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Original Article

Risk of *Borna Disease Virus* among Asian Psychiatric Patients : A Systematic Review and Meta-Analysis

Alireza Mohebbi[1,2,3,*], Mohammad Yasaghi[1], Zoleikha Mamizadeh[4], Ali Salehnia[1], Nazanin Lorestani[1], Alijan Tabarraei[3]

1. Student Research Committee, School of Medicine, Golestan University of Medical Sciences, Gorgan, Iran.
2. Stem cell research center, Golestan University of Medical Sciences, Gorgan, Iran.
3. Department of Microbiology, School of Medicine, Golestan University of Medical Sciences, Gorgan, Iran.
4. Department of Microbiology, Faculty of Advanced Sciences, Islamic Azad University, Tehran, Iran.

Abstract

Background and Aims: The impact of *Borna Disease virus* (BDV) in Asian psychiatric patients remains to be clear. Epidemiological studies would help to understand the rate of BDV incidence among different groups of patients with psychiatric disorders.

Objectives: A systematic review and meta-analysis on risk of BDV among Asian psychiatric patients.

Materials and Methods: Literature review was performed on the BDV prevalence in Asia. Data, including both subjects' characteristics and the epidemiology of the virus have been extracted and used for further meta-analysis on genomic and serological data. Odd ratio (OR) has been estimated by using comprehensive meta-analysis software V2. In this regard, I2 and Cochran's Q-value have been evaluated for heterogeneity. Odds ratio (OR) has been investigated by the confidence interval (CI) of 95%. The Funnel plot and Egger's and Begg's statistics were used for evaluating the publication bias. P-value less than 0.05 considered as significant.

Results: Data revealed higher incidence of BDV RNA (5.902 95% CI, 3.97-8.775) in psychiatric patients. Odd ratio was also higher in seropositive patients in comparison with control group (2.334 95% CI, 1.829-2.952). It was also found that ELISA and western-blot methods might over-estimate BDV existence in patients and cause heterogeneity.

Conclusions: High prevalence of BDV in psychiatric patients was found in Asia. Furthermore, the results obtained by ELISA and western blot are not reliable enough, which might be resulted from cross-reactive or closely related antibodies in human body fluids.

Keywords: Borna Disease Virus, Systematic review and meta-analysis, Comprehensive Meta-Analysis, Psychiatric Disorders, Schizophrenia, Bipolar disorder.

Introduction

Borna disease virus (BDV) is an enveloped, single-stranded, non-segmented RNA virus with negative polarity belonging to the family of Bornaviridae. BDV is widely spread, severely neurotropic, and non-cytolytic. The virus is an etiological agent of the central nervous system (CNS) diseases such as fatal encephalitis in several vertebrate's species, including horses, sheep, cats, and ostrich (1). It is suggested that BDV may be transmitted through the nose, saliva, and conjunctival secretions (2).

Depending on the age, immunity conditions, and the host species, the virus causes CNS disorders with diverse manifestations (3).

For example, BDV causes severe immune responses in infected brain cells of rats or induces persistent infection with cognitive disorders in newborn rats (4). As in animal models, the brain complications followed by psychiatric and neurological symptoms have been observed in men. Therefore, transmission

[*] **Corresponding author:** Alireza Mohebbi
E-mail: Mohebbi-a@goums.ac.ir
Tel: +98 935 467 4593
Fax: +98 1732325581.

of the virus through infected animals to humans is also possible (2). Behavioral health studies in animals infected with BDV led to the idea that BDV infection in humans may be related to psychiatric illnesses such as mood and psychoses (5). Epidemiological studies using peripheral-blood mononuclear cells (PBMC) and brain tissues have shown that BDV can infect human and may be associated with neuropsychiatric disorders (6).

There are several studies, in which BDV genome has been found in patients with psychiatric disorders (4,5). As there is evidence of the virus presence in healthy blood donors, the etiological role of the virus in the patients remains controversial (6,7). This is because of some reports on no the absence of BDV genome and specific antibodies in patients with cognitive illnesses (8–11). BDV genome (P24, P40) has been detected in PBMCs, brain tissues, and CSF by PCR (reverse transcriptase-PCR, nested RT-PCR, QF-PCR, and real time-PCR) methods. Xu et al have identified P24 sequence in 9.7% of patients with schizophrenia by RT-PCR (12).

In schizophrenic patients, the presence of antibodies against BDV antigens have been identified. Accordingly, Waltrip et al have shown 14.4% of schizophrenic patients who had antibodies against BDV (7). There is a possible relationship between BDV and affective diseases such as unipolar and bipolar disorders, as well as major depression (8). Amesterdam and colleagues have shown BDV antibodies in 4.5% of patients with affective disorders (9). By measuring antibodies against BDV in three innings of patients with major depression admitted to the hospital, Bode et al. has reached the positive result of 20% (13). Therefore, serological studies show more evidence of virus existence than genomics' (1–3), which is unclear whether this is because of hit-and-run property of the virus or existence of cross-reacting antibodies in the patients' body fluids.

Based on the importance of mental disorders and their impact on the quality of life of patients and their families, extensive research into the cause(s) of psychoses, subsequent prevention and treatment are crucial. In the present study, we looked into the BDV risk ratio for psychiatric patients and the most common genomic and serologic methods by which researchers have identified BDV evidences. For that, a meta-analysis has been done on published and unpublished (gray) data corresponding to the patients and control subjects in Asia. Our results have clearly implicated significantly higher risk of BDV infection in patients with psychosis disorders. It also identified that results of serological methods are not reliable enough to be trusted.

Methods

Search strategy and data clustering. To search for BDV prevalence in Asian countries, we have searched two PubMed and Google-Scholar scientific databases. For PubMed, keyword is as follows: “Borna Disease Virus” in the title and subsequently results have filtered through the “Epidemiology”. Last modification was done by switching data on Human subject/species. At the GoogleScholar, we have searched for the term of “Borna Disease Virus” exact phrase, plus “psychiatric disorder”. Data retrieved in any years and subjected for further evaluation .

Inclusion and exclusion criteria. Articles with no English abstract were discarded. Additionally, studies representing experiments on psychiatric or control subjects in any countries but Asia have also been rejected.

Grey studies or unpublished works were also included from our Department or other databases.

Quality assessment. After retrieving, the abstract of each study was screened and checked for illegibility. Then, text was read and data extracted by two authors. If there were any conflicts in articles’ data or materials, it was judged by the third author. Literatures were searched for the authors' names, country where the study has been performed, year of publication, number of patients and control subjects, gender, mean age, sampling, and type of method(s) of BDV detection in both case and control groups. Data are also provided in Table1.

Table 1 Data and characteristics of studies on *Borna Disease Virus* from two case- and control-based literatures.

ID	Authors	Country	Year	Method of Analysis[a]	Type of Sample	Patients	No. of patients	Gender		Age (Mean±S.D)	BDV RNA	BDV Antibody	No. of Healthy Controls	Gender		Age (Mean±S.D)	BDV RNA	BDV Antibody	Reference
								Male	Female					Male	Female				
1	Haga, et al	Japan	1997	Genomic	Brain tissue	Na[b]	Na	Na	Na	Na	Na	Na	30	23	7	52.8± 18.77	2	Na	(Haga et al., 1997)
2	Kishi, et al	Japan	1995	Genomic Serologic	PBMC/Serum	Psychiatrics	60	35	25	55.68± 9.56	22	18	Na	Na	Na	Na	Na	Na	(Kishi et al., 1995b)
3	Nakaya, et al[a,b]	Japan	1996	Genomic	Brain Tumor	Na	Na	Na	Na	Na	Na	Na	37	20	17	35.59 ±22.03	5	Na	(NAKAYA et al., 1996)
4	Nakaya, et al	Japan	1996	Genomic Serologic	PBMC	Psychiatrics	25	15	10	32.04± 10.05	3	6	Na	Na	Na	Na	Na	Na	(Nakaya et al., 1996)
5	Zhang, et al	China	2013	Genomic	PBMC	Psychiatrics	806	473	333	40.76± 10.74	50	23	873	486	387	41±12 .42	6	0	(Zhang et al., 2014)
6	Fukuda, et al	Japan	2001	Genomic Serologic	PBMC/Plasma	Psychiatrics	90	46	44	46	1	6	45	22	23	48	0	1	(Fukuda et al., 2001)
7	Iwahashi, et al	Japan	1998	Genomic Serologic	PBMC	Psychiatric	67	48	19	49.8±10.0	6	24	31	16	15	Na	1	0	(Iwahashi et al., 1998)

8	Horimoto, et al	Japan	1997	Serologic	Plasma	Psychiatrics	70	Na	Na	Na	Na	15	40	Na	Na	Na	Na	0	(Horimoto et al., 1997)
9	Iwata, et al	Japan	1998	Genomic	PBMC	Psychiatrics	126	70	56	46.5±1.48	5	Na	84	49	35	45.2	0	Na	(Iwata et al., 1998)
10	Nakamura, et al	Japan	2000	Genomic Serologic	Brain tissue/Serum/CSF	Psychiatrics	4	2	2	32±6.06	1	1	2	1	1	20±2.88	0	0	(Nakamura et al., 2000)
11	Li, et al	Japan	2009	Genomic Serologic	PBMC	Psychiatrics	65	37	28	42±9	6	6	46	28	18	37±11.53	0	Na	(Li et al., 2009)
12	Iwahashi, et al	Japan	1997	Genomic Serologic	Whole Blood/Plasma	Psychiatrics	67	Na	Na	49.25±10.95	6	24	26	Na	Na	45.8±8.7	0	0	(Iwahashi et al., 1997)
13	Kishi, et al	Japan	1995	Genomic Serologic	PBMC	Na	Na	Na	Na	Na	Na	Na	172	112	60	37.1±1.13	8	1	(Kishi et al., 1995a)
14	Kim, et al	Korea	1999	Genomic	PBMC	Psychiatrics	81	Na	Na	36.4±7.4	0	0	Na	Na	Na	Na	Na	Na	(Kim et al., 1999)
15	Chen, et al	Taiwan	1999	Genomic	PBMC	Psychiatrics	74	40	34	40	11	Na	114	45	69	42.5±10.61	8	Na	(Chen et al., 1999a)
16	Fujiwara, et al	Japan	1997	Genomic	PBMC	Psychiatrics	85	Na	Na	Na	25	Na	172	Na	Na	Na	8	Na	(Fujiwara et al., 1997)

17	Sae Na, et al	Korea	2009	Genomic	PBMC	Psychiatrics	198	83	115	32.60±10.44	0	Na	60	60	32	18.09±15	0	Na	(Na et al., 2009)
18	Flower, et al	Australia	2008	Serologic	Plasma	Psychiatrics	104	Na	Na	Na	Na	5	643	Na	Na	Na	Na	22	(Flower et al., 2008)
19	Mazaheri, et al	Iran	2014	Serologic	Plasma	Psychiatrics	114	62	52	37.42+1.103	Na	46	200	111	89	35.505±6.575	Na	59	(Mazaheri-Tehrani et al., 2014)
20	Yamaguchi, et al	Japan	1999	Serologic	Serum	Psychiatrics[c]	2345	1287	1058	52.63±16.88	Na	42	2528	1345	1251	47.02±12.65	Na	33	(Yamaguchi et al., 1999)
21	Chen, et al	Taiwan	1999	Serologic	Plasma	Psychiatrics	314	182	132	40	Na	38	491	216	275	39.33	Na	32	(Chen et al., 1999b)
22	Matsunaga, et al	Japan	2005	Serologic	Serum	Psychiatrics	171	53	118	44.1±15.8	Na	26	50	23	27	42.85±15.51	Na	1	(Matsunaga et al., 2005)
23	Terayama, et al	Japan	2003	Serologic	Serum	Psychiatrics	65	34	31	49.2±10.73	Na	16	25	11	17	46.8±10.2	Na	1	(Terayama et al., 2003)
24	Seyedi, et al	Iran	2015	Genomic	Serum	Psychiatric	30	Na	Na	36.03±11.28	8	Na	15	Na	Na	31.86±10.61	0	Na	(Seyedi et al., 2015)
25	Arab, et al	Iran	2016	Genomic	Plasma	Psychiatric	125	68	57	36.82±10.958	0	Na	125	68	57	38±13.765	0	Na	d
26	Mohammadi Manesh, et al	Iran	2016	Genomic	Plasma	Psychiatric	125	81	44	Na	1	Na	125	77	48	Na	0	Na	(Mohammadi Manesh et al., 2017)
27	Shatizadeh-Malekshahi, et al	Iran	2017	Genomic	PBMC	Psychiatric	120	78	42	35.91±10.77	1	Na	75	48	27	35.59±10.74	2	Na	(Shatizadeh-Malekshahi et al., 2017)

[a] Genomic studies are those which have used nested RT-PCR, Reverse Transcriptase, and quantitative Real-Time PCR, and Serologic studies are those which have used methods like ELISA, SA-ELISA, Western Blot, Immunofluorescence assay, and etc.
[b] Not applicable
[c] Patients with HIV infection (including AIDS), Alcohol addiction, Encephalitis, Degenerative diseases, Epilepsy, Autoimmune diseases, Leprosy, Multitransfused, and Ocular diseases did not consider as psychiatric patients.
[d] Unpublished data

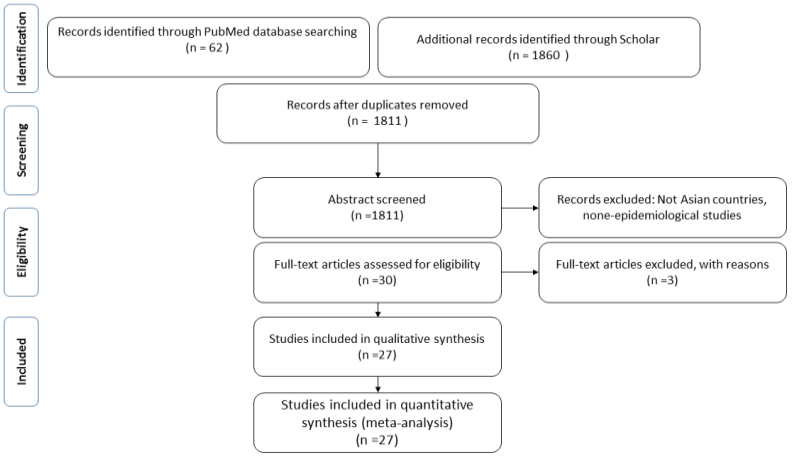

Fig. 1. PRISMA diagram, indicating the database search and eligibilities.

Data analysis. Meta-analysis has been performed by using the Comprehensive Meta-analysis Software V2 (14). Effect size data entry format was sat as two unmatched groups, representing events and non-events in each category. This made us able to compare the rate of evidence of the virus in two independent psychiatrics and control subjects. I2 and Cochran's Q-value were evaluated for heterogeneity. I2 more than 25% was implicated heterogeneity. Odds ratio (OR) was investigated with the confidence interval (CI) of 95%. Publication bias has also been esti-mated through funnel plot and two Egger's and Begg's statistics. P-value less than 0.05 is considered as significant.

Results

Data retrieval. After data retrieval, studies were divided into two genomic and antigen-antibody categories. Genomic and antigen-antibody studies are those that examined BDV RNA and antibodies, respectively. We also came to the idea that some studies with matched countries need to be merged for completing both patients and control groups. It was thought that combination of two studies focusing on patient or control groups would not affect the outcome. Furthermore, two studies performed on brain tissues of healthy people were discarded (15,16) because of no history of psychiatric disorders in patients. Accordingly, one paper from Thailand on HIV-positive patients did not meet our criteria; therefore, it was also excluded (12) (Fig.1).

Category one: Meta-analysis of BDV genomic data. After data retrieving and clustering, seventeen studies were matched with our criteria and incorporated for genomic-based meta-analysis. Of those, nine (52.94%) were from Japan, four from Iran (23.53%), two from South Korea (11.76%), one from China (5.88%), and one from Taiwan (5.88%).

As mentioned before, two studies performed by Kishi et al. and Nakaya et al. in Japan have merged together, filling the control groups' missing data (17,18). In addition, two other studies by Na et al. and Kim et al. that were conducted in South Korea were combined into one to have both case and control groups. Those merged studies were also checked for diagnosis methods to be identical. The authors have come to this idea that combination of data from countries working on a single population separately would not affect the outcome.

In this category, no heterogeneity was observed (Q=14.623 df(12), I2=17.936, tau-squared=0.13, p-value > 0.05). For this, fixed effect size was used for the analysis of the odd ratio (OR). As illustrated in Fig.2, fixed model meta-analysis of BDV RNA risk for psychosis was more than 5-fold higher than that for control group (5.902, 95%CI, 3.97-8.775, p<0.0001). The average OR was 6.5661± 5.994.

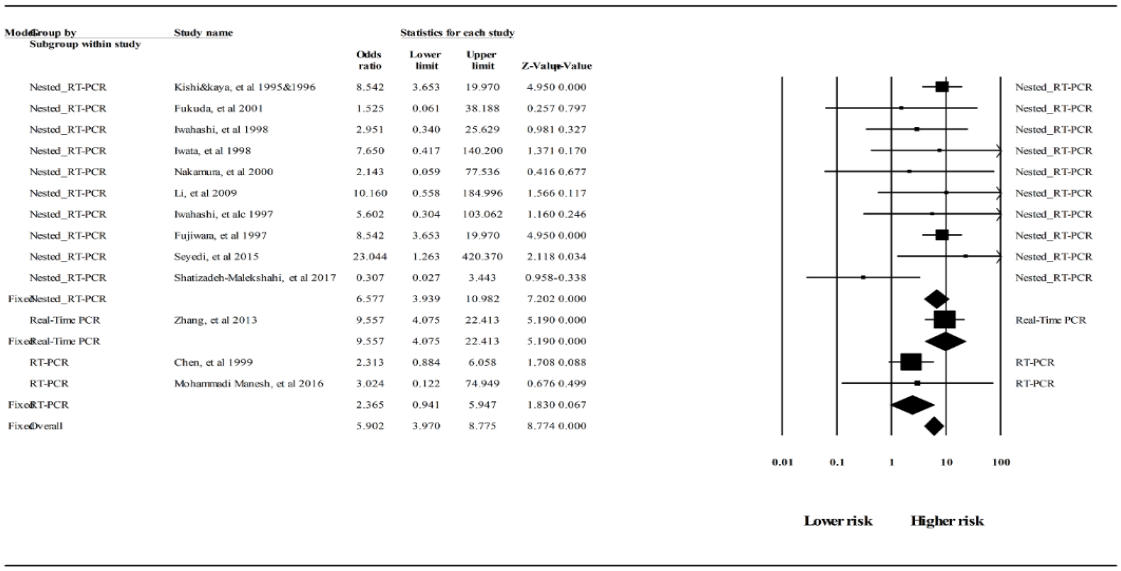

Fig. 2. Risk ratio of BDV RNA in patients with psychiatric disorders in comparison with the control group.

Further analysis was performed on the frequency of BDV RNA among patients and healthy subjects in Asian countries (Fig.3a). Results showed significant prevalence of the viral genome (p40 or p24) in patients (t-value<0.01, Fig.3b).

Two studies have recently been performed by our group (Arab, et al 2016 and Mohammadi Manesh, et al. 2016) on 500 subjects, including 250 psychiatric and 250 blood donors in Center and North of Iran were consistent with studies in South Korea, which did not find any significant BDV RNA in subjects (10,19–21).

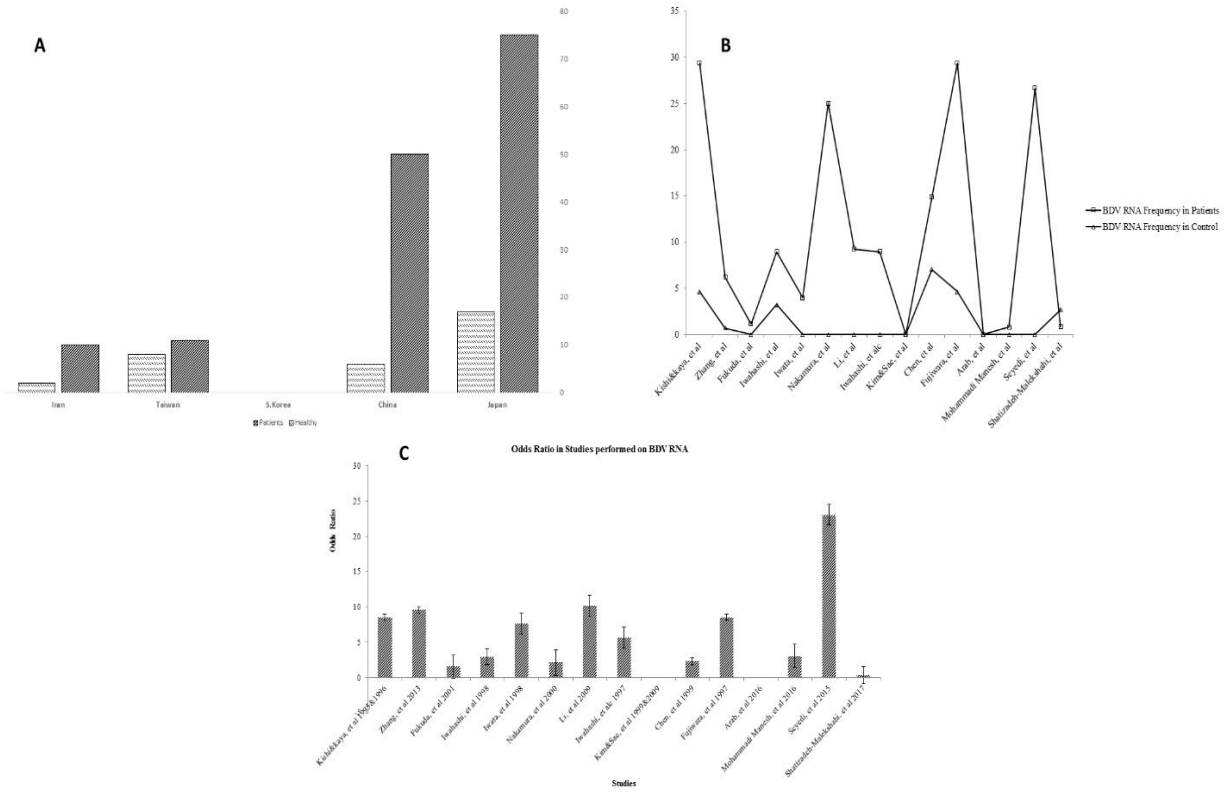

Fig. 3. BDV RNA Status. a) Total BDV RNA Frequency in Asian Countries, b) BDV RNA Frequency in Patients and Control, and c) Odds Ratio in Studies performed on BDV RNA.

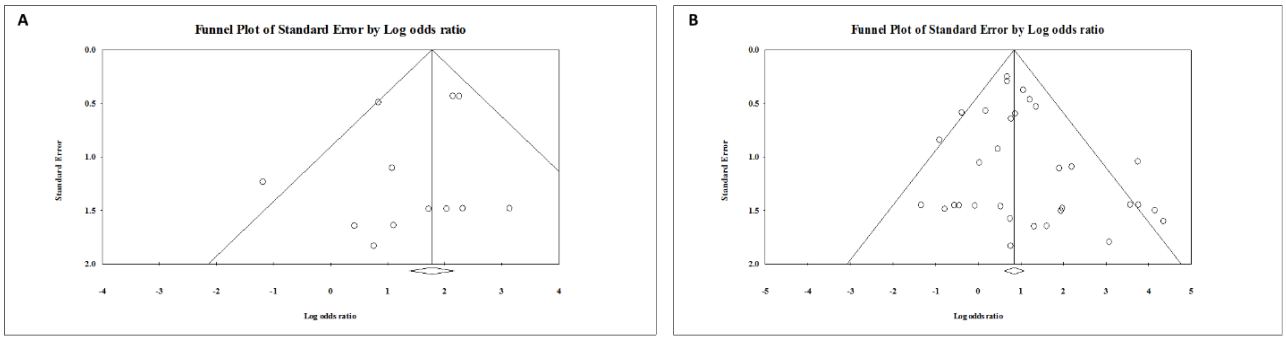

Fig. 4. Funnel plots of standard error by log odds ratio. a) in Genomic category and b) in Serological category.

Also, Seyedi, et al 2015 have found prevalent BDV RNA in schizophrenic patients in just a small size population (22). Accordingly, as it is shown in Fig.3b&c, Taiwan, Japan, China, and Iran with 10%, 8%, 3, and 2% viral RNA frequency, respectively, were at higher risk of BDV infection. Totally, Japan, among others, with mean OR of 5.9±3.32 was the most at risk country for the virus infection (Fig. 6&7).

Publication bias has not been observed as shown in Fig.4a, and studies were relatively well distributed. Additionally, Begg's and Egger's tests were not significant (1.19 df(11), p>0.05), suggesting no publication bias.

As it is shown in fig.2, the method of each study was used for subgroup analysis. Three methods, including nested reverse-transcriptase PCR (n=11), real-time PCR (n=1), and reverse-transcriptase PCR (RT-PCR) (n=3) have been used. No heterogeneity was found within these groups. For nested RT-PCR, the OR estimated point was 6.577 (lower limit to upper limit of 3.939-10.982) (Q=9.420 df(9), I2=4.46, p-value<0.0001). No statisticalFor real-time PCR group, the OR was 9.557 (4.075-22.413) (Q=0 df(0), I2=0.0, p-value<0.0001). Finally, the OR for RT-PCR was 2.365 (0.941-5.947) (Q=0.025 df(1), I2=0.0, p-value=0.067).

Category two: meta-analysis of BDV serological data

Sixteen papers examining anti-BDV antibody have met the criteria for study. Two studies with partial missing of serological data performed by Li et al. (5) and Kim et al. (10) in Japan (2009) and South Korea (1999), respectively, have discarded. Of 14 studies on anti-BDV antibody, 10 (71.43%) were from Japan, one (7.14%) from Australia, one (7.14%) from Taiwan, one from China (7.1%), and one (7.14%) study from Iran.

Heterogeneity has been found within these studies (Q=49.46 df(31), I2=37.324, tau-squared=0.31, p-value=0.019), so random size model was used for further meta-analysis. Fig. 5 shows anti-BDV antibody OR among two patients and control subjects. Results indicated more than 2-fold higher OR in patients (2.574, 95%CI, 1.776-3.729, p<0.0001).

The frequency of anti-BDV antibody was evaluated based on literatures. Differences between antibodies in patients and control subjects were significant (t-value < 0.0001; Fig. 6b).As it is illustrated in Fig. 6a, the rate of anti-BDV antibody was higher in Iran (33.44%) than Taiwan (8.7%), China (5.72%), Japan (5.09%), and Australia (3.61%).

However, the OR was as high as 21.04±1.16 in Japan, 17.44±1.43 in China, and other countries with less than 2-fold (Fig. 5 and Fig. 6c).

Publication bias has also been evaluated as mentioned above. Results show no normal distribution of data (Fig.4b). Furthermore, Begg's and Egger's statistics were significant (1.47 df(30) p<0.0001), indicating publication bias.

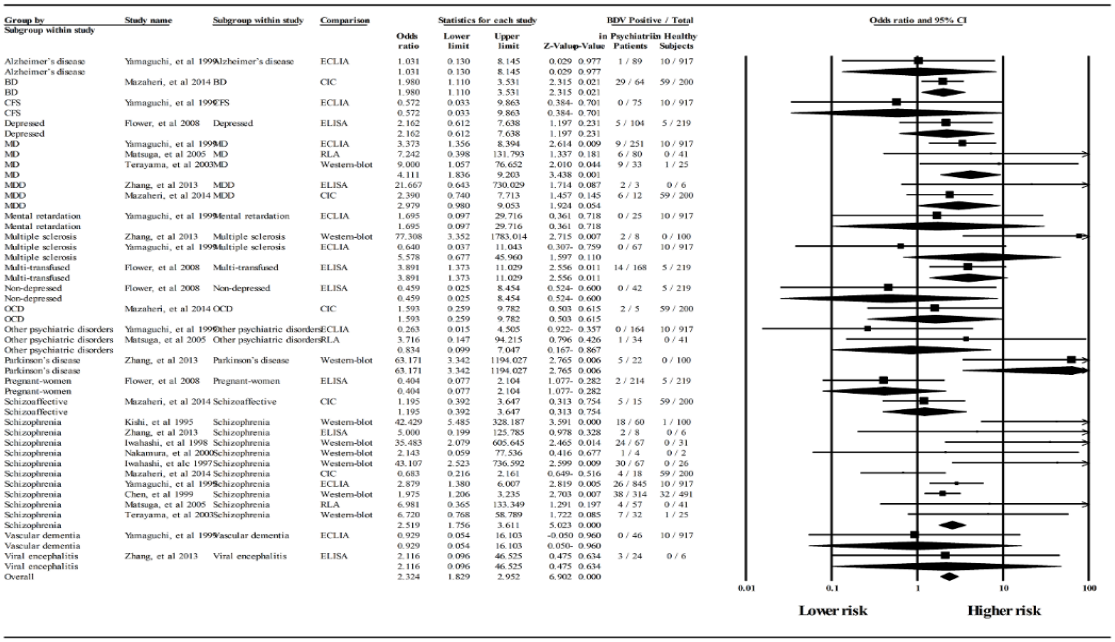

Fig. 5. Odd ratio of anti-BDV antibody between psychiatrics and controls.

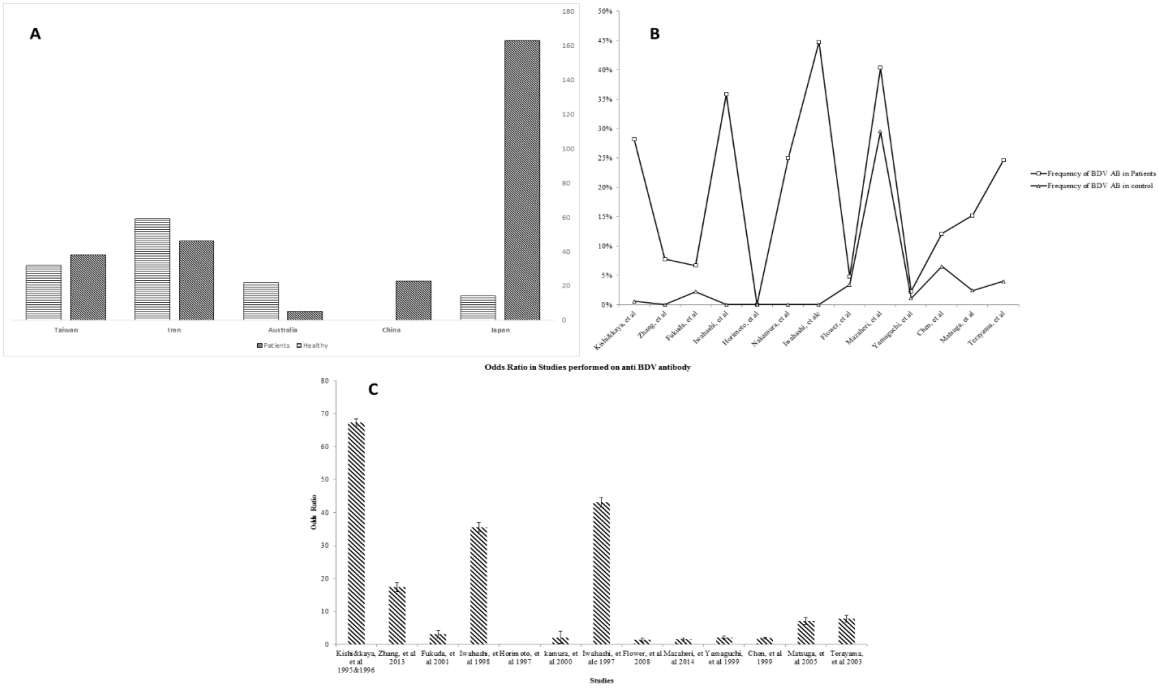

Fig. 6. Statues of anti-BDV antibody. a) Total anti-BDV antibody Frequency in Asian Countries, b) anti-BDVantibody Frequency in Patients and Control, and c) Odds Ratio in Studies performed on anti-BDVantibody.

To answer heterogeneity, two subgroups were used for identifying the reason of hetero-geneity. The subgroups were the methods of used for each study and group(s) of patients. The methods were CIC, ECLIA, ELISA, RLA, and western-blot. ELISA with OR of 2.169 (1.124-4.185) (Q=8.187 df(6), I2=26.713, p-value<0.05) and western-blot with OR of 3.371 (2.185-5.2) (Q=25.044 df(8), I2=68.056, p-value<0.0001) had heterogeneity. Other methods were homogenous. For CIC OR was 1.615 (1.057-2.466) (Q=3.332 df(4), I2=0.0, p-value<0.05). For ECLIA the OR was 2.266 (1.366-3.759) (Q=5.974 df(7), I2=0.0, p-value<0.01).

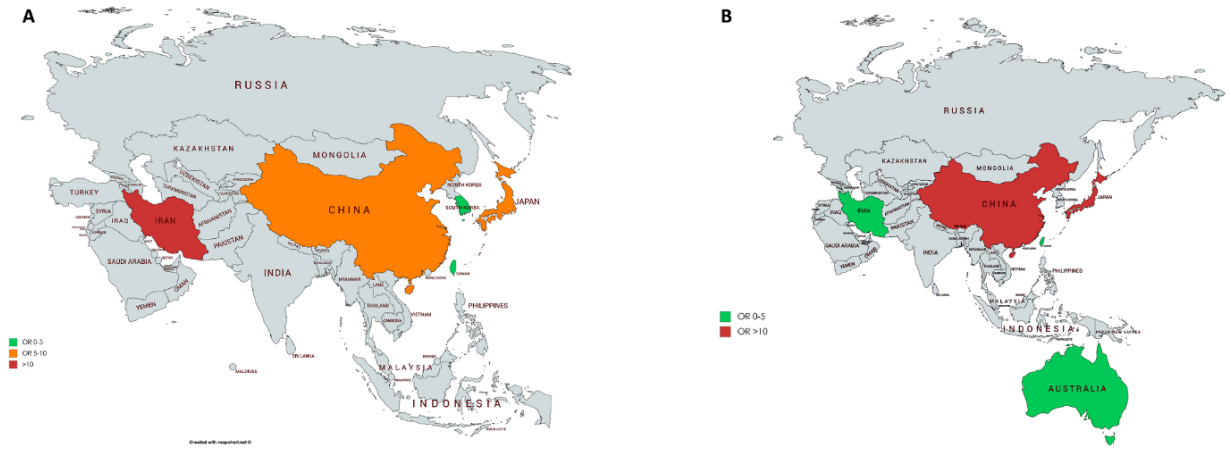

Fig. 7. BDV distribution map. a) shows BDV RNA prevalence and b) illustrates anti-BDV antibodies in Asian countries. MapChart online server (http://www.Mapchart.net) was used for this graphical presentation.

Table 2. The patients' groups and their statistics.

Groups	OR	Lower limit	Upper limit	Q	df	I2	p-value
Alzheimer's disease	1.031	0.13	8.145	0.0	0	0	>0.05
Bipolar disorder (BD)	1.980	1.11	3.531	0	0	0	<0.05
Chronic fatigue syndrome (CFS)	0.572	0.033	9.863	0	0	0	>0.05
Depression	2.162	0.612	7.638	0	0	0	>0.05
Major depression	4.111	1.836	9.203	0.841	2	0	=0.001
Major depressive disorder (MDD)	2.979	0.980	9.053	1.358	1	26.382	=0.054
Mental retardation	1.695	0.097	29.716	0	0	0	>0.05
Multiple sclerosis	5.578	0.677	45.960	4.916	1	79.656	>0.05
Multi-transfuse	3.891	1.373	11.029	0	0	0	<0.05
Non-depressed	0.459	0.025	8.454	0	0	0	>0.05
Obsessive-Compulsive Disorder (OCD)cc	1.593	0.259	9.782	0	0	0	>0.05
Other psychiatric diseases	0.834	0.099	7.047	1.455	1	31.294	>0.05
Parkinson's disease	63.171	3.342	1194.027	0	0	0	<0.01
Pregnant woman	0.404	0.077	2.104	0	0	0	>0.05
Schizoaffective	1.195	0.392	3.647	0	0	0	>0.05
Schizophrenia	2.519	1.756	3.611	21.925	9	58.951	<0.0001
Vascular dementia	0.929	0.054	16.103	0	0	0	>0.05
Viral encephalitis	2.116	0.096	46.525	0	0	0	>0.05

Finally, OR estimated point for RLA method was 5.890 (1.031-33.638) (Q=0.110 df(2), I2=0.0, p-value<0.05).

The second subgroup was patients' groups.

In that case, three groups, including Major Depression Disorder (MDD), Multiple Sclerosis (MS), and Schizophrenia were heterogeneous.

Table 2 shows statistics of each groups.

Discussion

In the total of studies, two genomic (16/27) and serological (14/27) categories have been chosen for meta-analysis. In the first category, OR of BDV RNA in patients and control has been assessed. There was no discrimination between p24 and p40, and both were assumed as a marker for BDV genome positivity. The

result showed more than 5-fold higher risk of viral infection within the case group. The lower OR was for the study of (23) with the OR of 0.307, and goes to as high as 23.044 in the study of (22) (Fig.2). This can be addressed to significant higher BDV genome prevalence (t-value<0.01, Fig.3) among patients than controls. Nested RT-PCR is frequently used for BDV genome detection. However, this method is prone to false-positive results due to artifact genome templates and cross-contamination in the laboratory where animal/human samples are commonly worked (24). It can be addressed to the works, in which BDV is detected for the first time with no previous history of animal experiments, as studies performed by Arab, et al and Mohammadi Manesh, et al in our lab. In another molecular study done by Seyedi, et al the same criteria are stated (22). Accordingly, method for each study was retrieved and used as subgroup analysis. No heterogeneity was found between three different nested RT-PCR, real-time PCR, and RT-PCR. The ORs for nested RT-PCR was 6.577, for real-time PCR was 9.557, and for RT-PCR was 2.365.

In the serological category, more than 2-fold higher risk of virus infection was found in patients (Fig.5). In the study performed by Zhang et al. on a large group of patients (25), OR has been estimated as high as 52.399 (P<0.006). Meanwhile, lower risk was for studies performed by Yamaguchi et al, Mazaheri et al, Chen et al, and Nakamura et al, with OR of less than 3 (1,26–29). The size of OR in the serological categories in comparison with that of genomic category, suggests earlier infection of patients/control subjects with the virus. However, publication bias has been observed in serological studies. This may be attributed to different sample sizes, patients' groups, and variety of methods, which have been used for serological examinations. Accordingly, different serological methods have no identical sensitivity as RT-PCR does (24), which we were tough that led to publication bias. In this regard, we performed subgroup analysis for both "groups of patients" and "methods of use". Eighteen different patients groups were obtained from serological studies. Of which, data from MDD, Multiple sclerosis, and schizophrenia were heterogeneous. In the subgroup of methods, two ELISA and western-blot found to have heterogeneity. Accordingly, From 2 studies on MDD with two ELISA and CIC methods, the OR estimated points for ELISA and CIC were 21.667 and 2.390, respectively (Fig.5). The OR for western-blot and ECLIA were 77.308 and 0.640, respectively. From 10 studies on schizophrenic patients, 6 studies have been used western-blot, 1 ELISA, 1 CIC, 1 ECLIA, and 1 RLA. The average OR for western blot was 21.98±20.36. Four other methods had the OR estimated point less than 5. This data clearly indicates that the bias observed in serological category is related to the methods of use. In addition, the heterogeneity observed among patients groups can be attributed to the methods of use. Here two methods ELISA and western-blot are shown to have over-estimated results for BDV detection.

The result has also revealed high proportions of anti-BDV antibody in Chinese psychiatric patients (Fig.6). As a Middle East country, Iran has a higher rate of circulating anti-BDV immune complex in both case and control groups. This can encourage other neighbor countries to evaluate BDV status in the psychiatric patients and healthy control groups (Fig.7a and 7b).

Higher OR of BDV antibody than that of anti-BDV genome can be a result of primary infection with the virus and subsequent neurological damage, which goes down after antibody production. Another explanation may reflect the specificity and sensitivity of molecular and serological tests. It was also evaluated that anti-BDV antibody is always higher than BDV RNA, implicating history of viral infection, which also suggests the absence of genome is not enough and not a good measure for viral infection analysis. Accordingly, there was also a positive correlation of 0.21 and 0.20 of viral RNA and antibody frequency in psychiatric patients and control groups, respectively.

The results of present study represent high OR of BDV infection in psychiatric patients. However, other factors like sex differences,

genetic heredity, etc. might be involved (30). There are two meta-analysis studies, one reports no evidence of BDV in psychiatric disorder and human illnesses based on the virus sequences (31), and another reports BDV as an etiological factor for virus-induced human depression (32). As mentioned in the former study (31), laboratory contamination may result in false positive results. By considering high-risk ratio of BDV for psychosis in Asia, development of novel screening methods is warranted.

Conclusion

It can be concluded that BDV infection is prevalent among psychiatric patients in Asia. Furthermore, the results from serological methods like ELISA and western-blot are not reliable. This might be resulted from cross-reactive or closely related antibodies in human body fluids, which implicates the urgent need of novel screening methods in countries with higher incidence of viral infection. Further investigations are also needed for fulfilling the gaps of studies in other Asian countries. For example, the data were from six countries of Japan, China, Iran, Australia, Taiwan, and South Korea, while there are other countries with unique geographical area that have not provided data.

Abbreviations

BDV: Borna Disease Virus, OR: Odd Ratio, CNS: Central Nervous System, PBMC: Peripheral Blood Mononuclear Cell, RT-PCR: Reverse Transcriptase Polymerase Chain Reaction, HIV: Human Immunodeficiency Virus

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Conflict of interests

The authors declare that they have no competing interests.

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