chronic stress or other factors (other infections, diseases, immunosupressive medications, for example) cause changes in immune functions. These alterations in the immune system are responsible for the reactivation of latent forms of BDV infection in the central nervous system. The reactivation of BDV directly influences CNS function due to the affinity of viral proteins to neurotransmitter receptors and indirectly influences it via the inflammatory reaction, which also leads to changes in neurotransmission. Individuals with a greater vulnerability (predisposition) for developing psychiatric disorders (genetic disposition) can develop psychiatric symptoms (Dietrich et al., 1998) (see Figure 1).

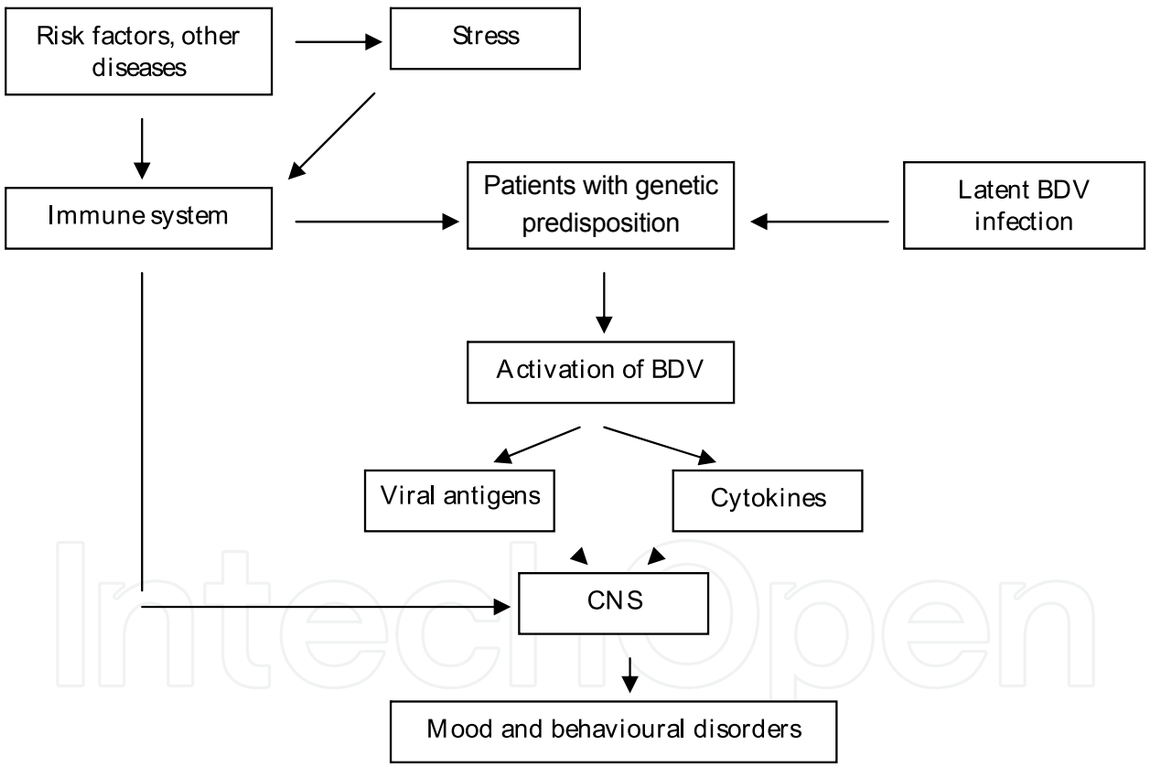

Fig. 1. Viro-psycho-immunological disease model of BDV infection and psychiatric disorders adapted from Dietrich et al., 1998

1.8 Laboratory diagnosis of BDV infection

The aims of laboratory diagnostics in BDV are the detection of BDV infection and the determination of infectious activity and its severity. Several questions can be asked: is the patient infected by BDV? Is this infection active? How intense or severe is this infection? Is treatment of BDV infection suitable?

Borna disease virus antigens (Ag), antibodies (Ab), circulating immunocomplexes (CIC) and viral ribonucleic acid (RNA) can be isolated and detected in brain tissue, cerebrospinal fluid (CSF), serum, plasma or in peripheral blood mononuclear cells (PBMCs).

The original diagnostics for BDV infection consisted of the detection of viral Ab via serological methods, especially immunofluorescence assays (IFA). These methods, which only detected BDV Ab, were not very sensitive and were not able to detect acute phases of BDV infection. Enzyme-linked immunosorbent assays (ELISA) were based on recombinant viral proteins and were used in several studies to detect BDV Ab, but they showed a surprisingly low sensitivity, which could explain the differences found in the study results. The use of electrochemiluminescence immunoassays (ECLIA) did not show any great advantages in the diagnosis of BDV infection.

Another laboratory method that has been used for the detection of BDV Ab is Western blotting (WB), but this was found to be less sensitive than new-generation ELISAs with native viral antigens. Positivity of BDV Ab can indicate a persistent form of infection (in the absence of active BDV infection) or previous contact with this infection, but not an acute state. The absence of BDV Ab in the serum does not mean the BDV infection result is negative; antibodies bind antigens and form circulating immunocomplexes.

Antigenaemia indicates an acute and productive phase of infection. During this phase of BDV infection antibodies bind to the viral antigens and form CIC, which are measurable for weeks or months. The frequency and stability of BDV CIC make them easily available screening markers of BDV infection. By using the ELISA method, it is possible to detect viral Ag in plasma. The disadvantage of this method of detection is the very short period of antigenaemia in the acute phase of BDV infection and the high risk of false negative results after the formation of BDV CIC.

Bode and colleagues developed an ELISA (triple ELISA) method that mainly detects BDV CIC but also free BDV antigens and antibodies (Bode et al., 2001).

Several authors used the detection of viral RNA in PBMCs (peripheral blood mononuclear cells) in brain tissue via polymerase chain reaction (PCR) for the diagnosis of BDV infection. However, other researchers did not use this method for the diagnosis of BDV infection and do not recommend RNA detection as the best diagnostic tool. The first reason is due to the possibility of sample contamination during the laboratory procedure (although contamination should not occur when the detection of BDV RNA is performed according to international security instructions). The second reason is because the absence of BDV RNA in samples does not exclude the possibility of BDV infection, since RNA detection is less reliable than the detection of other virus particles (Ag or CIC) because of the low replication rate of this virus and the small amount of RNA in PBMCs. Also, the presence of BDV RNA in the brain does not necessarily reflect an active state of BDV infection (Bode et al., 2001, Sauder & de la Torre, 1998; Thakur et al., 2009; Wolff et al., 2006).

Currently, the detection of BDV CIC by ELISA and viral isolation from PBMCs are recommended as the best screening methods of active BDV infection because of their relative stability and frequency. The best indicators (markers) of viral disease are antigen ELISA and CIC ELISA, which also both correlate well with the severity of the BDV infection. The ELISA method for the detection of BDV CIC was developed by Bode and Ludwig (Bode et al., 2001). Table 1 shows a summary of the diagnostic methods.

Test	Sample	Diagnostic parameter	Antigen	Sensitivity	Specificity	Indicative of infection	Indicative of disease
Complement fixation	serum	Ab	Native	Low	Good	Low	Poor
Double diffusion	serum	Ab	Native	Low	Good	Low	Poor
IFA	serum	Ab	Altered by fixation	Good	Very good	Good	Poor
	CSF			Poor	Very good	Very good	Poor
Cell ELISA	serum	Ab	Altered by fixation	Low	Good	Low	Poor
ECLISA	serum	Ab	Recombinant	Good	Very good	Good	Poor
Recombinant ELISA	serum	Ab	Recombinant	Good	Good	Good	Poor
Ab ELISA	serum	Ab	Native	Excellent	Excellent	Very good	Poor
Cell Ag ELISA	PBMCs	Ag	Native	Low	Excellent	Good	Good
Plasma Ag ELISA	serum	Ag	Native	Good	Excellent	Very good	Excellent
	CSF	Ag	Native	Low	Excellent	Very good	Excellent
CIC ELISA	serum	CIC	Native	Excellent	Excellent	Excellent	Excellent
WB	serum	Ab, Ag	Denatured	Low	Very good	Good	Poor
	CSF			Poor	Very good	Very good	Very good
Flow cytometry	PBMCs	Ag	Mild fixation	Good	Very good	Good	Good
RT-PCR	PBMCs	RNA		Very good	Excellent	Very good	Poor
	brain	RNA		Good	Excellent	Very good	Poor
	serum	RNA		Low	Excellent	Very good	Good
Isolation	PBMCS	virus		Poor	Excellent	Excellent	Very good
	brain	virus		Poor	Excellent	Excellent	Very good

Table 1. Diagnostic tools for the detection of Borna disease virus infection in humans (Thakur et al., 2009), abbreviations explained in text

1.9 Factors influencing BDV positivity

Borna disease virus positivity in psychiatric patients ranges from negative to highly positive. These differences in positivity can be caused by several factors; features of the psychiatric population (age, diagnosis, severity of the psychopathology, immune status), geographical region, differences in specificity and sensitivity of the laboratory methods used and which diagnostic parameters (Ab, Ag, CIC or RNA) are detected and which biological material (brain tissue, cerebrospinal fluid, serum) is used. Other factors include the seasonal occurrence of BDV infection and contact with animals.

1.9.1 BDV positivity and age

Several studies showed a higher rate of BDV positivity in younger individuals. Patti and colleagues investigated BDV CIC positivity in children in Italy; BDV positivity was detected in 57%. The prevalence of BDV infection was found to be significantly greater in children, particularly in the third year of life; then it decreased until 15 years of age, where another increase was observed (Patti et al., 2008). Another study performed by Scholbach and colleagues demonstrated higher rates of BDV Ag and CIC positivity in children. There were two age intervals of peak BDV positivity: the first was a peak at 6 months old and the

second was a peak around 2-3 years old. These findings support the possible vertical transmission of BDV infection. Two other possible explanations for the greater prevalence of BDV infection in children than in adults are the less well-developed immune status of children and the fact that children of 2-3 years old are more likely to have greater contact with animals and their secretions, which are associated with a greater risk of BDV transmission (Scholbach et al. 2008).

1.9.2 BDV positivity and the types of psychiatric disorder

Borna disease virus infection was detected in psychiatric patients with various disorders; the majority of these studies detected BDV in patients with affective (bipolar and depressive) disorders and psychotic disorders (schizophrenia and schizoaffective disorders). The highest rate of BDV positivity was found in patients with bipolar and depressive disorders (Ferszt et al., 1999). Rybakowski and colleagues reported significantly higher rates of BDV Ab seropositivity in Polish psychiatric patients with affective-anxiety spectrum disorders and mental retardation than in healthy controls, and the rate of BDV seropositivity was significantly higher in patients with recent disease onset compared to past disease onset (10.2% vs. 1.6%) (Rybakowski et al., 2001).

1.9.3 BDV positivity and psychopathology

Several research groups reported an association between BDV positivity and the type or severity of the psychopathology. In a study performed by Iwahashi and colleagues, a significantly higher rate of BDV seropositivity was detected in schizophrenic patients with a negative symptomatology than in patients with positive symptoms (Iwahashi et al., 1998). Waltrip and colleagues detected a higher rate of BDV seropositivity in schizophrenic patients with deficit syndrome than in patients with non-deficit syndrome (Waltrip et al., 1997).

Bode and colleagues detected a higher rate of BDV seropositivity (more than 30%) in patients with major depressive disorder and a lower rate of positivity (8%) in patients with dysthymia (Bode et al., 1993). Ferszt and colleagues confirmed the higher rate of BDV antigenaemia in patients with affective disorders. The number of previous depressive episodes with symptoms including fatigue and concentration difficulties was positively related to BDV Ag positivity (Ferszt et al., 1999). Bode and colleagues found significantly higher rates of BDV Ag and CIC positivity (including higher values) in severely depressed patients during an acute crisis and lower rates of BDV Ag and CIC positivity (lower rates and lower amounts of Ag and CIC) in patients with moderate depression. The severity of depressive symptoms correlated with the concentration and duration of antigenaemia (Bode et al., 2001). In study reported by Rackova and colleagues, a significantly higher rate of BDV CIC positivity was found in psychiatric patients with a more severe psychopathology than in patients with a milder symptomatology, as measured by psychiatric scales (Rackova et al., 2009).

1.9.4 Regional occurrence of BDV infection

Naturally occuring Borna disease virus infection is still confined to several areas of Central Europe, these regions are endemic for this infection. The presence of BDV infection in animals and humans has been detected not only in European areas but across the world (China, Japan, Israel and several other countries) (Durrwald & Ludwig 1997, Ludwig & Bode 2000).

1.9.5 BDV positivity and laboratory methods used

The high variability found for BDV positivity in humans can be influenced by the laboratory method used since they differ in terms of sensitivity and specificity. Another factor that can influence the detection of BDV infection is the infectious marker used: antibody, antigen, circulating immunocomplex or RNA.

The detection of BDV CIC by ELISA has shown a 10-fold higher incidence of BDV infection than was estimated for BDV Ab positivity by the immunofluorescence method in psychiatric patients with affective disorders. The rates of positivity of BDV Ab by IFA were 11% and 20% in patients with depression and 2% in blood donors vs. CIC positivity of 62%, 52% and 24% in the same groups (Bode et al., 2001). Similar results were reported by Bode and colleagues in 1994, where BDV Ab positivity was detected in 20% of psychiatric patients compared to the higher positivity of BDV Ag in 40-50% of the same psychiatric patients (Bode et al., 1994). Wolff and colleagues did not confirm these results. They analysed plasma samples with a high reactivity in the ELISA assay (high positivity of BDV antigens) by immunoaffinity purification and highly sensitive real-time RT-PCR (polymerase chain reaction): neither method provided any evidence for the presence of viral proteins or nucleic acids (Wolff et al., 2006).

1.9.6 Seasonal occurrence of BDV infection

Borna disease virus infection shows a seasonal prevalence, being more frequent in spring and early summer. Significantly higher numbers of seropositive animals (especially sheep and horses) have been detected during these periods and a higher occurrence of clinical cases was also observed (Durrwald & Ludwig 1997; Ludwig & Bode 2000; Staeheli et al., 2000; Vahlenkamp et al., 2002). The number of animals that become infected and succumb to the disease differs each year, but no correlation has been described between the seasonal occurrence of BDV in animals and humans.

1.9.7 Contact with animals

Several studies have described an association between the prevalence of BDV infection in humans and contact with animals, which are potential reservoirs of BDV infection. Weismann and colleagues reported a significantly higher rate of BDV antibody positivity (46%) in workers exposed to infected ostriches compared to controls (10%). There was a strong positive correlation between the intensity of exposure and the rate of seropositivity (Weismann et al., 1994). Takahashi and colleagues found a significantly higher rate of BDV seropositivity (from 2.6% to 14.8%) in blood donors from regions containing concentrations of horse farms compared to the BDV seropositivity of 1% in blood donors from other regions (Takahashi et al., 1997). These findings support the possible animal-to-human transmission of BDV infection. In contrast, another study from Bangladesh did not confirm this hypothesis. The authors surveyed horses and their caretakers for BDV antibody positivity and found a BDV positivity of between 25-30% in the horses but none of caretakers were positive for BDV (Khan et al., 2000). Thomas and colleagues measured BDV seroprevalence in agricultural workers in the United Kingdom. The seroprevalence was 2.3% in 1994, 3.1% in 1996 and 2.6% in 1999. People living or working on livestock farms had a higher rate of seroprevalence (2.6%) than those on mixed (2.3%) or arable (1.6%) farms, but this was not statistically significant. Exposure to horses, sheep and cats did not increase the risk of seropositivity. Furthermore, the seropositive people were not more likely to report symptoms of psychiatric morbidity (Thomas et al., 2005).

1.9.8 Other factors and BDV positivity

The activation of persistent BDV infection can be triggered by several stimuli (super-infection by other infectious agents and immunosuppressive medication, among others) that affect the immune system. This hypothesis (claim) is supported by studies reporting a higher rate of BDV positivity in HIV patients (Auwanit et al., 1996; Bode et al., 1992; Cotto et al., 2003). A lower rate of BDV seropositivity (4-8%) was detected in the early stages of HIV infection, which then increased (13.9%) during later stages of this disease (Bode et al., 1992).

1.10 BDV and psychiatric disorders

Borna disease virus infection in animals is characterized by various behavioural changes, such as changes in social behaviour, apathy, aggressive behaviour, changes in appetite and weight, and cognitive impairment, amongst others. Because these behavioural disturbances of naturally and experimentally BDV-infected animals resemble psychiatric symptoms and disorders in humans, especially affective disorders, early studies investigated a possible link between patients with these diagnoses and BDV infection. The possible connection between BDV infection and psychiatric disorders is explained in the viro-psycho-immunological model, shown in Figure 1 (Dietrich et al., 1998).

The earliest work that suggested a link between BDV infection and human psychiatric disorders was in 1985. Rott and colleagues examined serum samples from 979 psychiatric patients and 200 healthy volunteers for the presence of BDV Ab by indirect immunofluorescence. Borna disease virus antibodies were found in 16 of the psychiatric patients but none of the healthy volunteers. The patients who had positive serum samples also had a history of affective disorders (Rott et al., 1985).

Since 1985, several studies have demonstrated significantly higher rates of BDV infection positivity in psychiatric patients compared to healthy individuals, but several studies did not confirm these results. The rate of BVD positivity in psychiatric patients ranged from negative to highly positive (almost 100% in patients with affective disorders).

Several researchers found a significant association between BDV positivity (levels of BDV Ag and CIC) and severity of the psychopathology (Bode et al., 2001; Ferszt et al., 1999; Rackova et al., 2009) and between BDV seropositivity and negative symptoms in schizophrenia (Iwahashi et al., 1998; Waltrip et al., 1997). Borna disease infection is associated with a chronic course of the disease without full remission and with recurring psychiatric disorders. The reactivation of persistent BDV infection is caused by immune changes and influences neurotransmitter systems and, in vulnerable individuals, it can contribute to the onset of a new phase of a psychiatric disorder and influence its course.

1.11 Therapy of BDV infection

Non-pharmacological procedures that could lead to the elimination of BDV infection were used in the past. The separation of infected animals and improvements in hygiene were recommended, but these procedures only decreased the risk of BDV infection spreading but did not eliminate the infection. Vaccination with killed vaccines and then live vaccines became available in the twentieth century, but both types of vaccine were shown to be ineffective against the Borna disease virus. Vaccination against persistent viral infection in the central nervous system cannot be recommended (Ludwig & Bode, 2000).

Antiviral medications were also tested for the treatment of BDV infection. Hexamethylenetetramine was used for the treatment of horses, and then later hexamine

(Ludwig & Bode, 2000), ribavirine (Jordan et al., 1999), interferon alpha or beta (Hallensleben et al., 1999; Staeheli et al., 2001) and cyclosporine A (Stitz et al., 1989), but no effect was found on BDV infection. Some of these preparations showed a decrease in BDV replication in vitro, but they did not show efficacy in vivo.

Bechter and colleagues described several cases where an improvement in the psychic status of psychiatric patients with schizophrenia and depression was shown after cerebrospinal fluid filtration (Bechter et al., 2000).

Currently, amantadine is used for the treatment of BDV infection. Amantadine is a non-competitive N-methyl D-aspartate-type glutamate receptor antagonist that also binds to nicotinic acetylcholine receptors. Amantadine inhibits BDV replication. Initially, amantadine-sulphate was used in the prophylaxis of influenza A (Kandel et al., 2001), in the treatment of Parkinson's disease (Brenner et al., 1989), hepatitis C (Adinolfi et al., 2003) and cocaine dependence (Kampman et al., 2000). A mild antidepressant effect of amantadine was found in a double-blind study when compared to amitriptyline and a placebo in patients with depression without BDV infection (Vale et al., 1971). Amantadine is a virostatic agent effective in the treatment of BDV infection, since it influences BDV replication in vivo.

The use of amantadine was first described in two case reports in 1991 and 1997 in the treatment of two psychiatric patients with bipolar affective disorder, where improvements in the psychiatric status of both patients were associated with the decrease and elimination of BDV positivity (Bode et al., 1997). Later, several open trials were performed to test the efficacy of this drug in psychiatric patients and amantadine-sulphate was proven to be effective in the treatment of depression in BDV positive patients (Dietrich et al., 2000; Ferszt et al., 1999); the improvement in the depressive symptomatology was correlated with a decrease in BDV infection positivity. The patients were treated with 200 mg of amantadine per day for 12 weeks, and the majority showed significant improvements (clinical response) within the first three weeks (Dietrich et al., 2000). Ohlmeier and colleagues published the results of a double-blind trial that evaluated the effect of amantadine in the treatment of patients with the manic phase of bipolar disorder and amantadine reduced manic symptoms in BDV-infected bipolar patients (Ohlmeier et al., 2008).

2. Aims and methods

2.1 Aims

Because of the marked differences in BDV positivity in patients with different psychiatric disorders, we decided to review available studies on the detection of BDV infection in psychiatric disorders and attempt to explain these differences.

2.2 Method

We undertook a systematic review to determine the rate of positivity of Borna disease virus infection in psychiatric patients.

2.3 Data sources

PubMed, Medline, Journals@Ovid Full Text, Evidence-Based Medicine and the Cochrane database (1985-2011) were searched using the keywords 'Borna disease virus', 'psychiatric disorders' and 'prevalence' in conjunction with each of the following organic disorders,

addictions, psychotic disorders, affective disorders and anxiety disorders. Due to variations in the laboratory methods, materials and study groups used, a meta-analysis was not possible.

2.4 Study selection

The inclusion criteria were studies published from 1985 to January 2011, the study participants: psychiatric patients, investigation: antibody, antigen, circulating immunocomplexes or viral RNA, material: serum, peripheral blood cells, cerebrospinal fluid, brain tissue, and outcomes: prevalence data.

3. Results

We identified 53 studies published from 1985 to July 2011 describing Borna disease virus positivity in psychiatric patients (psychiatric disorders, affective and psychotic disorders, addictions, neurotic disorders), 29 studies investigated viral antibodies in the serum, 23 BDV RNA in peripheral blood cells, 4 detected circulating immunocomplexes, viral antigens and antibodies in serum, 2 detected BDV RNA in cerebrospinal fluid (CFS), 5 detected BDV RNA in brain tissue and 8 studies detected BDV RNA and Ab. The prevalence of BDV infection in these studies ranged from 0 to 100% for patients with bipolar affective disorder. Between 1985 and 1993 the presence of BDV infection in groups of patients with various neuropsychiatric disorders was detected using IFA for BDV Ab. The majority of the studies identified found BDV in patients with schizophrenia and affective disorders.

3.1 Borna disease virus infection and organic disorders

Borna disease virus infection causes cognitive impairment (memory and learning impairment) in infected experimental animals. This impairment is linked to cholinergic loss in the forebrain and is associated with the pathology of Alzheimer's disease (Solbrig et al., 2010). Only a few studies reported BDV positivity in organic disorders, especially dementia. We identified five studies that detected the presence of BDV infection in patients with vascular and Alzheimer's dementia; the rate of BDV positivity ranged from 0% to 1% (see Table2).

Authors	Country	Method/marker	Sample	Diagnosis	Total no.	No. and % of positives
De la Torre et al., 1996	USA	PCR/Ag, RNA	Brain	Alzheimer's disease	7	0/0%
Sauder et al., 1996	Germany	WB/Ab	Serum	Alzheimer's, vascular and other organic disorders Control	34 203	7/20.5% 3/1.4%
Igata et al., 1998	Japan	IFA/Ab	Serum	Vascular dementia Control	10 36	0/0% 4/11%
Yamaguchi et al., 1999	Japan	ECLIA/Ab	Serum	Alzheimer's disease Vascular dementia Control	46 89 917	0/0% 1/1.12% 10/1.09%
Czygan et al., 1999	Germany	RT-PCR/RNA	Brain	Alzheimer's disease Control	14 52	0/0% 0/0%

Table 2. Studies that detected BDV infection in patients with organic disorders

3.2 Borna disease virus infection and addiction

Borna disease virus influences dopaminergic neurotransmission, including the reward system, which plays a crucial role in the pathology of addictive disorders. We found four studies that detected BDV infection in addicted patients. Only one study detected BDV positivity in addicted patients at the start of detoxification and at the end of treatment. Rackova and colleagues demonstrated BDV CIC positivity in 36.6% and 42.9% of patients with alcohol and drug abuse; the positivity of BDV infection was not significantly higher than in healthy individuals (Rackova et al., 2010). The rate of BDV positivity ranged from negative results to positivity in 42.9% (see Table 3).

Authors	Country	Method/marker	Sample	Diagnosis	Total no.	No. and % of positives
Sauder et al., 1996	Germany	WB/Ab	Serum	Alcohol and drug addictions Control	22 203	1/ 4.5% 3/1.4%
Yamaguchi et al., 1999	Japan	ECLIA/Ab	Serum	Alcohol addictions Control	42 917	1/ 2.38% 10/1.09%
Czygan et al., 1999	Germany	RT-PCR/RNA	Brain tissue	Addictions Control	27 52	0/0% 0/0%
Rackova et al., 2010	Czech Republic	ELISA/CIC	Plasma	Alcohol and drug addictions Control	41 28 127	15/36.6% 12/42.9% 47/37.3%

Table 3. Studies that detected BDV infection in patients with alcohol and drug addictions

3.3 Borna disease virus infection and psychotic disorders (schizophrenia, schizoaffective disorders)

Borna disease virus infection causes changes in dopaminergic neurotransmission in adult experimental animals and influences brain development in infected neonatal animals; these changes are important in the aetiology of psychotic disorders in humans. We identified 29 studies that detected BDV infection in patients with schizophrenia or schizoaffective disorders, 13 studies that detected BDV RNA, 9 that detected BDV Ab and 7 that detected both infectious markers: Ab and RNA. The rate of BDV infection positivity ranged from 0% to 63.6% in schizophrenic patients and from 0% to 13.86% in control groups of healthy individuals (see Table 4 and 5).

3.4 Borna disease virus infection and affective disorders (depressive disorder, bipolar affective disorders)

The first studies to detect BDV positivity in psychiatric patients reported higher rates of BDV positivity in patients with recurring affective disorders. We found 19 studies that described BDV positivity in patients with affective disorders (depressive and bipolar disorders, dysthymia), 8 studies that examined BDV RNA, 7 studies that detected BDV Ab, 2 studies that detected BDV RNA and Ag and 1 study that detected BDV CIC, Ag and Ab. The rate of BDV infection positivity ranged between 0% and 90% in patients with affective disorders. The highest positivity rate was reported in patients with bipolar depression and severe psychopathology. The rate of BDV infection was from 0% to 32% in the control group of healthy individuals (see Table 6).

Authors	Country	Method/marker	Sample	Diagnosis	Total no.	No. and % of positives
Waltrip et al., 1995	USA	WB/Ab	Serum	Schizophrenia Control	90 20	13/14.4% 0/0%
Sauder et al., 1996	Germany	WB/Ab	Serum	Schizophrenia Control	114 203	16/11.42% 3/1.4%
Kubo et al., 1997	Japan	IFA/Ab WB/Ab	Plasma	Schizophrenia Control	179 70	2/1.1% 0/0%
Waltrip et al., 1997	USA	WB/Ab	Serum	Negative schizophrenia Positive schizophrenia	15 49	5/33.3% 4/8.2%
Deuschle et al., 1998	Germany	EIA/Ag, Ab	CSF	Schizophrenia	?	0/0%
Iwahashi et al., 1998	Japan	WB/Ab	Serum	Schizophrenia Control	67 31	30/44.8% 0/0%
Chen et al., 1999a	Taiwan	WB/Ab	Plasma	Schizophrenia Family members Mental health workers Control	314 132 82 274	38/12.1% 16/12.1% 8/9.8% 8/2.9%
Yamaguchi et al., 1999	Japan	ECLIA/Ab	Serum	Schizophrenia Control	845 917	26/3.08% 10/1.09%
Tsuji et al. 2000	Japan	WB/Ab	Plasma	Schizophrenia Control	229 229	0/0% 0/0%
Selten et al., 2000	Netherlands	IFA/Ab	Serum	Schizophrenia Control	26 29	3/11% 6/21%
Fukuda et al., 2001	Japan	WB/Ab	Plasma	Schizophrenia Control	45 45	2/4% 1/2%
Yang et al., 2003	China	WB/Ab	Serum	Schizophrenia Control	116 ?	10/8.6% 0/0%
Terayama et al., 2003	Japan	WB/Ab	Serum	Schizophrenia Control	32 25	7/21.9% 1/4%
Matsunaga et al., 2005	Japan	RIA/Ab WB/Ab	Serum	Schizophrenia Control	57 41	8/14% 2/1%
Na et al., 2009	Korea	IFA/Ab	Serum	Schizophrenia Control	60 60	0/0% 0/0%
Karakose et al., 2011	Turkey	ELISA/Ab	Serum	Schizophrenia Control	207 137	66/31.88% 19/13.86%

Table 4. Studies that detected BDV Ab in patients with schizophrenic disorders

Authors	Country	Sample	Diagnosis	Total no.	No. and % of positives
Sierra-Honigmann et al., 1995	USA	CSF	Schizophrenia	48	0/0%
Igata-yi et al., 1996	Japan	Plasma PBMCs	Schizophrenia Control	49 36	5/10.2% 0/0%
Sauder et al., 1996	Germany	Plasma PBMCs	Schizophrenia Control	11 23	7/63.6% 0/0%
Kubo et al., 1997	Japan	Plasma PBMCs	Schizophrenia Control	? 12	0/0% 0/0%
Lieb et al., 1997	Germany	Plasma PBMCs	Schizophrenia Schizoaffective disorders	59 10	0/0% 0/0%
Richt et al., 1997	Germany	Plasma PBMCs	Schizophrenia	26	0/0%
Iwahashi et al., 1997	Japan	Plasma PBMCs	Schizophrenia Control	67 31	6/8.9% 1/3.2%
Salvatore et al., 1997	USA, Europe	Brain	Schizophrenia	17	9/53%
Haga et al., 1997	Japan	Brain	Schizophrenia Control	9 31	3/33.3% 2/6.5%
Iwata et al., 1998	Japan	Plasma PBMCs	Schizophrenia Control	77 84	3/4% 2/2%
Czygan et al., 1999	Germany	Plasma PBMCs	Schizophrenia Control	13 52	0/0% 0/0%
Kim et al., 1999	Korea	Plasma PBMCs	Schizophrenia	39	0/0%
Chen et al., 1999b	Taiwan	Plasma PBMCs	Schizophrenia Mental health workers Control	74 45 69	10/14% 7/15% 1/1,4%
Nakamura et al., 2000	Japan	Brain	Schizophrenia Control	4 2	2/50% 0/0%
Tsuji et al., 2000	Japan	Plasma PBMCs	Schizophrenia Control	229 229	4/1.8% 1/0.6%
Fukuda et al., 2001	Japan	Plasma PBMCs	Schizophrenia Control	45 45	0/0% 0/0%
Kim et al., 2003	Korea	Serum	Schizophrenia	62	0/0%
Nunes et al., 2008	Brazil	Plasma PBMCs	Schizophrenia, schizoaffective disorders Relatives with psychiatric disorders Relatives without psychiatric disorders Control	27 24 20 27	12/44.4% 9/37.5% 10/50% 4/14.8%
Na et al., 2009	Korea	Plasma PBMCs	Schizophrenia Control	60 60	0/0% 0/0%
Karakose et al., 2011	Turkey	Plasma PBMCs	Schizophrenia Control	207 137	0/0% 0/0%

Table 5. Studies that detected BDV RNA in patients with schizophrenic disorders

Authors	Country	Method/marker	Sample	Diagnosis	Total no.	No. and % of positives
Amsterdam et al., 1985	USA	IFA/Ab	Serum	Unipolar and bipolar depression Control	265 105	12/4.5% 0/0%
Bode et al., 1993	Germany	IFA/Ab	Serum	Major depression Neurotic depression, dysthymia	? ?	?/30% ?/8%
Fu et al., 1993	Japan	WB/Ab	Serum	Affective disorders Control	138 117	9/6.5% 1/0.9%
Sauder et al., 1996	Germany	WB/Ab	Serum	Affective disorders Control	52 203	6/11.5% 3/1.4%
Bode et al., 1994	Germany	RT-PCR/RNA	Plasma PBMCs	Depression Control	3 10	2/66% 0/0%
Igata-yi et al., 1996	Japan	RT-PCR/RNA	Plasma PBMCs	Depressive disorders Control	6 36	1/16.4% 0/0%
De la Torre et al., 1996	USA	RT-PCR/RNA, Ag	Brain	Depressive disorders	36	4/11.1%
Kubo et al., 1997	Japan	IFA/Ab	Plasma	Mood disorders Control	123 70	0/0% 0/0%
Lieb et al., 1997	Germany	RT-PCR/RNA	Plasma PBMCs	Depressive disorders Bipolar disorders	41 10	0/0% 0/0%
Iwata et al., 1998	Japan	RT-PCR/RNA	Plasma PBMCs	Affective disorders Control	49 84	2/4% 2/2%
Deuschle et al., 1998	Germany	RT-PCR/RNA	CSF	Recurrent depressive disorders	32	3/9.4%
Yamaguchi et al., 1999	Japan	ECLIA/Ab	Serum	Affective disorders Control	251 917	9/3.59% 10/1.09%
Czygan et al., 1999	Germany	RT-PCR/RNA	Brain	Affective disorders Control	11 52	0/0% 0/0%
Kim et al., 1999	Korea	RT-PCR/RNA	Plasma PBMCs	Bipolar disorders Depressive disorders	33 9	0/0% 0/0%
Fukuda et al., 2001	Japan	RT-PCR/RNA	Plasma PBMCs	Affective disorders Control	45 45	1/2% 0/0%
Fukuda et al., 2001	Japan	WB/Ab	Plasma	Affective disorders Control	45 45	1/2% 0/0%
Terayama et al., 2003	Japan	WB/Ab	Serum	Mood disorders Control	33 25	9/27.3% 1/4%
Bode et al., 2001	Germany	ELISA/CIC, Ag IFA/Ab	Plasma	Affective disorders	187	62% CIC, 11% Ab, 15% Ag
					103	52% CIC, 20% Ab, 23% Ag
				Control	100	24% CIC, 2% Ab, 0 Ag

Authors	Country	Method/marker	Sample	Diagnosis	Total no.	No. and % of positives
Bode et al., 2001	Germany	ELISA/CIC, Ag IFA/Ab	Plasma	Severe depression	28	90% CIC
				Mild depression	28	90% CIC
				Control	65	32% CIC
Matsunaga et al., 2005	Japan	WB, RIA/Ab	Serum	Mood disorders Control	80 41	11/13.75% 2/1%
Na et al., 2009	Korea	RT-PCR/RNA IFA/Ab	Plasma PBMCs	Affective disorders Control	138 60	0/0% 0/0%

Table 6. Studies that detected BDV infection in patients with affective disorders

3.5 Borna disease virus infection and neurotic disorders

Only a few studies reported BDV positivity in neurotic disorders: we identified 10 studies and 7 of them examined patients with chronic fatigue syndrome. Six studies detected BDV Ab, two detected BDV RNA and one detected both RNA and Ab markers. The rate of BDV positivity ranged from 0% to 34% in psychiatric patients and between 0% and 5.9% in healthy controls (see Table 7).

Authors	Country	Method/marker	Sample	Diagnosis	Total No	No and % of positive
Sauder et al., 1996	Germany	WB/Ab	Serum	Neurotic, personality disorders Control	54 203	8/14.8% 3/1.4%
Bode et al., 1994	Germany	RT-PCR/RNA	Serum	Panic disorder OCD Control	1 1 10	0/0% 1/100% 0/0%
Nowotny & Windhaber, 1997	Germany	?	Serum	Panic disorders Control	55 34	4/7.3% 2/5.9%
Bode et al., 1992	Germany, USA	IFA/Ab	Serum	Chronic fatigue syndrome	50	0/0%
Nakaya et al., 1996	Japan	RT-PCR/RNA	Plasma PBMCs	Chronic fatigue syndrome	25	8/32%
Kitani et al., 1996	Japan	ELISA/Ab	Serum	Chronic fatigue syndrome	89	30/34%
Gow et al., 1997	UK	WB/Ab	Serum	Chronic fatigue syndrome Control	21 13	2/10% 0/0%
Evengard et al., 1999	Sweden	WB, ELISA/Ab RT-PCR/RNA	Serum Plasma PBMCs	Chronic fatigue syndrome	18	0/0%
Yamaguchi et al., 1999	Japan	ECLIA/Ab	Serum	Chronic fatigue syndrome Control	75 917	0/0% 10/1.09%
Li et al., 2003	China	WB/Ab	Plasma	Chronic fatigue syndrome Control	61 73	7/11.8% 0/0%

Table 7. Studies that detected BDV infection in patients with anxiety disorders and OCD

3.6 Borna disease virus and unspecified psychiatric disorders

Several studies examined psychiatric patients with various diagnoses and it was not possible to divide these groups according the diagnosis. We found 17 studies that detected BDV infection in unspecified psychiatric (or neuropsychiatric) patients, 5 studies that detected BDV Ab, 1 study that detected Ab and Ag, 1 that only detected Ag, 7 studies that detected BDV RNA, 2 that detected BDV CIC and 1 study detected BDV Ab and RNA. The rate of BDV positivity ranged between 0% and 66.7% in psychiatric patients and between 0% and 37.3% in healthy individuals (see Table 8).

Authors	Country	Method/marker	Sample	Diagnosis	Total No	No and % of positive
Rott et al., 1985	Germany, USA	IFA/Ab	Serum	Psychiatric patients Control	979 200	16/1.6% 0/0%
Bode et al., 1992	Europe, USA, Africa	IFA, immunoprecipitation/ Ab, Ag	Serum	Chronic diseases of the brain, immune system, infection (HIV, parasitosis) Control	Total number 3000	?/13-14% ?/2%
Bode et al., 1993	Germany	IFA/Ab	Serum	Psychiatric patients (screening)	70	1-3/2-4%
Bode et al., 1993	Germany	IFA/Ab	Serum	Psychiatric patients (follow-up test)	70	14/20%
Kishi et al., 1995	Japan	WB, ELISA/Ab	Serum	Control	100	1/1%
Kishi et al., 1995	Japan	RT-PCT/RNA	Plasma PBMCs	Psychiatric patients Control	60 100 72	22/37% 5/5% 3/ 4.2%
Bode et al., 1996	Germany	Ag	Plasma PBMCs	Recurrent depressive and bipolar disorders Other depressive and anxiety disorders Psychotic disorders	10 11 11	53 samples (collected in a week), 20 positive
Sauder et al., 1996	Germany	RT-PCR/RNA	Plasma PBMCs	Psychiatric disorders Control	26 23	13/50% 0/0%
Kubo et al., 1997	Japan	RT-PCR/RNA	Plasma PBMCs	Psychiatric patients Control	106 12	0.2% 0/0%
Salvatore et al., 1997	USA, Europe	RT-PCR/RNA	Brain	Neuropsychiatric disorders	75	11/14.7%
Lieb et al., 1997	Germany	RT-PCR/RNA	Plasma PBMCs	Psychiatric disorders	159	0/0%
Czygan et al., 1999	Germany	RT-PCR/RNS	Brain	Neuropsychiatric disorders Control	86 52	0/0% 0/0%
Vahlenkamp et al., 2000	Germany	RT-PCR/RNA	Plasma PBMCs	Psychiatric patients Control	27 13	10/37% 2/15.4%
Rybakowski et al., 2001	Poland	ECLIA/Ab	Serum	Psychiatric patients	946	23/2.4%

Authors	Country	Method/marker	Sample	Diagnosis	Total No	No and % of positive
Rackova et al., 2003	Czech Republic	ELISA/CIC	Plasma	Affective and schizophrenic disorders Control	46 126	12/26.1% 22.2%
Miranda et al., 2006	Brazil	RT-PCR/RNA	Plasma PBMCs	Schizophrenia and affective disorders Control	30 30	10/33.3% 4/13.3%
Matsunaga et al., 2008	Japan	RIA/Ab	Serum	Psychiatric patients Control	304 378	No significant difference
Rackova et al., 2009	Czech Republic	ELISA/CIC	Plasma	Affective and schizophrenic disorders Control	39 126	26/66.7% 28/22.2%
Karakose et al., 2011	Turkey	ELISA/Ab	Serum	Psychiatric disorders Control	131 137	17/12.98% 19/13.86%
Karakose et al., 2011	Turkey	RT-PCR/RNA	Plasma PBMCs	Psychiatric disorders Control	131 137	0/0% 0/0%

Table 8. Studies that detected BDV infection in psychiatric patients

3.7 Borna diasease virus and other disorders

The influence of BDV infection on other disorders was also studied, particularly on neurological and infectious diseases. Prudlo and colleagues did not find any increase in BDV Ab positivity in neurologic patients (with amyotrophic lateral sclerosis) compared to surgical patients (Prudlo et al., 2002). Li and colleagues detected BDV RNA in patients with viral encephalitis, but no BDV positivity was found in other neurological disorders (Li et al., 2009; Salvatore et al., 1997). Flower and colleagues reported higher rates of BDV CIC positivity in multitransfused patients (Flower et al., 2008), and BDV RNA and Ag were detected in the cerebrospinal fluid of patients with multiple sclerosis (Deuschle et al., 1998). A higher rate of BDV positivity was not detected in patients with epilepsy (Czygan et al., 1999; Hofer et al., 2006) or Parkinson's disease (Haga et al., 1997). Several studies detected higher rates of BDV infection positivity in HIV-positive patients (Auwanit et al., 1996; Bode et al., 1992; Cotto et al., 2003) but not in therapeutically immunosuppressed patients (Cotto et al., 2003).

4. Conclusions

The Borna disease virus is a neurotropic RNA virus belonging to the family Bornaviridae, order Mononegavirales, which has a high affinity for the central nervous system, especially for limbic structures. The Borna disease virus causes an infection in birds and mammals including humans. Some infected animals develop symptoms which are very similar to human psychiatric disorders (cognitive impairment, behavioural changes, changes in social behaviour, appetite, sleeping...). Because of this similarity BDV has begun to be associated with several psychiatric disorders, especially with mood and psychotic disorders. The association of BDV and psychiatric disorders is explained by the viro-psycho-

immunological disease model. A BDV persistent infection of the central nervous system is activated by changes in the immune system, an activated BDV infection influences neurotransmitter functions and contributes to the onset of psychiatric disorders in vulnerable individuals (with a genetic predisposition).

In the 1980s the presence of a BDV infection was found in patients with neuropsychiatric disorders. Since the 1980s many studies have detected a BDV infection in patients with psychiatric disorders (the majority of them tested BDV positive in affective disorders and schizophrenia) and in patients with neurological disorders, HIV infection and others. The positivity of a BDV infection ranges from negative results to very high positivity rates, more than 90% in patients with affective disorders in comparison with BDV positivity between 0%-40% in healthy individuals. The Borna disease virus positivity in psychiatric patients ranges from negative to highly positive. These differences in positivity can be caused by several factors; features of the psychiatric population (age, diagnosis, severity of the psychopathology, immune status), geographical region, differences in specificity and sensitivity of the laboratory methods used and others. The significantly higher rates of BDV positivity were detected in younger individuals, especially in children. Several research groups reported an association between higher BDV positivity and the severity of the psychopathology.The high variability of BDV positivity in humans can be influenced by the laboratory method used**.** The detection of BDV CIC by ELISA has shown a 10-fold higher incidence of BDV infection than was estimated for BDV Ab positivity by the immunofluorescence method.

4.1 Arguments supporting the association of BDV infection with psychiatric disorders include

Characteristics of the Borna disease virus - its ability to infect and spread through the central nervous system, causing persistent infection and its activation, have led to the connection with psychiatric disorders. An experimental BDV infection shows the influence of BDV on neurotransmitter receptors which lead to behavioural changes, cognitive impairment and neurological disturbances.

Many studies have detected the significantly higher BDV positivity in psychiatric patients in comparison with healthy individuals. The Borna disease virus was isolated from PBMCs in plasma, cerebrospinal fluid and brain tissue. Higher levels of BDV antigens and circulating immunocomplexes have been found in acutely depressed patients than in patients with mild depression. Levels of BDV antigens and circulating immunocoplexes correlate with the severity of psychiatric symptoms. Depressed patients who were treated with virostatic medication – amantadine, improved their psychopathology significantly and more quickly. The improvement of depression symptoms correlates with the decrease or disappearance of BDV positivity (levels of antigens).

4.2 Arguments against the BDV role in ethiopathology in psychiatric disorders include

Many studies have failed to detect BDV infection in psychiatric patients or did not find significant differences in BDV positivity between psychiatric patients and healthy individuals. Some researchers detected high BDV positivity in healthy individuals and considered BDV infection to be a normal part of human life without any influence on health.

There are reports about the effect of antiviral treatment with amantadine in BDV positive patients with depression disorders. The improvement of depression symptomatology during this treatment could be explained by the antidepressive effect of amantadine. Some studies did not prove the virostatic effect of amantadine in the treatment a BDV infection.
Several studies criticize the unreliability of some laboratory methods, in these studies BDV was not isolated from BDV CIC positive samples.
What can we conclude? The role of BDV in psychiatric disorders is still unclear. But very probably this infection can be involved in the onset and the course of psychiatric disorders in a determinate subpopulation of psychiatric patients. German and Italian researchers examined the presence of BDV infection in children. These studies are crucial to obtaining information about the possible influence of neurotropic viruses on brain development. A BDV infection in early life can contribute to the onset of psychiatric disorders in adults in predisposed individuals.
For future research, which is important for answering still unclear questions about the Borna disease virus we need more and larger studies testing comparable patient groups and using comparable laboratory methods. We are also missing more double-blind studies with amantadine in BDV positive psychiatric patients. Studies testing for a BDV infection from childhood to adulthood are necessary to answer the question: What is first?: BDV infection and secondly the development of psychiatric disorders or first psychiatric disorders which secondarily leads to several changes in the immune system and then the activation of the BDV infection.

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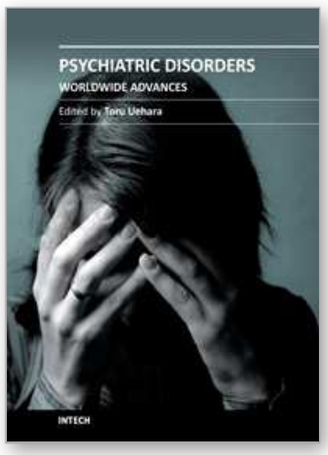

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A psychiatric disorder is defined as any complex condition that involves the impairment of cognitive, emotional, or behavioral functioning. Aside from knowing the physical organic factors, its causal pathology has remained a mystery. Regarding recent advances in psychiatry and neurosciences, psychiatric disorders have been closely associated with socio-cultural, psychological, biochemical, epigenetic or neural-networking factors. A need for diverse approaches or support strategies is present, which should serve as common knowledge, empathetic views or useful skills for specialists in the filed. This book contains multifarious and powerful papers from all over the world, addressing themes such as the neurosciences, psychosocial interventions, medical factors, possible vulnerability and traumatic events. Doubtlessly, this book will be fruitful for future development and collaboration in â€œworld psychiatryâ€.

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