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Borna disease virus antibodies and the deficit syndrome of schizophrenia

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Abstract

We detected anti-Borna disease virus (BDV) antibodies at a 14.4% rate in patients with schizophrenia. The hypothesis of a higher rate of BDV seropositivity in deficit syndrome was borne out in a subset of 64 patients categorized according to the Schedule for the Deficit Syndrome with 5/15 seropositive deficit and 4/49 seropositive nondeficit ($p<0.05$). This suggests that the antibodies and possibly a BDV-like virus are pathogenetically linked to this form of schizophrenia.

Keywords: Borna disease virus; Schizophrenia; Deficit syndrome

1. Introduction

BDV is an incompletely characterized virus that is enveloped and has an 8.9-kb negative strand RNA genome (Bautista et al., 1994; Cubitt and de la Torre, 1994). BDV is the cause of Borna disease, an immune-mediated meningoencephalitis in horses and sheep in Europe, and has a wide experimental host range, including birds, rodents, and primates. The spectrum of natural hosts is also broad, including cattle, rabbits, goats, deer, llamas, alpacas, ostriches, and domestic cats (Rott and Becht, 1995).

Evidence has accumulated that BDV, or a BDV-like agent infects humans. Antibodies to BDV (by indirect immunofluorescence assay) have been identified in some patients with psychiatric diseases (Bode, 1995). Discovery of BDV in peripheral blood mononuclear cells from infected rats by RT-PCR (Carbone et al., 1991; Rubin et al., 1995) has led to the detection of BDV-like antigens (Bode et al., 1994) and BDV-specific RNA sequences in peripheral blood cells of patients with psychiatric disorders (Bode et al., 1995; Kishi

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et al., 1995). Recently, BDV-like antigens and RNA sequences have been detected by immunohistochemistry, in situ hybridization, and RT-PCR in post-mortem tissue from four out of five human brains in an Alzheimer's disease autopsy series selected from 600 brains based on the presence of hippocampus sclerosis and astrocytosis (de la Torre et al., 1996a). Infectious BDV has been isolated from patients with psychiatric disorders by cocultivation of peripheral blood mononuclear cells with human neural cells (Bode et al., 1996; de la Torre et al., 1996b). These latter findings strongly suggest that BDV does infect humans, making the question of whether BDV causes psychiatric disease highly relevant.

In animal hosts, BDV infection has a breadth of behavioral manifestations, ranging from asymptomatic to subtle changes in social affiliative behavior to fatal meningoencephalitis (Sprankel et al., 1978; Dittrich et al., 1989; Bautista et al., 1995, 1994). Animal data suggest that BDV is an interesting candidate for an infectious agent in schizophrenia. Infections with BDV can result in behavioral abnormalities in the absence of an inflammatory response (Sprankel et al., 1978; Dittrich et al., 1989; Bautista et al., 1994, 1995). The limbic system, a site for schizophrenia-associated pathology, is a major target for BDV replication (Narayan et al., 1983; Gosztonyi and Ludwig, 1984; Solbrig et al., 1994) and BDV infection results in early localization to hippocampus and subsequent damage to the dentate gyrus (Carbone et al., 1991). BDV infection also results in abnormalities in agonist sensitivity, transmitter depletion, and receptor binding in the dopamine system (Solbrig et al., 1994, 1996a,b). As noted above, diagnostically mixed psychiatric cohorts have presented evidence for a BDV association. Using a new Western blot technique, we reported an excess of BDV seropositivity in schizophrenia subjects compared to normal controls (Waltrip et al., 1995).

Since schizophrenia is considered to be a heterogenous clinical syndrome (Buchanan and Carpenter, 1994), BDV is not expected to account for all cases. We have proposed a method for reducing syndrome heterogeneity and making within-schizophrenia comparisons to control for common sources of artifact (Carpenter et al., 1993). For this purpose, patients with deficit psychopathology are distinguished from those without this pathology. Evidence points toward a distinctive pathophysiological process of CNS damage associated with deficit schizophrenia (Buchanan et al., 1990, 1993, 1994; Tamminga et al., 1992).

The deficit syndrome is based on negative symptoms but requires separation of primary from secondary and transitory from persistent symptoms. It is defined by primary, trait restricted (not state related) affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose, and diminished social drive (Kirkpatrick et al., 1989). Deficit patients (compared to nondeficit schizophrenia patients) have increased volitional saccadic eye movement latency (Thaker et al., 1989), hypometabolism in parietal and frontal cortices and thalamus (Kirkpatrick et al., 1989), poorer premorbid adjustment (Buchanan et al., 1990), and neurological impairment (Buchanan et al., 1990). Enlargement of the right caudate in deficit patients is seen in brain structure volumes determined by magnetic resonance imaging (Buchanan et al., 1993).

The deficit form of schizophrenia is of interest in relation to BDV as a model system. O'Donnell and Grace (O'Donnell and Grace, 1995) have proposed and validated a model in which the hippocampus plays a central role in modulating (gating) prefrontal cortex-nucleus accumbens interactions such that hippocampal damage leads to hypofrontality and a hypodopaminergic state. BDV shows a predilection to infect areas in the mesocorticolimbic dopamine system (Narayan et al., 1983; Solbrig et al., 1994, 1996a,b). BDV infection also is specifically associated with hippocampal damage in that, with or without inflammation, infection leads to a marked loss of hippocampal neurons (Narayan et al., 1983; Carbone et al., 1991, 1996). The prefrontal system is regarded to be central in the pathophysiology of the schizophrenia deficit syndrome (Weinberger, 1987; Carpenter et al., 1993). This system could be affected by BDV.

We previously reported an increase in seropositive subjects in a cohort of schizophrenic patients compared with normal controls. We now examine

the relevance of deficit pathology to seropositivity for BDV in 64 of these patients.

2. Methods

Sixty-four patients from an original cohort of 90 (Waltrip et al., 1995) who were assigned to deficit ($n=15$) or nondeficit ($n=49$) status are the subjects of this study. The deficit/nondeficit categorization was made using the Schedule of the Deficit Syndrome (SDS), an operationalized method of demonstrated reliability in this population (Kirkpatrick et al., 1989). The sample consisted of 49 (76.6%) males and 15 (23.4%) females and the race distribution was 41 (64.1%) white and 23 (35.9%) black, with a mean age of 35.4 (± 7.0) (see Table 1). The DSM-III-R (American Psychiatric Association, 1987) diagnostic evaluation was described previously (Waltrip et al., 1995). Age of onset defined as age of first psychotic symptoms, and age of first hospitalization were determined by interview of patient and available informants and review of all clinical records. Premorbid adjustment was assessed using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982). In addition to comparing the total deficit and non-deficit samples, a subset of nondeficit patients was selected from the total nondeficit population by matching on sex, race and as closely as possible on age while blind to anti-BDV serological status, to address the relationship between BDV seropositivity and deficit/nondeficit categorization independent of demographic effects.

The sera were stored at $-70°C$ until they were assayed in a Western blot utilizing proteins from BDV-infected and uninfected human neuroblastoma cells (SY5Y), and seropositivity was defined as sera that recognized two or more different BDV proteins (Waltrip et al., 1995). All Western blots were run with positive controls of BDV-infected rabbit serum and normal rabbit serum. Clinical and serum data were always collected independently (blind).

3. Results

Western blot revealed that five of 15 deficit and four of 49 nondeficit patients were seropositive (χ^2 with Yates correction $=4.11$, $p=0.04$) as defined by antibodies that recognize two or three different BDV proteins. There were no seropositives among the 15 sex-, race-, and age-matched nondeficit comparison patients (Fisher's exact $p<0.05$). We previously reported no seropositive subjects among the 20 normal controls, distinguishing the deficit patients from this cohort as well (Waltrip et al., 1995). Demographic results are presented in Table 1.

There were no significant differences in age of first psychotic symptoms, age of first hospitalization, duration of illness or differences in age-related premorbid functioning among nondeficit, seropositive deficit and seronegative deficit patient groups. For the number of hospitalizations, the means (SD, n) for the nondeficit patients, the seronegative deficit patients, and the seropositive deficit patients were 6.5 (10.17, 14), 4.22 (3.23, 9), and 2.00 (1.00, 5), respectively. The total duration of hospitalization to date means (SD, n), in weeks, were 77.36 (128.6, 14) for the nondeficit patients, 37.90 (32.88, 10) for the seronegative deficit patients, and 14.80 (16.16, 5) for the seropositive deficit patients. Although there was no difference among the groups for the number of hospitaliza-

Table 1
Demographics

	Sex (M/F)	Race (white/black)	Age, mean (SD)
64 patients	49/15	41/23	35.4 (7.0)
Deficit ($n=15$)	12/3	8/7	36.7 (7.9)
Matched nondeficit ($n=15$)	12/3	8/7	35 (5.6)
All nondeficit ($n=49$)	37/12	33/16	35.03 (6.7)
Matched subset			
BDV seropositive			
Deficit	4/1	1/4	38.79 (9.2)
Nondeficit	0	0	0
BDV seronegative			
Deficit	8/2	7/3	35.62 (7.5)
Nondeficit	12/3	8/7	35.0 (5.6)

tions ($F=0.72$, df=2,25, $p>0.05$) or total weeks of hospitalizations to date ($F=1.03$, df=2,26, $p>0.05$), there was a pattern of the means toward a lower value in the seropositive deficit patients, suggesting that institutional exposure is not related to BDV seropositivity.

4. Comment

Using well-characterized patients and a more stringent BDV serological test, we found a 14.4% rate of BDV seropositivity in schizophrenic patients and 0 in controls (Waltrip et al., 1995). We now report this finding to be associated with a defined subgroup of schizophrenia. The pathogenesis of BDV in the Lewis rat includes specific damage to the hippocampus (Carbone et al., 1991, 1996) and abnormalities in the dopamine system (Solbrig et al., 1994, 1996a,b). We noted above the bases for considering BDV as a candidate pathogen in schizophrenia.

In any disease leading to institutionalization, such as schizophrenia, association of the psychiatric condition with infection may be spuriously related to the amount of hospitalization. Our data suggest that we are not observing nosocomial but etiologically related infection by BDV because the tendency in our data is for seropositive subjects to have less hospital exposure than nonseropositive subjects. There are many other potential artifacts (e.g., neuroleptic drugs may alter neuronal structures and present antigens similar in structure to BDV or BDV infection may upregulate cellular proteins of the same molecular weight as BDV proteins that also bind antibodies), but the within-schizophrenia comparison is intended to reduce differences due to sampling artifact and the use of a two or greater BDV protein recognition criteria for seropositivity reduces the likelihood of antibodies being due to cross-reactivity. Also, there was no association between BDV serological status and particular neuroleptic, use of anticholinergics or neuroleptic dose in the parent cohort (Waltrip et al., 1995), making a neuroleptic-induced cross-reactivity phenomenon unlikely. Finally, matching procedures within schizophrenia reduce the likelihood that demographic differences account for these findings.

That an association between the deficit syndrome and anti-BDV seropositivity is of pathogenic significance is further strengthened by recent data showing that BDV does infect humans (Bode et al., 1996; de la Torre et al., 1996b). The major research question now with this interesting agent is what role it plays in human disease. Further research will determine to what extent BDV infection contributes to deficit pathology in schizophrenia.

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