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Detection of anti-Borna Disease Virus antibodies in patients hospitalized in psychiatric hospitals situated in the mid-western region of Poland

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The seroprevalence of anti-Borna Disease Virus antibodies in the population of patients hospitalised in psychiatric hospitals of mid-western Poland was assessed with the ECLIA method.

Key words: Borna Disease Virus, antibodies, psychiatric disorders

Introduction

According to the contemporary view, psychiatric disorders are caused by an interaction of genetically determined vulnerability with adverse psychosocial and biological environmental factors. Several recently published studies suggest the role of infections, particularly of viral origin, in the etiopathogenesis of psychiatric disorders [1, 2, 3].

Borna Disease Virus (BDV) is a single-stranded RNA virus, classified as a member of the recently created Bornaviridae family. BDV is highly neurotropic, spreads transsynaptically, replicates in the nucleus and is not cytopathic (does not cause the death

of neurons) [4, 5, 6, 7, 8, 9]. The virus may infect many warm-blooded animal species. Its replication may occur both in neurons and in peripheral blood mononuclear cells, despite the production of specific antibodies. In the endemic areas, BDV is a cause of encephalitis in horses and sheep. First reported epidemics of BDV-encephalitis in horses took place in the vicinity of Borna town in Saxony in 1920's, which gave the virus its name. In the experimental infections i.e. in rats- BDV may cause diverse behavioural symptoms and cognitive impairment [10, 11, 12, 13, 14, 15]. The behavioural presentation of animal infection such as apathy, withdrawal, psychomotor agitation and autoagressive behaviour, may in some cases resemble psychopathological symptoms of human psychiatric disorders, [16]. Because of that, the search of the BDV infection markers in psychiatric disorders has been initiated.

The hypothesis of the role of BDV in the etiopathogenesis of psychiatric disorders could be supported by the higher prevalence of anti-BDV antibodies in psychiatric patients than in healthy control subjects. Such an observation was reported for the first time by Amsterdam et al. [17] and Rott et al. [18] in 1985. The serological studies performed in other centres confirmed the initial reports, however they were limited by the lack of standardised method of the anti-BDV seropositivity assessment.

The detection of the BDV RNA in the blood of psychiatric patients [19, 20], isolation of the virus from the blood of patients with bipolar illness [21] and detection and isolation of the virus during the post-mortem study of brain tissue of schizophrenic patients [22] seem to confirm the role of BDV infection in the ethiopathogenesis of some psychiatric disorders. To date, the results of various studies do not indicate the role of BDV infection in specific diagnostic category, however, in the majority of studies the markers of BDV infection were more prevalent in patients with psychoses, anxiety disorders and some personality disorders [23, 24, 25].

The aim of present study was to the assess the prevalence of anti-BDV antibodies in patients hospitalised inpsychiatric hospitals of Wielkopolski and Lubuski regions, and to analyse whether the seropositive cases are specific for any diagnostic category. The comparison of seroprevalence of anti-BDV antibodies between psychiatric patients and healthy controls is the subject of another report.

Previous studies of anti-BDV seroprevalence showed substantial methodological problems. The initially used indirect immunofluorescence assay (IFA) was unspecific, and seropositivity assessment was made subjectively [24]. Subsequent studies using Western Blot method were more specific, however time – and work-consuming [26, 27]. In 1998 one of the authors (K.Y.) developed the ECLIA (Electrochemiluminescence Immunoassay) method which is characterised by a computer-based assessment of seropositivity and high efficiency, with high specificity [28]. The ECLIA method enables the detection of the two BDV proteins – p24 and p40.

In the present study, the ECLIA method was used to assess anti-BDV seropositivity in Polish psychiatric patients in the mid-western region of Poland. This region is situated in the distance of about 400km from the areas of the endemic farm animal infections (Borna town).

Material and methods

The patients group

The study included 946 patients hospitalised in psychiatric hospitals of Wielkopolski and Lubuski regions, located in Cibórz, Gniezno, Gorzów, Kościan, Międzyrzecz, Sokołowka, Złotow and patients from Psychiatric Departments of the University of Medical Sciences in Poznań. All subjects have signed the informed consent for the study, and the project was approved by the Ethical Committee of the University of Medical Sciences in Poznań. The participants were characterised by demographic variables. The diagnoses were made according to the ICD-10 criteria. Five ml of venous blood was drawn from every participant. All the procedures were performed in the year 1999.

Assessment of anti-BDV seropositivity

The blood was taken with no anti-coagulant and centrifuged. The sera were separated and frozen in temperature of -20C. The sera samples were coded and sent to the serological laboratory in Kumamoto, Japan. The assessment was done with the ECLIA method, described previously [28]. In short, the method is based on the placement of the two recombinant BDV proteins – p24 and p40 on the microbeads and incubating the microbeads with the analysed sera. Then, second monoclonal antibody – anti-IgG, with luminescent marker is used to detect anti-BDV in the analysed sera. The analysis of luminescence is performed in the automatic, computer-based way (ECLIA analyzer, Picolumi 8220, Sanko Junyaku, Tokyo, Japan). The laboratory staff was only aware of the code of every sample.

Results

The patients group consisted of 502 female and 444 male subjects. The mean age of women was 55; SD 15 (19-90), and men 52; SD 15 (19-85). The number of patients from each centre was presented in Table I. Generally, the anti-BDV seropositivity was detected in 23 of 946 patients, which gives the seroprevalence rate of 2.4%. Only anti-p24 antibodies were detected. The seroprevalence rate did not differ significantly in any centre participating in the study. In the sample studied no difference in seroprevalence rate between male and female subjects was observed. In the seropositive group we found 13 female and 10 male patients. The seropositive cases were detected in every age group. Seropositive cases were also found in individuals living both in urban and rural areas. The results are presented in Table 2. The anti-BDV antibodies were detected in patients with different diagnoses, according to ICD-10 criteria, which was shown in Table 3. No statistically significant differences in seropositivity rates between diagnostic categories were noticed. The comparison of clinical variables of seropositive and seronegative subjects of various diagnostic categories would be the subject of the separate publication.

Discussion

In the current study, for the first time, the presence of anti-BDV antibodies in Polish population of psychiatric patients was demonstrated. This observation supports the reports indicating, that BDV infections in humans are not restricted to the endemic areas of BDV encephalitis in horses and sheep. To date, anti-BDV antibodies were reported in American, German, Japanese and Chinese populations [17, 23, 29].

The detection of only anti-p24 antibodies may limit the conclusions of the study, however the results of the Japanese population assessment brought the same seropositivity pattern, and such a result may be associated with a lower sensitivity of the method towards anti-p40 antibodies and/or technical limitations of the method.

Previously reported seroprevalence rates in psychiatric patients ranged from 4.5% to 30%, depending on the method of assessment [17, 24, 26, 27]. However, in the study of Japanese population, using the ECLIA method, the seropositivity rates were similar to these observed in the Polish psychiatric patient population (schizophrenia – 3.08%; bipolar affective disorder – 3.59%). The above differences may result from the lower specificity of previously used assays. At the same time, we did not observe significant differences between centres participating in the current study, which suggest the similar prevalence of BDV infection in the region of Western Poland. Lack of statistically significant differences in seroprevalence rates between sexes is consistent with the results of previous assays [23, 24].

The serological studies performed in other populations of hospitalised psychiatric patients indicated, that anti-BDV antibodies are especially prevalent in younger people with psychiatric disorders, which suggest that BDV infections are not associated with institutionalisation [23]. In the current study we did not observe such an effect, and seropositive cases were present in all age groups.

Borna Disease Virus causes natural infections of horses and sheep. The increased anti-BDV seroprevalence in blood donors living in the proximity of horse stables, and in the veterinarians exposed to the infected animals may suggest the possibility of the zoonotic infection [29]. We did not observe the difference in seroprevalence rates between patients living in the urban and rural areas, which does not support the hypothesis of the animal origin of infections.

The casual relationship between the BDV infection, and the occurrence of psychiatric disorders has not been unequivocally established [30]. In some studies, several cases of BDV infection in healthy blood donors were reported, and BDV RNA was detected in the brain tissue of a neuropsychiatricaly healthy individual [31]. The comparison of anti-BDV seroprevalence rates in the Polish population of psychiatric patients and healthy blood donors will be performed in other publications. In the study of Japanese cohort, with the same serological methodology, the difference in seropositivity rates was about 2%. It indicates that a statistically significant difference between the groups is possible to observe only after the assessment of about 400 sex and age matched individuals without a psychiatric diagnosis.

German authors postulated the role of BDV in some cases of bipolar affective disorder [24]. This association may be confirmed by the isolation of the virus from the

individuals with the acute phase of this disease [21]. The efficacy of amantadine (antiviral drug) was reported in patients with affective disorders, who show the anti-BDV seropositivity [32]. The hypothesis on the main etiopathogenic role of Borna virus in some cases of bipolar affective disorders was put forward [33]. Other researchers proposed the etiological link between BDV and schizophrenia [34, 27]. Preliminary reports suggested the association between BDV infection and the deficit symptoms of this illness [35, 36]. In the current study we did not observe the relationship between anti-BDV seropositivity and any specific diagnostic category (ICD-10). This may suggest, that BDV infection is not causally associated with any psychiatric diagnosis. However, the results of the studies on the experimental animal infections showed, that behavioural symptoms of the BDV infection may be very diverse, depending on both the genetic and immunologic characteristics of the host [7, 9, 37].

Despite almost 20 years of research the causal relationship between the BDV infection and psychiatric disorders is not definitely proved [5, 38]. The first step in elucidating such a relationship should be based on the serological assays including a large number of patients and using highly specific methodology. The current study will be the beginning of further analyses of clinical and molecular variables, which shall be performed on BDV-seropositive psychiatric patients.

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TABLES

Table 1

Number of patients from each centre participating in the study, and number of anti-BDV seropositive subjects

Psychiatric hospital	No. of patients	No. of seropositive cases	Percentage of seropositive cases
Gdańsk	284	6	2.1%
Gniezno	60	1	1.7%
Gorzów	171	5	2.9%
Kościan	41	1	2.4%
Międzyrzecz	158	5	3.2%
Szczecinek	87	1	1.1%
Złotów	60	1	1.7%
Poznań	85	3	3.5%
TOTAL	946	23	2.4%

Tabela 2

Seropositivity rates in patients with different age, sex and place of residence

Sex	Female		Male	
	13,502 = 2.6%		10444 = 2.4%	
Place of residence	Rural area		Urban area	
	12,804 = 3.0%		11552 = 2.0%	
Age group	<40 years	40-59 years	>60 years	
	5,470 = 2.2%	7,480 = 1.7%	11,347 = 3.2%	

Tabela 3

Number of seropositive subjects in different diagnostic categories (ICD-10)

Diagnostic category	Seropositive cases, number of subjects	Percentage of seropositive subjects
Organic mental disorders	1/57	1.8%
Substance related disorders	0/15	0%
Schizophrenia	13/617	2.1%
Delusional disorders	0/26	0%
Schizoaffective disorders	0/31	0%
Bipolar affective disorders	3/90	3.3%
Recurrent depression	2/34	5.9%
Anxiety disorders	2/34	5.9%
Personality disorders	0/10	0%
Mental retardation	2/32	6.2%

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