The Association Between Borna Disease Virus and Chronic Fatigue Syndrome: A Systematic Review and Meta-Analysis

Milad Azami,[1] Mohammad Reza Adhami Mojarad,[2] Akram Mansouri,[3] and Zainab Tardeh[1,*]

[1]Faculty of Medicine, Ilam University of Medical Sciences, Ilam, IR Iran
[2]Department of Infectious Diseases, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, IR Iran
[3]School of Nursing and Midwifery, Ahvaz Jundishapour University of Medical Sciences, Ahvaz, IR Iran

[*]*Corresponding author*: Zainab Tardeh, Student Research Committee, Ilam University of Medical Sciences, Ilam, IR Iran. Tel: +98-9337416255, E-mail: z.tardeh@gmail.com

Abstract

Context: Several studies have controversial results regarding the association between Borna disease virus (BDV) and chronic fatigue syndrome (CFS). The present systematic review and meta-analysis investigated the association between CFS and BDV.

Evidence Acquisition: The present study was conducted based on the PRISMA guidelines for systematic review and meta-analysis studies. To avoid bias, all procedures of the study were performed by two researchers independently. A comprehensive search was performed using online databases, including PubMed, Scopus, Embase, PsycINFO, science Direct, Cochrane Library, web of science, and Google scholar using the MeSH keywords until December 12th, 2016. Heterogeneity among studies was evaluated using Cochran's Q test I^2 Index. Finally, the random effect model was used for combined Odds Ratio (OR) using Review Manger software version 5.3.5.

Results: Among 9 eligible studies comprising 610 cases and 2176 controls, the total OR for association between BDV and CFS was estimated to be 10.41 (95% confidence interval [CI]: 4.24 - 25.55, P < 0.0001). For subgroup analysis by the diagnostic methods (ELISA, RT-PCR, and Western blot), OR was 2.47 (95% CI: 0.77 - 7.96, P=0.13), 12.20 (95% CI: 1.66 - 89.57, P=0.01), and 28.36 (95% CI: 3.76-213.85, P=0.001), respectively (test for subgroup differences: P=0.08; I^2=59.5). Subgroup analysis for BDV and CFS association by antigens and antibodies had an OR of 12.20 (1.66, 89.57) and 8.20 (3.32, 20.22), respectively (test for subgroup differences: P=0.72; I^2=0).

Conclusions: This study supports the association between BDV and CFS and shows the role of viral agents in etiology of CFS. Therefore, viral agents may play a role in the etiology of neuropsychiatric disorders.

Keywords: Borna Disease Virus, Chronic Fatigue Syndrome, Meta-Analysis

1. Context

Chronic fatigue syndrome (CFS) or systemic exertion intolerance disease (SEID) (1) has a prevalence of 0.2% to 2.6% and is characterized by recurrent or persistent fatigue for at least 6 months without any medical explanation (2). This syndrome occurs more frequently in females than males (3). The etiology of this disease is unknown, yet symptoms include a variety of somatic symptoms, impairment of neurocognitive functions, and quality of sleep. The origin of the disease is suggested to be a viral infection in some studies (4) and exacerbation of CFS seems to be caused by viral and non-viral agents (5). The diagnostic criteria of CFS, as defined by the Institute of Medicine, include a decline in personal or occupational activities for more than 6 months, post exertional malaise, and unrefreshing sleep with at least 2 of the following signs: cognitive impairment or orthostatic imbalance (6).

Several viruses are proposed to play a role in the etiology of CFS, such as retroviruses, human herpes virus type 6 (HHV-6), Enteroviruses, Coxsackie B disease virus, Adenovirus, Ross river virus, and Borna disease virus (BDV) (7, 8).

BDV is an enveloped, non-segmented, negative-strand RNA virus from Bornaviridae family and order Mononegavirales (9). The BDV can lead to neuronal chronic slow progressive infections and occasionally involve glial cells in vivo and could lead to the involvement of several classes of cells in vitro (10). Numerous studies have been conducted on the effect of BDV on several psychiatric and neurological disorders. Results of a meta-analysis conducted by Isabel Arias et al. in 2012 showed an association between BDV and schizophrenia (P < 0.01) (11). Miranda et al. compared psychiatric patients with a control group and reported a higher rate of BDV RNA in the patients (12) and Puerto confirmed the possible role of BDV (through West-

ern Blot [WB] diagnostic method) in neuropsychiatric diseases (13). Another study also reported the association between BDV and encephalitis (through diagnostic methods of WB and RT-PCR [reverse transcription polymerase chain reaction]), yet there was no association with other neurological disorders and controls (14). However, one meta-analysis study did not confirm the association between human BDV infections and psychiatric diseases (15). In addition, Indirect Immunofluorescence Antibody (IFA) and rRT-PCR tests rejected the possible role of BDV in patients with psychiatric diseases (16).

Regarding the association between BDV and CFS, controversial results have been reported by previous studies. In a study by Bode et al. the role of BDV in the etiology of CFS was no significant (17). Evengardand et al. did not support the role of BDV in the pathogenesis of CFS (18). In a Japanese study by Nakaya et al. the prevalence of BDV p24RNA and antibody in Peripheral Blood Mononuclear Cells (PBMCs) and serum of patients with CFS was 32%, supporting the association between BDV and CFS (19). Some studies suggested a strong association in some cases of CFS (20, 21).

2. Objectives

Because of the controversy on this issue, a systematic review and meta-analysis is essential to review all the relevant documents and come to a final conclusion (22, 23). Considering the fact that CFS has a wide range of symptoms that are common among different disorders, CFS has several differential diagnoses, and so it is important to diagnose CFS. Moreover, the underlying mechanism or etiology of CFS has not been well established. Thus, identifying the possible etiologic agents could help in the diagnosis of this disabling disease. One of the probable etiologies is BDV, yet, the role of BDV in patients with CFS has not been proven. Therefore, we conducted a systematic review and meta-analysis to assess the effect of this infectious agent on the etiology of CFS.

2.1. Data Source

The present systematic review and meta-analysis was conducted using preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (24). To avoid bias, all procedures of the current study were performed by two researchers independently.

3. Evidence Acquisition

3.1. Information Sources and Search Strategy

A comprehensive search on the following databases was performed until December 2016: PubMed, Scopus, Embase, PsycINFO, Science Direct, Cochrane Library, web of science and Google scholar search engine to identify studies addressing the association between CFS and BDV. The online search consisted of the following MeSH keywords: Borna disease virus, chronic fatigue syndrome, neurological disorders, and neuropsychiatric disorders. In addition, a reference list of relevant articles was evaluated to access additional articles related to the study objectives.

3.2. Inclusion and Exclusion Criteria

Inclusion criteria were epidemiologic studies addressing the association between BDV and CFS with at least an English abstract. Exclusion criteria were: 1. Irrelevant to topic; 2. Not chronic fatigue syndrome patients in case group; 3. Not assessing Borna disease virus; 4. Conference presentations, letters to editors and review article.

3.3. Study Selection

The initial search resulted in 400 studies, and 200 duplicate articles were excluded from our research by EndNote software. After screening the title and abstract of all articles, 38 studies were selected for full-text assessment. Finally, 9 studies were included in quantitative synthesis (Figure 1).

3.4. Quality Assessment

The selected articles were reviewed by two researchers using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (25). The checklist contains 22 items. Each item was given a score between 0 and 2 and the data that gained a score above 16, entered the analysis.

3.5. Data Extraction

Two researchers independently reviewed all studies that were entered in the analysis process. The following characteristics were extracted and recorded for each paper: author(s) name, country of study, year and design of study, BDV measure (PBMCs, Plasma, and Serum), name of journal, characteristics for patients and controls (e.g. gender and mean age and SD, and size), diagnostic methods, diagnostic criteria, odds ratio, number of positive BDVs in cases and controls. Disagreement between researchers was resolved by a third researcher.

3.6. Meta-Analysis

We pooled odds ratios (ORs) and 95% confidence intervals (CI). Heterogeneity between studies was measured by Cochran's Q test and I2 index using forest plots of OR. P values < 0.05 for Cochran's Q test or I2 values >50% were considered as heterogeneity (26). Cochran's Q test showed P=0.03 and I2 index was 62%. Since the heterogeneity was
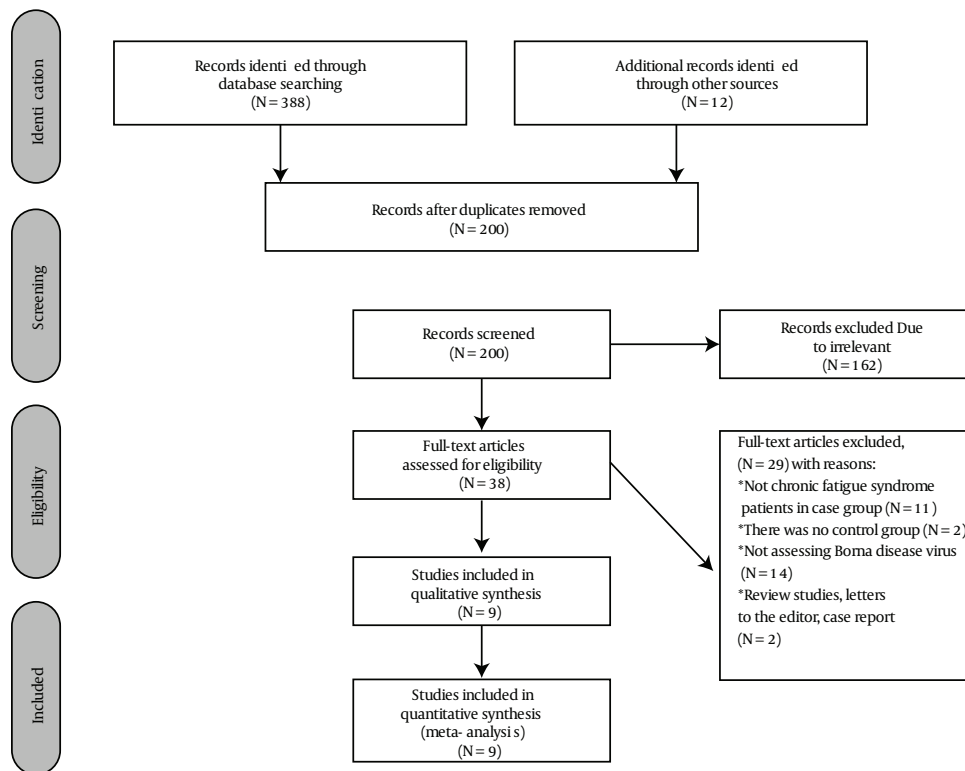
Figure 1. Study Selection Diagram

apparent, we used the random effects model to combine studies. Data was analyzed using Review Manger software version 5.3.5. P < 0.05 was considered statistically significant. To explore potential sources of heterogeneity, we conducted subgroup analysis for different methods and assays. Publication bias was assessed by Egger's and Begg's tests using comparative meta-analysis (CAM) software ver. 2.

4. Results

4.1. Characteristics of the Study Populations

Nine studies with a total sample size of 610 cases and 2176 controls were obtained for the meta-analysis (Table 1).

4.2. Overall Association Between BDV and CFS

The total OR was estimated to be 10.41 (95% CI:4.24-25.55), which was statically significant (P < 0.0001)(Figure 2).

4.3. Subgroup Analysis Based on Different Methods

OR for ELISA, RT-PCR and WB methods was estimated to be 2.47 (95% CI: 0.77- 7.96, P=0.13), 12.20 (95% CI: 1.66- 89.57, P=0.03) and 28.36 (95% CI: 3.76-213.85, P=0.001), respectively (test for subgroup differences: P=0.08; I^2=59.5 (Figure 3).

4.4. Subgroup Analysis Based on Different Assays

OR for assays of antigens and antibodies was estimated to be 12.20 (95% CI: 1.66- 89.57, P < 0.0001) and 8.20 (95% CI: 3.32- 20.22, P=0.01), respectively (test for subgroup differences: P=0.72; I^2=0 (Figure 4).

4.5. Publication bias

P-value for publication bias in Egger's and Begg's tests was estimated to be 0.41 and 0.50, respectively, which was not statically significant (Figure 5).

5. Discussion

In the present study, after searching databases and the process of study selection and quality assessment, 9 studies were finally analyzed, which resulted in a total OR of

Table 1. Comparison of the Data Obtained from Studies to Evaluate the Association Between BDV and CFS

Authors Name	Year	Place	Case				Control				Assays	Technique/Sample
			Positive BDV, N	Negative BDV, N	Male/Female	Mean age (SD)	Positive BDV, N	Negative BDV, N	Male/Female	Mean age (SD)		
Yamaguchi et al. (27)	1999	Japan	0	75	45/30	32 (9.8)	10	907	632/285	35.1 (13.1)	anti p24 and p40 Ab	ECLIA/Serum
Kitani et al. (28)	1996	Japan	30	59	-	32.6	3	97	-	37.9	anti p24 Ab	ELISA/Serum
Nakaya et al. (20)	1999	Japan	7	0	-	-	1	2	-	-	anti p24, p40 and gp18 Ab	Immunobloting/Plasma
Evengard et al. (18)	1999	Sweden	27	142	-	-	2	60	-	-	anti BDV p40,p24,gp18A	ELISA/Serum
Li Yj et al. (29)	2003	China	7	54	-	-	0	73	-	-	anti p24Ab	WB/Plasma
Li Yj et al. (30)	2005	China	17	65	-	-	0	73	-	-	anti p24Ab	WB/Plasma
Kitani et al. (28)	1996	Japan	7	50	-	-	8	164	-	-	P24RNA	Nested RT_PCR/PBMCs
Nakaya et al. (19)	1996	Japan	6	1	-	-	0	3	-	-	P24RNA	Nested RT_PCR/PBMCs
Zhang et al. (21)	2013	China	8	55	38/25	37.4 (10.8)	6	767	426/347	40.5 (8.5)	p24 or p40RNA	Nested RT_PCR/PBMCs

Figure 2. Meta-Analysis of Studies on Association Between BDV and CFS
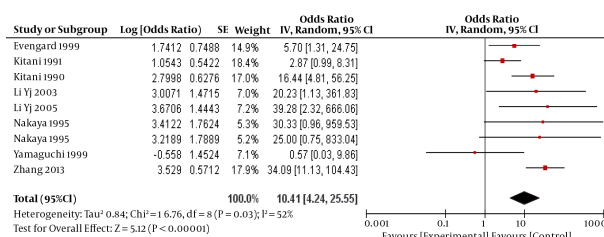
Mean point of each segment shows the estimation of Odd Ratio (OR) and the length of each segment shows 95% confidential interval in each study. The lozenge shows OR in each study.
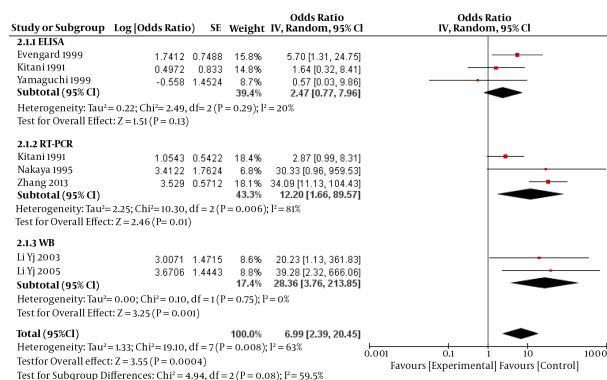
Figure 3. Meta-Analysis of Studies Regarding the Association Between BDV and CFS According to Diagnostic Method

10.41 (95% CI: 4.24 to 25.55, P < 0.0001). The OR for most of these 9 studies was significant, indicating BDV as a strong etiologic agent that influences CFS. However, the heterogeneity of studies was moderate (52%) (P = 0.03), and therefore, random effects model was used in the meta-analysis (to investigate heterogeneity according to I2 index, there
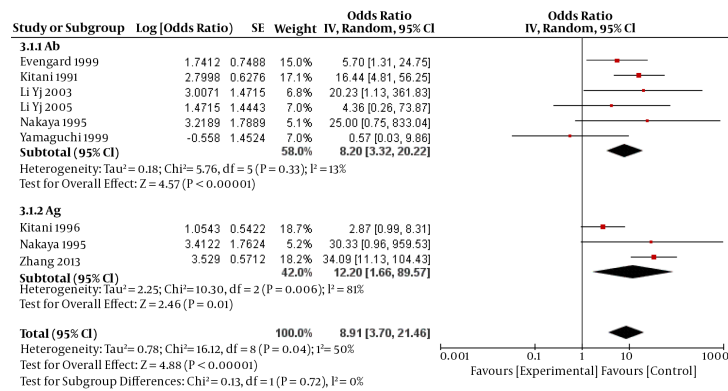
Figure 4. Meta-Analysis Regarding the Studies of Association Between BDV and CFS According to Assays
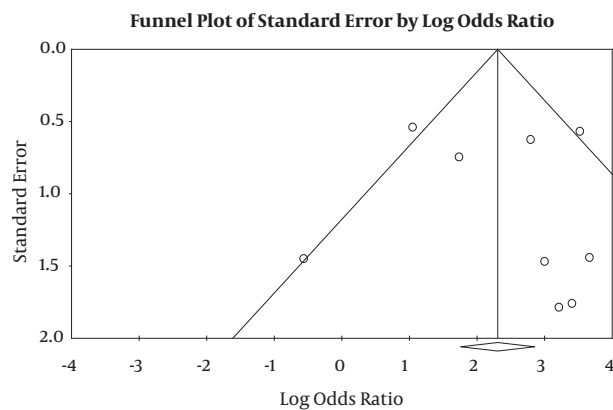

Figure 5. Publication Bias in Meta-Analysis of Studies of the Association Between BDV and CFS

are three classifications: less than 25% [low heterogeneity], 25-75% [moderate heterogeneity] and more than 75% [high heterogeneity]); the analysis was performed according to diagnostic methods and assays, was no significant (P = 0.08, and 0.72, respectively).

Among these 9 studies, 2 studies did not find an association between BDV and CFS. Evengard et al. reported that in Swedish patients, there was nonspecific immunoreactivity in ELISA to BDV in CFS sera (due to infectivity with other microbes or viral agents, as well as being bound to b-galactosidase), which was not confirmed by WB; in addition to RT-PCR detection of P-gene transcripts in PBMC (18). However, the geographic differences and other factors could be the reason for this discrepancy. The studies that found no association declared that failure to find an association does not mean lack of any kind of association and suggested further studies.

However, studies had a moderate discrepancy and accurate meta-analysis should be performed on the gene-bank of the patients, rather than the studies published to minimize the confounders and differences of studies (31). Moreover, it has been posited that BDV might be positive only in the acute phase of CFS disease (32).

The present study had some limitations including issues with access to full text of all articles, using different methods (WB, RT-PCR, ELISA), samples (Serum, Plasma, PBMCs) and assays (anti bodies, antigens) for detecting BDV in patients with CFS in different studies. However, the strength of our study was using subgroup analysis of studies according to different methods and assays.

This study supports the association between BDV and CFS and shows the role of viral agents in the etiology of. Therefore, viral agents may play a role in the etiology of neuropsychiatric disorders. By understanding the underlying factors of a psychiatric disease, we can take a crucial step forward to its treatment on a medical basis and decrease the prevalence of uncured cases with neuropsychiatric disorders, including treatment of infectious disease

to help health programs.

Further studies are required to find the exact association and to find other etiologic agents. In addition, a high-quality technique needs to be used for detection of BDV.

Acknowledgments

Footnotes

Authors' Contribution: Milad Azami and Zainab Tardeh conceived and designed the study. Milad Azami performed the statistical analysis. Milad Azami, Mohammad Reza Adhami Mojarad, Akram Mansouri, and Zainab Tardeh collected and interpreted the data, drafted, and revised the manuscript, and read and approved the final manuscript.

Declaration of Interest: There was no conflict of interest in the current research.

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