Eur Psychiatry 2001 ; 16 : 3-10

S0924933800005290/REV

REVIEW

Borna disease virus and psychiatry

O. Taieb[1,2], J.M. Baleyte[2], P. Mazet[2], A.M. Fillet[1]*

[1] Department of Virology, CERVI, 47-83 Boulevard de l'Hôpital, 75013 Paris, France; [2] Department of Child and Adolescent Psychiatry, Groupe Hospitalier Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France

(Received 15 January 2000; accepted 5 June 2000)

Summary – Borna disease virus (BDV), a noncytolytic neurotropic nonsegmented negative-stranded RNA virus with a wide geographic distribution, infects several vertebrate animal species and causes an immune-mediated central nervous system (CNS) disease with various manifestations, depending on both host and viral factors. In animal infections, BDV can persist in the CNS and induce alterations in brain cell functions, neurodevelopmental abnormalities and behavioral disturbances. An association between BDV and psychiatric disorders (essentially schizophrenia and affective disorders) has been suggested by some serologic and molecular studies but further investigations are required to substantiate the possible contribution of this virus to the pathogenesis of these disorders. © 2001 Éditions scientifiques et médicales Elsevier SAS

autism / bipolar disorder / borna disease virus / neurodevelopmental hypothesis / schizophrenia

INTRODUCTION

Although Borna disease (BD) was first recognized in the early 1800s as an encephalopathy with an infectious basis that affected horses and sheep in southeastern Germany, Borna disease virus (BDV) has only been recently characterized as the causative agent. BDV provides an interesting model to study changes in brain functions involved with viral persistence in the central nervous system (CNS).

We will review the etiology of BD, the natural and experimental infections in animals, the pathogenesis of the disease and, by studying serologic and molecular data, the possible link between BDV and psychiatric disorders.

VIROLOGY AND ANIMAL INFECTIONS

Etiology

BDV has been characterized as an enveloped nonsegmented negative-stranded RNA virus with a genomic size of approximately 9 kb and a nuclear site for replication and transcription (for reviews see [10, 15, 20]). The genomic organization is similar to that of members of the *Mononegavirales* order, therefore, BDV is the prototype of the new family *Bornaviridae* within this order. The genome can be divided into three main gene blocks: the first codes for the nucleoprotein and polymerase cofactors, represented by p40 and p24 proteins; the second codes for the matrix and virus envelope

* *Correspondence and reprints.*

proteins, represented by p16 and p56 proteins; the third codes for the viral polymerase. BDV is also characterized by its neurotropism, a noncytolytic strategy of replication and a genomic stability.

Natural infection and transmission

BD is a transmissible, progressive and lethal encephalomyelitis of horses and sheep, which are the main natural hosts, associating neurologic impairments and behavioral disorders (for reviews see [24, 44, 45]). BD has also been described in cats, cattle, rodents, birds, etc. The host range is likely to include all warm-blooded animals. Natural infection by the BDV may remain inapparent and there is evidence that BDV is no longer limited to the known endemic areas. Neither the reservoir nor the mode of transmission of natural infection is known. The virus is assumed to be transmitted through saliva, nasal or conjunctival secretions. Milk has also been incriminated. Animals become infected by direct contact with secretions, or by exposure to contaminated food or water. An olfactory route for transmission has been proposed first because intranasal infection is efficient and the olfactory bulbs of naturally infected horses show lesions early in the course of the disease. An oral/gastric route could also be involved. Rodents and healthy infected animals may represent a virus reservoir and vector.

Experimental infection

BD can be transmitted experimentally to a wide variety of laboratory animals from birds to nonhuman primates. The rat is the most commonly used model for the study of BDV pathogenesis. Experimental infections of the rat have allowed the study of the dissemination pathway of BDV (for reviews see [20, 21]). In the early phase of infection, spread of BDV is axonal and transsynaptic (transneuronal) in an anterograde or retrograde direction towards the CNS. The type of neurotransmitter receptors in the synapse and their interaction with viral proteins may modulate the spread of infection. The neuronal system first infected at the entry site determines the spread of infection according to its natural connections. For example, intranasal inoculation leads to the olfactory and limbic system, including the hippocampus where viral antigens have a stratified distribution, that has been correlated with aspartate and glutamate neurotransmitter systems. The hypothalamus and the thalamus become infected later with the neocortex. At the same time, central cerebellar nuclei also become infected through their thalamic connections. Starting from here, infection reaches Purkinje cells. The retina is also infected. In the late stages of infection, BDV spreads centrifugally to the peripheral nerves and breaks through the barrier to non-neural tissues. Non-neural cells of the CNS are permissive for BDV, but the virus replicates primarily in neurons and secondarily in glial cells. Extraneural organs and tissues appear to become infected only if the virus is delivered via the peripheral axons for a long period of time. Hippocampal structures and the retina have an elective vulnerability to BDV infection.

Host factors, the age at the time of inoculation, the genetic background and the immune status, as well as viral factors, influence the course of infection. The BDV-specific T-cell response and the role of CD8+ T-cells in the destruction of virus-infected cells are central in the pathogenesis of BD [57].

In adult rats, BDV usually causes an immune-mediated biphasic behavioral disease very similar to that described for naturally infected horses [20, 45]. After a varied incubation period, the onset of a hyperactive phase is observed, which can lead to rapid death in some animals. Excitability and hyperactivity, together with movement and posture disorders, are consistent clinical features in both natural and experimental infections. Some animals may have stereotyped behaviors. An important inflammatory reaction increases the virus-induced cytopathology and can lead to neuronal destruction. A chronic hypoactive phase with somnolence follows in conjunction with a decrease in the inflammatory reaction and high levels of virus in the CNS. During this chronic phase, symptoms resembling those of the initial phase may reemerge in a form of recurrent episodes. Some rats develop an obesity syndrome. It has been proposed that some behavioral manifestations in BD, such as the hyperactive syndrome, might be related to disturbances in the function of the dopamine system [54]. High levels of BDV RNA and abnormal mesocortical dopamine activity, but no alteration in specific binding of D1 or D2 receptor radioligands have been found in the prefrontal cortex in one-month-old infected rats [55]. Changes in dopamine receptors' radioligands binding in the nucleus accumbens have also been noted [56].

In contrast to the robust disease observed in adult-infected rats, a persistent, tolerant infection of newborn (PTI-NB) rats with no overt signs of acute BD can be produced by inoculation with BDV [20, 21, 45]. This persistent infection is characterized by the absence of a cellular immune response to the BDV with a viral load in the CNS similar to that found in acute BD. It provides a model for studying the effects of virus replication on brain development without inflammation [1, 2, 20, 21]. In PTI-NB rats, BDV induces abnormalities in the postnatal development of the hippocampus and cerebellum. One of the first sites of replication is the hippocampal formation, preferentially replicating in neurons of the dentate gyrus (DG) and CA3 and CA4 region of the hippocampus proper. Only the DG neurons are progressively destroyed. The mechanisms of DG degeneration remain unknown. Progressive spatial learning and memory deficits that coincided with a gradual decline in the DG neuron density have been demonstrated in PTI-NB rats [47]. The DG degeneration may occur by loss of mature virus-infected neurons with simultaneous BDV-associated prevention of the normal replacement of DG neurons by postnatal neurogenesis and migration. This hypothesis is consistent with cerebellar injury in PTI-NB rats examined at various times up to 30 days post-infection where there is evidence both of gradual death of BDV-infected mature neurons (Purkinje cells) and abnormal neurogenesis and/or migration of granule cells' precursors leading to significant loss in granule cells, these cells being non-infected by the BDV [2]. The infected Purkinje cells could cease their support of granule cell division, maturation and stabilization. A correlation between the developmental stage of the rat brain at the time of the virus infection and specific neuroanatomical and behavioral signs has been found: unlike rats infected with BDV on postnatal day one, postnatal day 15 inoculated rats did not show signs of cerebellar hypoplasia [48]. Recently, deficits in play behavior and other social interactions in PTI-NB rats have been observed, supporting, according to the authors, the value of this model as an animal model of autism [41]. The same authors have also demonstrated that neonatally BDV-infected adult rats were hyperreactive to aversive stimuli [42]. Similarities in behavioral and anatomic pathology in autism and in PTI-NB rats suggest the utility of this infection-based model for defining common pathways for dysregulation of developmental programs [25].

BDV AND PSYCHIATRY

Serologic studies

Between 1985 and 1993, seroepidemiologic studies, conducted in Germany and in the USA, have shown an increased prevalence of anti-BDV antibodies in patients with psychiatric disorders (essentially mood and psychotic disorders) (for reviews see [20, 24]) *(table I)*. However, important variations in prevalence rates have been observed, ranging from 0.6 to 19.7% in psychiatric patients and 0 to 3.5% in controls. These results should be cautiously evaluated for three reasons: prevalence rates have been estimated on variable numbers of patients, from 71 to 5000; patients' clinical characteristics such as psychiatric diagnosis and geographic origin were often not specified; and differences in serologic laboratory methods may also have affected the results, in particular because of the lack of sensibility and specificity of the immunofluorescence assay mainly used in these first studies.

Since 1993, performance of serologic assays (Western immunoblot assay) has improved. Waltrip et al. [59] were interested specifically in the seroprevalence in schizophrenia with an estimate of 14.4% in a group of 90 patients. There were no relationships between seropositivity and demographic characteristics, schizophrenia diagnostic subtype, premorbid adjustment and medications. However, seropositivity tended to be associated with increased neurologic impairment. Brain structure volumes obtained by magnetic resonance imaging (only for 46 patients) showed that seropositive patients had a significantly larger putamen volume, and tended to have smaller bilateral amygdalae and left amygdala-hippocampal process. In a group of 64 patients from this study, seropositivity tended to be associated with a deficit syndrome [60]. According to the authors, BDV hippocampal damage would lead to the prefrontal dopaminergic hypoactivity. In a recent study, Chen et al. [11] investigated a group of 132 schizophrenic patients' family members and a group of 82 mental health workers who had contact with patients *(table I)*. They found that both groups also had a higher seroprevalence rate than controls, and concluded that these results provided some evidence for a possible human-to-human transmission of BDV.

Table I. Serologic studies in psychiatric patients since 1993.

Authors	*Geographic area*	*Method*	*Subjects' diagnosis*	*Number of subjects*	*Percentage positive*
Bode et al. 1993 [4]	Germany	IF	Psychiatric patients (mainly mood disorders)	71	2–4% (20% in follow-up)
Fu et al. 1993 [19]	USA	WB	Psychiatric patients:		
			– major depression	138	6.5%
			Healthy controls	117	0.9%
Waltrip et al. 1995 [59]	USA	WB	Schizophrenic patients	90	14.4%
			Healthy controls	20	0%
Kishi et al. 1995 [32]	Japan	WB	Psychiatric patients	60	30%
Kishi et al. 1995 [33]	Japan	WB	Blood donors	100	1%
Sauder et al. 1996 [50]	Germany	WB	Psychiatric patients:	416	9.6%
			– schizophrenia and other psychotic disorders	114	14%
			– anxious and personality disorders	54	14.8%
			– mood disorders	52	11.5%
			Surgery patients	203	1.4%
Kubo et al. 1997 [34]	Japan	IF	Psychiatric patients:		
			– schizophrenia	179	1.6%
			– mood disorders	123	0%
			– others	44	0%
			Healthy controls	70	0%
Waltrip et al. 1997 [60]	USA	WB	Deficit schizophrenic patients	15	33.3%
			Nondeficit schizophrenic patients	49	8.2%
Iwahashi et al. 1997 [27]	Japan	WB	Schizophrenic patients	67	44.8%
			Healthy controls (medical staff)	26	0%
Nowotny and Windhaber 1997 [38]	Austria	?	Patients with panic disorder	55	7.3%
			Healthy controls	34	5.9%
Chen et al. 1999 [11]	Taiwan	WB	Schizophrenic patients	314	12.1%
			Family members	132	12.1%
			Mental health workers	82	9.8%
			Controls (blood donors and nonpsychiatric patients)	274	2.9%

IF: immunofluorescence, WB: Western blot.

Detection of BDV antigens and RNA in human peripheral blood mononuclear cells (PBMC)

With the knowledge of the sequence and genomic organization of BDV [9, 12], new procedures have been introduced. The detection of BDV RNA in the PBMC can be done by the reverse trancriptase polymerase chain reaction (RT-PCR) *(table II)*. BDV RNA was first detected in four of six psychiatric patients [5]. For two of them, BDV RNA persisted 7.5 months after the initial evaluation.

In Japan, Iwahashi et al. [27] have found a higher proportion (45%) of anti-BDV antibodies and/or BDV RNA among 67 schizophrenic patients than among 26 controls (0%). Controls were chosen from the medical staff at the same psychiatric hospital. There were no apparent associations between BDV infection and age, age at onset of schizophrenia, period of hospitalization, history of transfusion, family history of psychiatric disorders, doses of psychotropic drugs received or contacts with animals. But seropositivity seemed to be associated with negative symptoms [28], which is similar to the results of Waltrip et al. [60].

Bode et al. [7] reported the case of a 67-year-old woman who presented a depressive episode (during the course of a bipolar disorder) with BDV RNA and antigens in PBMC. After about 10 days of treatment by amantadine, depression improved and antigen and RNA were eliminated 2 and 6 weeks after treatment. The authors suggested that amantadine antidepressive action was the consequence of its anti-BDV efficacy. Others have thought that the antidepressive properties

Table II. Detection of BDV RNA by RT-PCR in PBMC of psychiatric patients.

Authors	*Geographic area*	*Subjects' diagnosis*	*Number of subjects*	*Percentage positive*
Bode et al. 1995 [5]	Germany	Psychiatric patients:		
		– major depression	3	66%
		– obsessive compulsive disorder	1	100%
		– organic mood disorder	1	100%
		– panic disorder	1	0%
		Blood donors	10	0%
Kishi et al. 1995 [32]	Japan	Psychiatric patients	60	36.7%
Kishi et al. 1995 [33]	Japan	Blood donors	172	4.7%
Igata-Yi et al. 1996 [26]	Japan	Psychiatric patients :		
		– schizophrenia	49	10.2%
		– depression	6	16.7%
		Blood donors	36	0%
Sauder et al. 1996 [50]	Germany	Psychiatric patients:	26	50%
		– schizophrenia	11	63.6%
		Healthy controls	23	0%
Kubo et al. 1997 [34]	Japan	Psychiatric patients	106	0.2%
		Healthy controls	12	0%
Richt et al. 1997 [43]	Germany –USA	Psychiatric patients:	52	0%
		– schizophrenia	26	
Iwahashi et al. 1997 [27]	Japan	Schizophrenic patients	67	8.9%
		Healthy controls (medical staff)	26	0%
Lieb et al. 1997 [36]	Germany	Psychiatric patients:	159	0%
		– schizophrenia	59	
		– major depression	41	
		– bipolar disorder	10	
		– schizo-affective disorder	10	
Iwata et al. 1998 [29]	Japan	Psychiatric patients:	126	4%
		– schizophrenia	77	4%
		– mood disorder	49	4%
		Blood donors	84	2%
Kim et al. 1999 [31]	South Korea	Psychiatric patients:	81	0%
		– schizophrenia	39	
		– bipolar disorder	33	
		– major depression	9	

of amantadine could be explained by its antagonist activity on N-methyl-D-aspartate receptors [35], and its lack of antiviral effect in BDV infection in vitro and in infected animals seemed to be confirmed [13, 23, 58]. Ribavirin decreases BDV replication and transcription in in vitro assays [30, 37].

Bode and Ludwig [8] reported two other cases of patients with major depression in whom clinical improvement was associated with the disappearance of the BDV RNA and antigens in PBMC. The persistence during 8 months of BDV RNA in the blood of a 47-year-old patient with schizophrenia and somatisation disorder was reported [39]. Longitudinal studies seem to be essential to evaluate the relationship between infection and disease; higher prevalence could be found in follow-up testing, as it has been observed by Bode et al. [4]. Several other studies have failed to show an association of BDV infection with psychiatric disorders *(table II)* [31, 36, 43]. Low prevalence of BDV RNA has been reported in Japan [29, 34].

There is, therefore, controversy as to the prevalence of BDV RNA in the PBMC of psychiatric patients. The high sensitivity of the nested RT-PCR procedures used has raised the concern that contamination with a laboratory source of BDV nucleic acid could account for some positive reported cases. The comparison of the discrepant results obtained by different investigators is especially hampered by the lack of standardized controls to assess the sensitivity and the reproducibility of the RT-PCR assay. The number of PBMC used for RNA preparation, the fraction of granulocytes in PBMC population, and the amount of RNA, have a

critical influence on the outcome of RT-PCR [20, 29, 40, 51]. Currently, the number of PBMC harboring BDV RNA in infected humans is unknown, but evidence suggests an extremely low prevalence in the range of one or two infected cells per 5,106 PBMC as it has been estimated in persistently infected rats [45, 46, 50]. In three psychiatric patients, Planz et al. [40] have reported that when the PBMC population contained less than 20% granulocytes, no BDV RNA was detected. Presence of BDV RNA was not always associated with seropositivity and vice versa. Both RT-PCR and serology should be used to evaluate BDV infection in humans [51]. It is also noteworthy that levels of BDV in blood do not necessarily reflect viral load in CNS as was found in infected animals.

Sequence analysis of BDV RNA from human PBMC

In some studies, sequence analysis revealed both a high degree of inter- and intrapatient conservation and a close genetic relationship between human- and animal-derived BDV sequences, even if some differences have been described [16, 29, 32, 40, 50].

BDV has been isolated from PBMC of three German patients (two bipolar with a depressive episode, and one with an obsessive compulsive disorder) by cocultivation and long-term passaging with a human cell line [6]. Each human BDV isolate had a unique sequence, but all displayed a high degree of sequence conservation with respect to BDV isolates from naturally infected animals of different species [16]. Isolation of BDV from granulocytes of a patient with schizophrenia has also been reported by Planz et al. [40].

The value of these findings is controversial. The sequence similarities between human BDV isolates and laboratory strains question human origin. For Schwemmle et al. [52], it is impossible to decide whether any authentic human BDV have to date been identified.

Detection of anti-BDV antibodies, BDV antigens and RNA in cerebrospinal fluid (CSF)

Bechter et al. [3] have made investigations of CSF in 38 BDV seropositive psychiatric patients. BDV antibodies were intrathecally produced in 10.5–29% of patients, indicating an active inflammatory process in the CNS of these patients but methodologic limits make these results uncertain. Sierra-Honigmann et al. [53] have failed to detect BDV RNA in CSF from 48 schizophrenic patients.

Anti-BDV antibodies and BDV antigens were sought in CSF of 128 patients with psychiatric disorders (including 65 with depressive episode, eight with bipolar disorder, 27 with schizophrenia) and 102 with neurologic diseases [18]. Unfortunately, corresponding serum or blood samples were not available. Antigens were detected only in the CSF from three patients with recurrent depressive episode and from two patients with multiple sclerosis. Antibodies were present only in CSF from two of the three antigen-positive patients with recurrent depressive episode.

Detection of BDV antigens and RNA in human brain

De la Torre et al. [17] have demonstrated that BDV could infect human brain tissue. They searched for human autopsy brain cases with the main histopathologic findings demonstrated in BDV-infected animals (i.e., sclerosis of the hippocampus and astrocytosis). Five of 600 cases examined were identified as having these histopathologic features. Using immunocytochemistry, RT-PCR, and in situ hybridization, they detected both BDV antigen and RNA in autopsy brain samples from four of these five patients, who had a history of memory alterations and depression. In contrast, BDV markers were not found in seven patients with Alzheimer's disease and two normal controls. Another study had examined postmortem brain samples from 75 North American and European individuals (17 with schizophrenia, five with bipolar disorder, six with major depression, two with unspecified psychotic disorder, 19 with Alzheimer's disease, 11 with Parkinson's disease, five with multiple sclerosis, and ten controls) and had found BDV RNA by RT-PCR in 11 cases: nine patients with schizophrenia and two with bipolar disorder [49]. In Japan, Haga et al. [22] found BDV RNA in postmortem brain samples from three of nine patients with schizophrenia, from two of 31 controls and one of six patients with Parkinson's disease. In Germany, Czygan et al. [14] have detected BDV RNA in autopsy brain samples from three psychiatric patients with prominent hippocampal sclerosis, but not in 86 randomly selected samples from patients with various psychiatric disorders (including schizophrenia, affective disorders and suicide victims) and Alzheimer's disease, not in 16 surgical brain samples from patients

with epilepsy-associated hippocampal sclerosis and not in 52 samples from healthy controls.

CONCLUSION

The data reviewed above support that BDV can infect humans and persist in the CNS. The association between BDV and psychiatric disorders needs confirmation from more comprehensive serologic and molecular epidemiologic studies using standardized diagnostic methods. However, the contribution of BDV to the physiopathology of mental disorders is not proven by this association. Identifying at-risk patients is difficult because no single psychiatric disorder has been associated with BDV infection; however, it should be an essential objective of future studies. Most studies have sought BDV infection markers in patients with schizophrenia and mood disorders, but BDV may also be involved in other disorders, such as autism. The abnormalities in brain development and maturation observed in experimental infections, like what has been suggested for the pathogenesis of psychiatric disorders (particular by schizophrenia), provide further impetus for investigation of the effects of BDV in humans.

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