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Original article

Clinical and demographic characteristics of psychiatric patients seropositive for *Borrelia burgdorferi*

T. Hájek [a,b,*], J. Libiger [a], D. Janovská [c], P. Hájek [d], M. Alda [a,b], C. Höschl [a]

[a] *Prague Psychiatric Center, Charles University, 3rd School of Medicine, Prague, Czech Republic*
[b] *Department of Psychiatry, Dalhousie University, QEII, HSC, A.J.Lane Building, Room 4031, 5909 Veteran's Memorial Lane, Halifax, NS, Canada B3H 2E2*
[c] *Department of Epidemiology, Charles University, 3rd School of Medicine, Prague, Czech Republic*
[d] *Barts and the London School of Medicine and Dentistry, University of London, UK*

Abstract

***Purpose.* –** *Borrelia burgdorferi* (Bb) infection can affect the central nervous system and possibly lead to psychiatric disorders. We compared clinical and demographic variables in Bb seropositive and seronegative psychiatric patients and healthy controls.

***Method.* –** Nine hundred and twenty-six consecutive psychiatric patients were screened for antibodies to Bb and compared with 884 simultaneously recruited healthy subjects.

***Results.* –** Contrary to healthy controls, seropositive psychiatric patients were significantly younger than seronegative ones. None of the studied psychiatric diagnostic categories exhibited stronger association with seropositivity. There were no differences between seropositive and seronegative psychiatric patients in hospitalization length, proportion of previously hospitalized patients and proportion of subjects with family history of psychiatric disorders.

***Conclusion.* –** These findings elaborate on potential association between Bb infection and psychiatric morbidity, but fail to identify any specific clinical 'signature' of Bb infection.

Keywords: Borrelia burgdorferi; Antibodies; Psychiatric diagnoses

1. Introduction

Lyme disease (LD) is a multisystem infection caused by the gram-negative spirochete *Borrelia burgdorferi* (Bb) [2]. Bb is related to *Treponema pallidum* (Tp), the etiologic agent of "neurosyphilis"—the well-known infectious disorder associated with neuropsychiatric symptoms. Nowadays Bb is the most frequently recognized arthropod-borne infection of the central nervous system in Europe and the USA [11,13].

Bb and Tp share many common features. Both infections run in distinctive clinical stages, have high affinity for central nervous system and cause a wide range of neurological symptoms. In both, there may be a long latent period between infection and manifestation of the disease. An unresolved question remains, whether Bb can also cause psychiatric disorders?

Several case studies associated Bb infection with affective, panic, organic psychiatric disorders and psychosis [5–7,9,14]. However, such reports cannot exclude the possibility of coincidental co-morbidity. Our recent epidemiological survey compared the frequency of antibodies to Bb in a sample of psychiatric patients ($N = 926$) and healthy controls ($N = 884$). Seropositivity was significantly more frequent in psychiatric patients in both unmatched and sex and age matched samples. There were 1.7 times more seropositive psychiatric patients than matched healthy controls [8].

If there is an association between Bb infection and a particular psychiatric diagnostic category, then there should be a higher percentage of antibody-positive subjects in this diagnostic category. In case Bb triggers psychopathology for example in only genetically predisposed subjects, then seropositive patients should be more likely to have positive family history. If the higher prevalence of seropositivity in psychiatric patients is a consequence and not a cause of their hospitalization in psychiatric hospitals, then more seroposi-

* Corresponding author. Tel.: +1-902-473-4677; fax: +1-902-473-1583.
E-mail address: hajek@pcp.lf3.cuni.cz (T. Hájek).

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tive psychiatric patients should have previous history of psychiatric hospitalization. Patoplastic effects of Bb infection on psychopathology would be revealed by differences in age and proportion of gender between seropositive and seronegative psychiatric patients. Patients suffering from neuropathogenic effects of Bb might require longer hospitalization due to underlying infectious etiology not affected by psychopharmacological treatment.

This is an extension of our previous study, which investigated the differences in prevalence of antibodies and their subtypes between psychiatric patients and healthy controls. In this paper we focus on clinical/demographic variables not previously addressed. To the best of our knowledge, this is the largest published dataset of psychiatric patients assessed for Bb. Following questions are investigated based on above mentioned rationale: Is Bb infection associated with any specific psychiatric diagnosis? Are there any differences between seropositive and seronegative psychiatric patients in sex, age, family history of psychopathology and hospitalization length? These new research questions may help to further elucidate the role of Bb in psychiatric morbidity beyond the previous observation of higher prevalence of antibodies in psychiatric subjects.

2. Subjects and methods

A total of 926 consecutive psychiatric patients from the whole of Czech Republic, admitted to Prague Psychiatric Center (Teaching Psychiatric Hospital, School of Medicine, Charles University, Prague) between 1995 and 1999 participated in the study. The control group consisted of 884 currently healthy subjects recruited in the same period for epidemiological survey of antibodies to Bb in the general healthy population of the Czech Republic. Exclusion criteria for this group were acute illness, hospitalization or immunodeficiency. Detailed description of the studied populations has been published elsewhere [8].

The diagnoses were ascertained by qualified, experienced psychiatrists at the Prague Psychiatric Center. The data concerning hospitalization length, family history of psychiatric disorder (defined by psychiatric hospitalization of either parents, siblings or children) and previous hospitalizations were obtained from the clinical charts retrospectively, by raters blind to the serological status of the patients. The diagnoses, age and sex were coded at the admission to the study, also blindly. The data were incomplete in a small proportion of subjects. Family histories were thus obtained in 880 patients, hospitalization length in 890 patients and information concerning previous psychiatric hospitalizations in 894 patients.

The project was approved by the Ethics Committee of the Prague Psychiatric Center. The control group consented specifically to screening for antibodies to Bb, while the patient group provided written consent for routine screening and diagnostic assessments.

3. *B. burgdorferi* antibody detection

Samples were analyzed by the National Reference Laboratory for Lyme disease of the Czech Republic. Samples from both groups were arriving at the laboratory during the same period of time. They were processed coded, and laboratory technicians were not aware of sample origin. Whole cell sonicate enzyme-linked immunosorbent assay (ELISA) with *Borrelia afzelii* Kc90 Cz was applied [10,17]. Serum IgG extinction values >900 and serum IgM values >1000 were defined as positive.

Circulating immune complexes were isolated by polyethylene glycol precipitation [3,15]. Dissociated serum immune complexes were analyzed by ELISA for anti *Borrelia* IgM and IgG antibody simultaneously with patient's serum samples and with seven negative and eight positive control samples. Each test was run in duplicate. Serum CIC IgG values >900 and serum CIC IgM values >1200 were defined as positive.

Seropositive patients were defined as being positive in at least one of these tests. We also performed recombinant immunoblot IgM, IgG (BAG *Borrelia* Blot) to confirm the reliability of ELISA [12], for details see [8].

4. Statistical analysis

Log-linear modeling was used for three way comparisons of categorical variables (proportion of seropositive patients, proportion of patients with positive family history of psychopathology, proportion of previously hospitalized patients and proportion of seropositive patients in diagnostic groups). We concentrated primarily on five diagnostic categories (F0x, organic and symptomatic mental disorders; F2x, schizophrenia, schizotypal and delusional disorders; F3x, mood disorders; F4x, neurotic, stress-related and somatoform disorders; F6x, disorders of adult personality and behavior) in which the number of patients in each group, e.g. seropositive and seronegative exceeded 10. For evaluation of differences in age and hospitalization length, ANOVA for equal and unequal variances (Brown–Forsyth) was used. To test the assumption of homogeneity of variances we used Levene's test.

5. Results

5.1. Differences in proportion of seropositive patients between diagnostic groups and sexes

When analyzing the most prevalent diagnostic categories (F0x, F2x, F3x, F4x, F6x), the log-linear model that best fitted these data, was the one including seropositivity and interaction between diagnostic category and sex (likelihood ratio $\chi 2 = 16.3$, DF = 9, $P = 0.06$). According to this model distribution of males and females differed between diagnostic categories. However, there were no significant differences

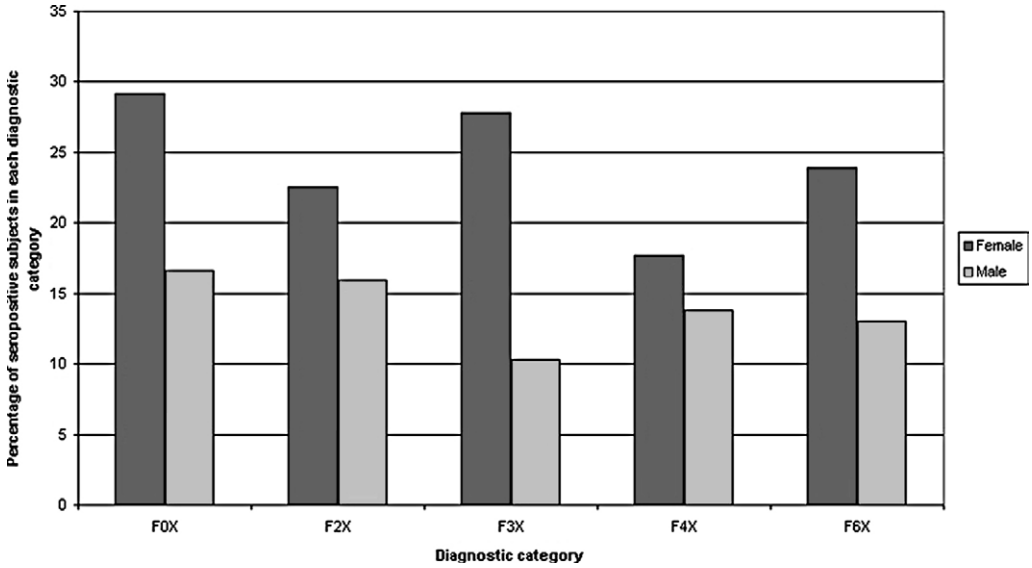

Fig. 1. Percentage of seropositive patients for each diagnostic category broken down by sex.

in proportions of seropositive subjects between the individual diagnostic categories or between male and female subjects. For details see Fig. 1.

5.2. Differences in family history, history of psychiatric hospitalization and seropositivity

Eighty (25.6%) out of 313 seropositive patients had family history of psychiatric disorder compared to 158 (27.9%) out of 567 seronegative patients. In 19 seropositive and 27 seronegative patients the data concerning family history were missing. One hundred and sixty-six (52.0%) out of 319 seropositive patients had a prior history of psychiatric hospitalization compared to 289 (50.3%) out of 575 seronegative patients. The data concerning previous hospitalizations were missing in 13 seropositive and 19 seronegative patients.

The log-linear model that best fitted these data was the one including seropositivity and interaction between previous hospitalizations and family history (likelihood ratio $\chi 2 = 10.56$, DF = 7, $P = 0.16$). According to this model patients with family history had higher number of previous hospitalizations, but the proportion of previously hospitalized patients or patients with family history was comparable between seropositive and seronegative subjects.

5.3. Differences in age—psychiatric patients vs. controls

The mean age of seropositive psychiatric patients at the time of assessment was 33.6 years (S.D. = 13.9, $N = 332$) and 36.8 years (S.D. = 13.8, $N = 594$) in seronegative ones. The mean age of seropositive healthy controls at the time of assessment was 32.2 years (S.D. = 22.3, $N = 163$) and 26.2 years (S.D. = 19.9, $N = 721$) in seronegative healthy controls. Psychiatric patients were significantly older than healthy controls (Brown–Forsyth ANOVA $F = 32.25$, DF = 1, 344, $P < 0.001$). Seropositive psychiatric patients were significantly younger than seronegative psychiatric patients, whereas seropositive healthy controls were older than seronegative ones (Brown–Forsyth ANOVA $F = 18.67$, DF = 1, 344, $P < 0.001$). Seropositivity did not influence the age distribution (Brown–Forsyth ANOVA $F = 1.74$, DF = 1, 343, $P = 0.19$).

5.4. Differences in age at first hospitalization—seropositive vs. seronegative psychiatric patients

This analysis was performed in a consecutive subsample of 420 psychiatric patients with diagnoses F0x, F2x, F3x, F4x, F6x admitted for their first hospitalization. The five diagnostic categories differed with respect to age (Brown–Forsyth ANOVA $F = 9.78$, DF = 4, 29, $P < 0.001$), but seropositivity did not influence the age distribution (ANOVA $F = 0.66$, DF = 1, 410, $P = 0.42$). There was no interaction between seropositivity and diagnostic category (Brown–Forsyth ANOVA $F = 0.37$, DF = 4, 30, $P = 0.82$). For details see Table 1.

5.5. Differences in hospitalization length—seropositive vs. seronegative psychiatric patients

In a group of psychiatric patients from the most prevalent diagnostic categories (F0x, F2x, F3x, F4x, F6x), hospitalization length did not differ between seropositive and seronegative patients (Brown–Forsyth ANOVA $F = 1.75$, DF = 1, 18, $P = 0.20$), nor between diagnostic categories (Brown–Forsyth ANOVA $F = 0.29$, DF = 4, 17, $P = 0.88$). There was no interaction between these factors (ANOVA $F = 1.51$, DF = 4, 845, $P = 0.2$). For details see Table 1.

Table 1
Age at first hospitalization and hospitalization length of seropositive and seronegative patients across ICD 10 diagnostic categories

	First admissions [a]		Whole sample [b]	
	Age at first hospitalization		Hospitalization length	
	Seropositive subjects, mean (S.D., *N*)	Seronegative subjects, mean (S.D., *N*)	Seropositive subjects, mean (S.D., *N*)	Seronegative subjects, mean (S.D., *N*)
F0x	49.3 (16.2, 7)	50.3 (22.7, 9)	44.5 (45.0, 10)	29.8 (19.1, 13)
F2x	26.8 (9.4, 36)	30.7 (12.0, 61)	41.3 (23.5, 95)	38.3 (17.0, 155)
F3x	40.2 (15.3, 44)	43.2 (13.1, 74)	41.8 (25.4, 101)	39.7 (17.9, 164)
F4x	30.3 (9.2, 51)	33.8 (11.2, 118)	36.8 (18.4, 87)	39.8 (18.9, 186)
F6x	34.0 (16.9, 8)	30.2 (11.8, 12)	38.5 (18.4, 16)	33.4 (18.0, 28)
All psychiatric	33.2 (13.6, 153)	35.9 (13.7, 286)	39.8 (23.4, 318)	38.5 (18.3, 572)

[a] N =420.
[b] N =890. Out of 926 recruited patients, data concerning hospitalization length were missing in 14 seropositive and 22 seronegative patients.

6. Discussion

The purpose of this study was to examine clinical and demographic patterns of patients seropositive for Bb. Seropositive subjects were uniformly distributed among studied psychiatric diagnostic categories, with none exhibiting stronger association with seropositivity. Sex differences between diagnostic categories were controlled for in this comparison. Bb infection does not seem to be associated with particular diagnostic category. In order to reduce the risk of type I error stemming from multiple comparisons, we concentrated primarily on global differences between main diagnostic categories. The possibility of more specific syndromic sequelae of Bb infection warrants further, preferentially prospective investigations.

Retrospective design makes it impossible to distinguish between the cause and the consequence. It is possible that patients with psychiatric disorders are in greater risk of acquiring the infection due to previous hospitalizations in psychiatric hospitals, which are often situated in parks with mature trees and bushes, where ticks may be prevalent. If it is the psychiatric hospitalization that leads to Bb infection and not vice versa, then more seropositive psychiatric patients should have a prior history of psychiatric hospitalization. There was, however, no statistically significant difference in proportion of previously hospitalized subjects between seropositive and seronegative psychiatric patients in this sample. The reversed causality explanation therefore seems unlikely.

In Central Europe (Alsace, Southern Germany, Bohemia, etc.) ticks are also often infected with a flavivirus responsible for viral encephalitis. These findings could thus be an artifact of frequent co-morbidity of Bb with other viral infections of the central nervous system. However, we cannot address this issue, since the subjects were not tested for presence of viral antibodies. Differences caused by varying prevalence of Bb infection throughout Czech republic cannot be ruled out, since psychiatric patients and healthy controls were not closely matched for place of living. However, selection bias is unlikely in such a large sample, where both groups were recruited from the whole of Czech Republic. The most parsimonious explanation remains that there is a non-specific association between Bb infection and main psychiatric diagnoses. The nature of the putative association between Bb and psychopathology remains speculative. It does not seem that Bb infection raises the risk of psychopathology primarily in genetically predisposed subjects, as there was no interaction between psychiatric family history and seropositivity.

Assuming that there is an association between Bb infection and psychopathology, a question arises, whether patients with Bb associated psychopathology differ in their clinical or demographic variables. Patients with putative neuropathogenic manifestations of Bb infection should require longer hospitalization since the symptomatic psychopharmacological treatment does not address the underlying infectious etiology of the disorder. In this sample the seropositive patients did not differ from seronegative ones in the hospitalization length. This could be due to limited hospitalization length allowed for by insurance companies of the Czech Republic (8 weeks). However, hospitalization length is too rough an indicator. More detailed prospective observation of the clinical course and response to medication in seropositive and seronegative patients would be warranted.

There were no differences in age at first hospitalization of seropositive subjects between studied diagnostic categories (F0x, F2x, F3x, F4x, F6x). Putative effects of Bb infection on psychiatric morbidity do not seem to interact with age of onset. This is contrary to our a-priori assumption. We would expect higher mean age in seropositive psychiatric patients compared to seronegative ones, since psychiatric morbidity associated with Bb might arise at every point in life, leading to greater variance and probably also mean.

Seropositive healthy subjects were older than seronegative ones, which is in agreement with epidemiological literature on LD. It was the other way around in psychiatric patients, with seropositives being younger than seronegatives. Bb infection may cause psychopathology only in a vulnerable time period of brain development or aging. The mean age of seropositive psychiatric patients was 33.6 years. Myelination is still progressing at this age [1]. Association of Bb infection with psychopathology may thus be mediated by white matter damage. Supportive of this hypothesis are the findings of white matter abnormities in LD [4] and cross reactivity of antibodies to Bb and myelin basic protein [16].

7. Conclusion

These findings suggest that Bb may be a non-specific etiopathogenic agent, diffusely raising the risk of main psychiatric diagnoses, without stronger association to any particular one. Since the proportion of previously hospitalized patients did not differ between seropositive and seronegative patients, higher proportion of seropositives among psychiatric patients does not seem to be the consequence of putative exposure to ticks in psychiatric hospitals. There was also no difference in proportion of patients with family history of psychopathology among seropositive and seronegative subjects. Bb infection does not seem to interact with genetic vulnerability for psychopathology. As for the other findings, seropositive and seronegative psychiatric patients did not differ in hospitalization length. Seropositive psychiatric patients were younger than seronegative psychiatric patients, as opposed to older seropositives than seronegatives among healthy controls. Overall the possibility of causal association between Bb infection and psychopathology remains open and warrants further studies.

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