# Activated Borna Disease Virus in Affective Disorders

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**Background:** Borna disease virus (BDV) is an animal pathogen that causes behavioral changes in animals. Previous studies have found a high prevalence of serum antibodies as well as Borna disease viral antigens (BDVAGs) and RNA in the white blood cells of psychiatric patients, especially those with affective disorders. The present study attempts to offer a better description of the BDVAG cohort using clinical parameters. **Methods:** The prevalence of BDVAG was examined in the peripheral mononuclear leukocytes of patients with a major depressive episode. A subgroup of patients underwent further clinical analysis. **Results:** In this pilot study, at least, there was a significant difference in the prevalence of BDVAG between psychiatric inpatients with a major depressive episode and control individuals. It also appeared that BDVAG is more frequent in patients with recurrent major depression or bipolar disorder than in those with any other psychiatric disorder studied. The number of previous depressive episodes, as well as symptoms involving fatigue and concentration difficulties were positively related to BDVAG. **Conclusions:** The high rate of BDVAG, especially in fatigued patients with recurrent major depression or bipolar disorder, may be a nonspecific aspect of immunosuppression. The question remains whether this neurotropic virus may contribute to the pathogenesis of some types of affective disorder.

## Introduction

There are many ways in which both conventional and unconventional viruses can modify or directly cause affective disorders. Usually, an inflammatory lesion in the brain is involved, as in acute herpes virus encephalitis [29,38] or a postencephalitic residual state, as in von Economo's disease [15,16]. In addition, fatigue syndromes resembling "atypical depression" [12] have been reported during influenza or in the aftermath of it [36,39], and in viral hepatitis [5,34]. In addition, there seems to be a distinct postviral fatigue syndrome following infectious mononucleosis [19,46], and the latter has also been associated with the onset of bipolar disorder [17]. Serological studies attempting to identify an association between antibodies (presence or titer) against herpes simplex virus (HSV) types I and II, cytomegalovirus (CMV), varicella zoster virus (VZV) and Epstein-Barr virus (EBV) and affective disorders have yielded inconclusive results [48].

Although considerable efforts have been made, clear-cut and reproducible signs of inflammatory or degenerative processes have not been detected in affective disorders. A virus model for "functional" affective psychoses would encompass selective and persistent viral infection of the central nervous system without visible cytopathological effects, but with neurotransmitter imbalance and chronically recurring functional disturbances resembling psychiatric disorders. Borna disease virus (BDV) infection is a candidate for such a model.

Natural Borna disease is a contagious, acute or subacute, and sometimes lethal form of encephalomyelitis in horses, cattle, cats, and also primates [31,42]. The disease was named after the township of Borna near Leipzig, Germany, where an outbreak was reported as early as 1894 [35].

Experimental infection is possible in a variety of animal species. The natural form, fulminant and fatal lymphocytic encephalomyelitis, which is well known in horses, is transmitted mainly via the nasal epithelium, with the agent spreading through the limbic system; this form is readily reproduced in rabbits. Neonatal infection in the rat may also result in persistent infection, with no inflammatory infiltrates being present in the brain, although BDV-specific antigens can readily be detected in morphologically unaltered neurons [21]. When submitted to a neuropsychological test battery, however, these clinically healthy animals displayed characteristic disturbances in spatial discrimination tasks and pain avoidance experiments; subtle emotional alterations were also observed [14].

Antibodies against BDV were first reported in humans in 1985 [3,42] in patients suffering from major depression and bipolar disorder. In 1995, our group demonstrated the presence of BDV antigen/mRNA in the peripheral blood mononuclear cells (PBMCs) of patients with major depression, panic disorder, obsessive compulsive disorder and organic affective disorder [7,9]. The prevalence of BDV antigen/mRNA in PBMCs of healthy controls is between 2% and 5% ([27] and *Bode*, unpublished data). In addition, infectious BDV has been isolated from PBMCs in two patients with bipolar disorder, in one patient suffering from obsessive-compulsive disorder (OCD), and in another patient with a chronic fatigue syndrome [10]. Finally, BDV mRNA has been demonstrated post mortem in the brains of

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patients with bipolar disorder, schizophrenia, and Parkinson's disease, as well as in "normal" brains [18,44].

## Patients and Methods

Seventy-eight in-patients (20 men, 58 women; mean age 46.7 ± 17.2 years) who were admitted to our psychiatric ward between June 1993 and August 1994 were diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders (Revised)* (DSM-III-R; [2]) as having a major depressive episode. The physical examinations were normal in all the patients, no clinical signs of viral infection were reported, and there were no laboratory abnormalities apart from occasionally elevated hepatic enzymes, very probably due to medication. All patients were receiving psychotropic medication. Electroconvulsive therapy had not been performed in any of them. Exclusion criteria were DSM-III-R diagnoses 290.00 to 294.80, i.e., known or probable organic psychiatric disorders, even mild infectious diseases, or malignant tumors. A subgroup of these depressive patients (n = 39; 10 men, 29 women; mean age 48.8 ± 16.7) who met these criteria were approached by one of the authors (E.S.) during their first week of hospitalization and informed of the ongoing study, and they consented to further clinical analysis. The study was fully described to them. If the patient agreed to participate, written informed consent was obtained and a comprehensive interview followed on the same day, during which the following rating scales were applied: the Hamilton Psychiatric Rating Scale for Depression (HAMD; [20]); the Montgomery-Åsberg Depression Rating (MADR) scale [37]; a German symptom list ("Beschwerden-Liste," BL; [49]); a German depression scale (DS; [50]); the Self-Rating Anxiety Scale (SAS; [51]); and the 100-mm visual analogue scales (VAS; [1]). In addition, the following data were assessed: duration of the current episode (more or less than one year); number of previous episodes; and presence or absence of psychotic features, as well as additional psychiatric diagnoses. From this group of patients, additional blood for BDVAG testing was drawn at weekly intervals during their stay in hospital. A group of 199 healthy blood donors (148 men, 51 women; mean age 41.7 ± 12.2 years) served as additional control individuals.

Blood samples from all patients and controls were taken from an antecubital vein, centrifuged at 3000 rpm for 10 minutes at room temperature, and stored in plastic tubes. Borna antigen was examined using a method involving immunocytochemistry and flow cytometry, the details of which have been published elsewhere [8]. Peripheral blood mononuclear cells were isolated from citrate-treated blood by centrifugation on Ficoll-paque (density 1.077), fixed with paraformaldehyde and treated with Triton X100. PBMs were identified within PBMC populations by scattergram analysis according to size and granularity, and checked using CD14 fluorescent BDV antibodies. They were then studied with monoclonal antibodies against the major viral proteins and phycoerythrin-labeled anti-mouse IgG.

### *Data analysis*

All statistical calculations were carried out using the Statistical Package for the Social Sciences (SPSS 8.0 for Windows) program. Firstly, BDVAG prevalence rates were determined for four groups: group 1, healthy blood donors (n = 199); group 2, all depressed patients randomly admitted to our ward (n = 78); group 3, a subgroup of these with a monophasic course (n = 34); and group 4, a subgroup with more than one phase (n = 44). Comparisons of BDVAG rates (positive vs. negative) were carried out between all depressed patients and controls, and between subgroups 3 and 4, using Fisher's exact test. Secondly, BDVAG prevalence rates were determined for the 39 patients who consented to further analysis, and between two subgroups of these: those with either a single episode (n = 13) or with more than one phase (n = 26). Comparison of the BDVAG prevalence in both subgroups was made using Fisher's exact test. Differences between the BDVAG prevalences and DSM-III-R diagnoses, presence of psychotic features, length of the acute episode (more or less than one year), and sex were analyzed descriptively and, where applicable, using Fisher's exact test. The Mann-Whitney U test was used to test differences regarding the items in the rating scales and the number of depressive episodes. The *t*-test was used to test differences with respect to age between the BDVAG prevalences in the group of 39 patients. Altogether, 116 items per patient were analyzed. No $\alpha$-adjustment was carried out, and the results therefore have to be interpreted at an exploratory and descriptive level.

## Results

### *BDVAG prevalences in the group of depressive patients and blood donor controls*

BDVAG was found in 37.2% of the depressive patients (n = 78) and in only two control individuals (1%). In the subgroups of patients with a single episode or with a polyphasic course, the prevalences were 23.5% and 47.7%, respectively (Figs. **1** and **2**; Table **1**).

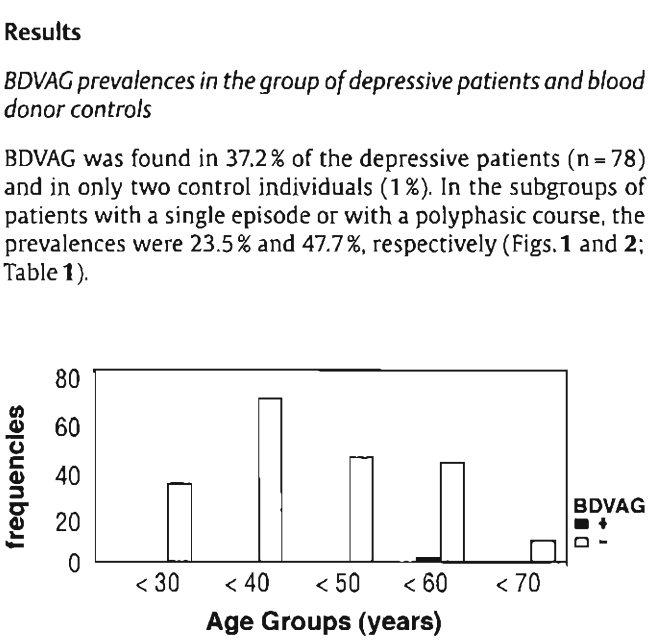


**Fig. 1** Age distribution of Borna disease virus antigen (BDVAG) in the group of blood donors, showing the low prevalence of BDVAG.

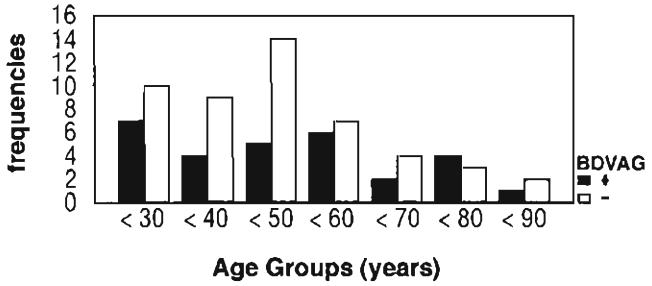


**Fig. 2** Age distribution of depressive patients (n = 78) with and without Borna disease virus antigen (BDVAG), showing a prevalence of more than one-third BDVAG-positive cases in most age groups.

**Table 1** Borna disease virus antigen (BDVAG) prevalences in healthy blood donors (n = 199), all depressed patients (n = 78), and two subgroups of these, either with a monophasic (n = 34) or a polyphasic course (n = 44)

| Group | Total | BDVAG status | | | | Point estimation of prevalence | Confidence intervals* |
|---|---|---|---|---|---|---|---|
| | | Positive | | Negative | | | |
| | n | n | % | n | % | | |
| Healthy blood donors | 199 | 2 | 1.01 | 197 | 98.99 | 0.0101 | 0.00122–0.03583 |
| Depressed patients | 78 | 29 | 37.2 | 49 | 62.8 | 0.3718 | 0.2650–0.4887 |
| Monophasic | 34 | 8 | 23.5 | 26 | 76.5 | n.a. | n.a. |
| Polyphasic | 44 | 21 | 47.7 | 23 | 52.3 | n.a. | n.a. |

* Confidence interval estimations after Clopper and Pearson at a confidence level of $P = 0.95$; n.a.: not applicable.

Compared with patients with a single episode, there was a disproportionately higher prevalence of positive BDVAG findings in the group with a polyphasic course (Fisher's exact test, $P = 0.035$). A comparison of BDVAG prevalences for controls and all depressed patients was highly significant (Fisher's exact test, $P = 0.000$). There are insufficient data to eliminate the influence of age and sex on the prevalence rate between the controls and the depressive patients. A $t$-test for the age distribution shows that the mean age in the two groups differed by five years, with unequal variances ($t = -2.435$, df = 108.64, $P = 0.017$) (Fig. **3**). As we were aware of this problem, the group of blood donors seemed to be an acceptable control group for a pilot study. So far as we are aware, no influence of sex on BDV status has ever been reported. In addition, it appears highly improbable that the age difference of five years between blood donors and depressive patients could alone account for a BDVAG prevalence of roughly 1% in blood donors compared with a prevalence of 37% in depressives.

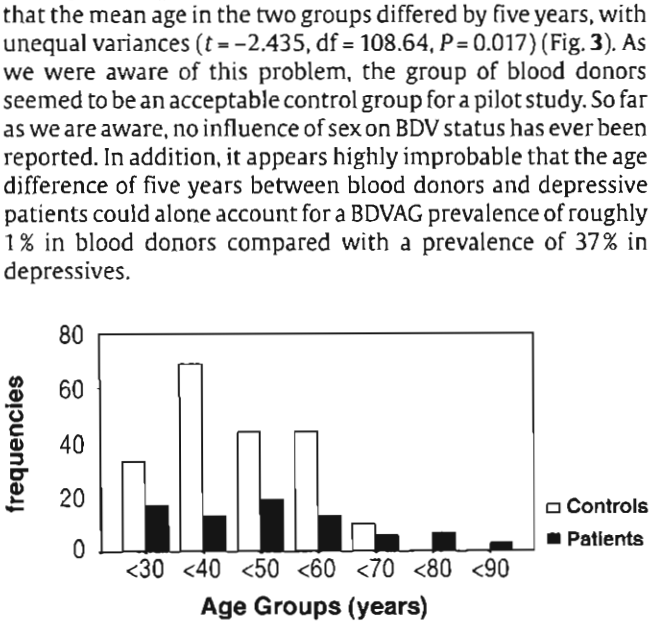


**Fig. 3** Age distributions of blood donors and depressive patients (n = 78).

### *BDVAG prevalences in the subgroup of depressive patients undergoing further analysis*

The subgroup of depressive patients (n = 39) undergoing further analysis did not differ from the remaining group of depressed patients (n = 39) either with respect to sex (10 men, 29 women in each group) or age (48.8 ± 16.7 vs. 44.3 ± 16.7 years; $t = 0.594$, df = 37, $P = 0.556$). The BDVAG prevalence rates are shown in Table **2**. In line with results already obtained in the total group of depressive patients, the diagnosis of recurrent depression (DSM-III-R: 296.30) was more frequently represented, and the diagnosis of major depression, single episode (DSM-III-R: 296.2) less frequently (Fisher's exact test, $P = 0.005$) in the BDVAG-positive group than in the group lacking BDVAG (Fig. **4**).

**Table 2** Borna disease virus antigen (BDVAG) prevalences in patients who consented to further analysis (n = 39) and two subgroups of these, either with a monophasic (n = 13) or a polyphasic course (n = 26)

| Group | Total | BDVAG status | | | |
|---|---|---|---|---|---|
| | | Positive | | Negative | |
| | n | n | % | n | % |
| Depressed patients | 39 | 15 | 38.5 | 24 | 62.8 |
| Monophasic | 13 | 1 | 13.3 | 12 | 86.7 |
| Polyphasic | 26 | 14 | 53.8 | 12 | 46.2 |

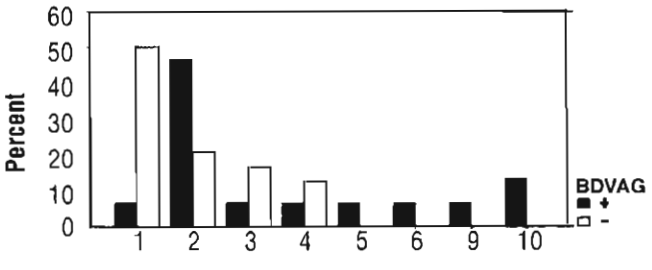


**Fig. 4** Patients (subgroup, n = 39) experiencing an initial episode of major depression have strikingly lower prevalences of Borna disease virus antigen (BDVAG) than polyphasic patients. All patients who had previously experienced more than three phases of major depression expressed BDVAG during the current episode.

BDVAG positivity went along with a higher number of depressive episodes (Mann-Whitney, U = 91, $P_{(one\text{-}tailed)} = 0.004$). According to our data, this was not due to age differences (monophasics 46.08 ± 19.6 years, polyphasics 50.1 ± 15.4 years; $t = -0.706$, df = 37, $P = 0.485$) (Fig. **2**). Apart from this, item 6 on the MADR scale, "difficulties in collecting one's thoughts, mounting to incapacitating lack of concentration" yielded higher scores among patients expressing BDVAG (Mann-Whitney, U = 114.5, $P_{(one\text{-}tailed)} = 0.026$), as did item 6 on the DS scale, "I feel melancholic and depressed" (Mann-Whitney, U = 121.5, $P_{(one\text{-}tailed)} = 0.036$).

## Discussion

The weakness of any study on Borna disease virus infection in humans lies in the controversy there is regarding adequate methods of monitoring past and present — i.e., active —

infection. For many years, this was done using serological methods exclusively; antibodies from patients' sera reacted with BDV-infected animal cells. Most serological data were obtained by indirect immunofluorescence, quite possibly leading to difficulties when antibody levels were very low. The possible occurrence of nonspecific autoreactive antibodies in psychiatric patients was a further methodological problem. Reverse transcriptase polymerase chain reaction (RT-PCR) is a highly sensitive method of measuring BDV-specific RNA in infected tissue, with which high prevalences of Borna disease virus RNA have been reported in psychiatric patients. Interestingly, these findings have also been made in peripheral leukocytes, corroborating our results with Borna disease virus antigen in PBMCs. Yet others have failed to replicate these data, and there is currently some controversy concerning possible laboratory contamination as a source of false-positive findings. The problem is further complicated by the fact that various laboratories employ different strains of Borna disease virus for BDV assays. It has been maintained that as yet, all negative results have been generated by groups using strains other than the human BDV strain employed in this study (*Bode*, unpublished data).

Despite these methodological questions, and regardless of the methods employed, there is overwhelming evidence in the literature for a generally higher prevalence of BDV infection in psychiatrically ill individuals [28,45]. Whether certain subgroups are particularly prone to BDV infection remains open to discussion. The observation originally put forward by Amsterdam [3] that particularly high prevalences of BDV infection could be seen in depressive patients has become a matter of debate, with the findings being corroborated by some and dismissed by others [10,27,28,43]. High prevalences of BDV infection have been reported in schizophrenic patients [23]. Negative results have been obtained in patients with dementia [22]. The finding that BDV antigen could be detected more often in patients with recurrent affective episodes accords well with the fact that it has only been possible to isolate infectious BDV from individuals with multiple episodes, especially in the context of bipolar disorder [10]. With regard to fatigue, amantadine – a drug that has been shown to inhibit or eliminate BDV infection in vitro [11] — has clinically relevant anti-fatigue properties in multiple sclerosis [30]. Moreover, high BDV antigen titers have recently been reported in the cerebrospinal fluid of patients suffering from multiple sclerosis [13]. Amantadine also seems to possess anti-anergic properties in chronic schizophrenic patients [47]. Furthermore, BDV antibodies appear to be more closely associated with negative than with positive symptoms in schizophrenia [2426]. Avolition, which has some overlap with anergia, constitutes one of the major components of what are termed "negative symptoms" (DSM-IV). At the descriptive level, it seems that the activation of Borna disease virus occurs in a variety of clinical conditions that share a common syndrome, i.e. lassitude, fatigue, and cognitive difficulties.

To our knowledge, this is the first study reporting on the prevalence of BDV antigen in PBMCs from psychiatric inpatients suffering from a major depressive episode in the context of recurrent major depression or bipolar disorder. In more than one-third of these patients, BDV antigen expression – a clear indicator of active infection – was demonstrated, compared to less than 2% in healthy blood donors as controls. In addition, patients with a high number of past episodes were positive significantly more often for BDV antigen, while chronicity as such – i.e., the length of the depressive episode – had no significant influence on BDV positivity; nor did the many parameters studied that represent the severity of the current depressive episode.

Another point may be of interest in attempting to describe the BDV antigen-positive patient further clinically. The number of bipolar patients in the present study is too low to provide statistically significant data, yet seven of the 16 bipolar patients were BDV-positive, possibly indicating that apart from the number of previous episodes, bipolarity could prove to be a useful criterion.

While data are accumulating to indicate that patients expressing Borna disease virus antigen have certain features – not necessarily diagnoses – in common, the question of causality remains unanswered. Individuals suffering from such symptoms (for example, concentration difficulties and fatigue) might nonspecifically manifest BDV infection due to some underlying common immunological deficit. Whether BDV infection goes beyond this and actually influences psychiatric disorders remains unclear. Many animal experiments would suggest such a possibility.

To help clarify this question, it might be useful to study conditions that are characterized by an immunodeficient state, monitoring both BDV infection and psychopathological symptoms. For example, we are not aware of any data reporting the prevalence of BDV activation (BDV antigen or mRNA) in patients with acquired immune deficiency syndrome (AIDS). This approach would be of special interest, as this group of patients had the highest percentage of BDV antibody-positive individuals among all groups of patients studied so far using immunofluorescence, Western blot or enzyme-linked immunosorbent assay (ELISA) [4, 6]. In addition, a dramatic increase in depressive symptoms has been reported in human immunodeficiency virus (HIV) infection, starting 18 months before AIDS [32], but not during the earlier stages of the disease [40,41].

In addition, the issue of stress-related secondary BDV activation might be clarified by the simultaneous use of a dexamethasone suppression test, an indicator of hypothalamo-pituitary-adrenocortical axis activity in depressed patients. In addition, the simultaneous measurement of BDV activation and biochemical markers of inflammation, known to be present in a subset of major depressive individuals — e.g., the acute-phase response, interleukin-1β, interleukin-6 [33], would be extremely helpful in addressing the issue of possible functional consequences of BDV activation. Unfortunately, apart from antibodies, no data exist concerning the presence of the mRNA/antigen of HSV I or II, CMV, EBV or VZV in major depression [48].

The dramatic effect of amantadine in a chronically depressed patient with active BDV infection might possibly have been due to the antiviral properties which amantadine allegedly has [11]. On the other hand, amantadine is a drug with well-known psychotropic properties that may well suffice to explain occasionally successful antidepressive therapy, quite independently of antiviral mechanisms. Double-blind studies in which BDVAG-positive and BDVAG-negative depressive patients undergo treatment with amantadine are warranted.

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