



ORIGINAL ARTICLE

Anxiety and depression in patients infected with *Borrelia burgdorferi*



M. Makara-Studzińska^a, R. Rolla-Szczepańska^b, A. Urbańska^c,
K. Nowakowska-Domagała^d, P. Stecz^{d,*}

^a Department of Health Psychology, Faculty of Health Sciences, Jagiellonian University Medical College, Cracow, Poland

^b Chair and Department of Infectious Diseases, I Faculty of Medicine, Medical University of Lublin, Poland

^c II Department of Psychiatry and Psychiatry Rehabilitation, Chair of Psychiatry, I Faculty of Medicine, Medical University of Lublin, Poland

^d Department of Preventive and Addiction Psychology, Institute of Psychology, Faculty of Educational Sciences, University of Lodz, Poland, Poland

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depression and anxiety in patients with *Borrelia burgdorferi*

Abstract

Background and objectives: The aim of the study was to evaluate the symptoms of depression and anxiety associated with fibromyalgia and *erythema migrans* in *Borrelia burgdorferi* infection.

Methods: A group of 87 patients with clinically and serologically diagnosed *B. burgdorferi* (mean age 53.37) was formed. They were examined using the State-Trait Anxiety Inventory, Beck's Depression Inventory and various immunological tests, as well as for fibromyalgia. A demographic survey with additional questions was also administered.

Results: Our results confirm that fibromyalgia is associated with higher anxiety and depression symptoms. It is possible that serological markers of infection could act as indicators of depression level in patients with *B. burgdorferi*. The examined patients with *B. burgdorferi* infection reported a low prevalence of anxiety and depression symptoms.

Conclusions: The studied population is not very likely to experience neurologically-determined mood disorders, taking into consideration the above-mentioned results.

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* Corresponding author.

E-mail address: patryk.stecz@uni.lodz.pl (P. Stecz).

Introduction

Lyme borreliosis is a multisystem inflammatory anthrozoosis caused by a complex interaction between the spirochete *Borrelia burgdorferi sensu lato* (*B. burgdorferi* s.l.) and the immune system of the infected individual at the site of infection.¹

Annually, more than 25,000 new cases of Lyme disease are diagnosed in the USA (incidence 7.9/100,000), and around 85,000 in Europe.² The NIZP-PZH, the Polish National Institute of Public Health-National Department of Hygiene, reports that the incidence of *B. burgdorferi* infection in Poland increased by almost 50% in the period 2011–2014.³ Although in Poland, the incidence varies according to province, it was found to be 39.7/100,000 for the whole of Lublin province in 2014.⁴

The epidemiology of tick-borne disease depends on a number of factors, including the specificity of natural resources and type of employment in the region, with Eastern Poland being one of the more exposed regions in the European Union.⁴

The symptomatology of the *B. burgdorferi sensu lato* complex varies according to the species of *Borrelia* present. Eighteen species have been diagnosed, with individual types characterized by different tissular affinity: i.e. neural system or dermal, generalized or particular; a high level of pathogenicity has been found in three species.⁵ All types can cause the occurrence of a primary lesion known as *erythema migrans*. A diagnosis of borreliosis must take into account the epidemiological aspect, the tick bite, the clinical aspect and the serological aspect, with a two-step diagnostic procedure based on an immune enzymatic test and Western blotting.⁶ The disease is characterized by a multiorgan symptomatology and differentiated clinical picture, which can be attributed to, among other things, its considerable adaptability to the human organism.⁵

Asbrink and Hovmark⁷ define three clinical pictures of infection: early local type, early disseminated type and late type. The early local type is present in half the patients as *erythema migrans* between three and 30 days following infection. The early disseminated type can develop several days or months following the bite: some symptoms from central nervous system can appear, sometimes without signs of *erythema migrans*. Late treatment of early types can result in numerous consequences: changes in the osteoarticular system in 60% of cases, neurological symptoms (i.e. mildly declined executive cognitive functions) in 10–40%, and cardiological complications in 5%,^{8,9} which can lead to a prolonged decline in the health-related quality of life.¹⁰

An important potential comorbidity observed in patients with borrelia is fibromyalgia: a conditions manifested by widespread pain and which known to intensify mood and sleep disturbances.¹¹ Fibromyalgia could be considered an additional burden triggered by Lyme borreliosis which affects psychological function.¹² Chronic Lyme disease is another irrelevant and controversial term used to diagnose a broad spectrum of diverse, medically unexplained symptoms.¹³ From a methodological perspective, evidence-based studies should refer to *B. burgdorferi* infection rather than CLD, and recognize the existence of early Lyme Borreliosis as a condition instead of using it as a basis for the diagnosis of Chronic Lyme disease.¹⁴

Most of the mental disorders experienced during early Lyme disease are considered to be the direct consequences of an inflammatory state in neural tissue and the psychological consequence of chronic illness. Mental symptoms are not specific for neuroborreliosis, although they have been observed during various stages of the infection.¹⁵ Several ill-conceived studies suggest that the early stage of borreliosis can present symptoms typical for fibromyalgia and mild depression, while the late stage may manifest Lyme encephalopathy characterized by symptoms of memory deficits, fatigue, spatial disorientation and mood disturbances.¹⁶

The co-occurrence of fibromyalgia and *B. burgdorferi* infection can also be problematic in determining whether the presentations of these illnesses are associated with depression or anxiety symptoms. The nonspecific chronic syndromes observed in some patients seem to have an unknown medical explanation. Many complaints remain subjective and resistant to medical treatment.¹⁷ Generally, the adjustment to chronic disease itself is regarded as a dynamic process which is challenging enough to a sick person, and one which depends on the individual characteristics of the patient and the quality of healthcare, including accurate diagnosis and treatment.¹⁸ It is argued that some patients with recognized Lyme disease are incorrectly diagnosed due to comorbidities and the atypical presentation of symptoms.¹⁹ A further point of controversy is whether patients diagnosed with Lyme disease also suffered from mental disorders before the diagnosis.

The aim of this research was to learn how the factors accompanying *B. burgdorferi* infection such as fibromyalgia or *erythema migrans* were associated with self-reported anxiety and depression comprising the majority of affective disorders. Additionally, the objective was to investigate whether Western-blot tests might predict the level of anxiety and depression symptoms in *B. burgdorferi* infection. It was hypothesized that:

1. Patients diagnosed with *B. burgdorferi* infection associated with fibromyalgia would report a higher level of anxiety and depression than patients without fibromyalgia.
2. Patients diagnosed with *B. burgdorferi* infection associated with *erythema migrans* would report a higher level of anxiety and depression than patients without *erythema migrans*.
3. There would be a relationship between Western blot IgM/IgG (immunoglobulin M/immunoglobulin G) test results and the level of anxiety and depression in patients with *B. burgdorferi*.

Materials

Patients diagnosed and treated for *B. burgdorferi* infection were recruited at the Outpatient Clinic, Department of Infectious Diseases, Medical University of Lublin. In total, 87 participants (43 females and 44 males) completed the study, including psychological diagnosis, medical record analysis, medical interview with demographic questions and additional medical tests. The overall response rate of 87% was achieved by encouragement from academics and keeping

the questionnaires brief. All patients were ethnically white European. *B. burgdorferi* was diagnosed according to criteria proposed by the British Infection Association and the Polish Association of Epidemiologists and Infectious Disease Specialists²⁰:

1. A clinical image of the infected joints (Lyme arthritis), defined as migrating joint pain or recurrent pain in the large joints, particularly the knees or shoulder, and less commonly, ankle and wrist pain limiting active and passive mobility, accompanied by stiffness in the morning.
2. The presence of erythema migrans noted in interviews, and/or risk factors such as being in contact with ticks, working in a forest, farming, working in the garden or picking forest fruits.
3. Positive serological tests performed according to a two-step procedure: ELISA test for IgM and IgG verified by Western blot, identifying a serological profile of IgM(+) IgG(-) for borreliosis lasting less than four weeks; or IgM(+), IgG(+) or IgM(-) IgG(+) for borreliosis lasting longer than four weeks (four to ten weeks).

In the analyzed group, 27 people, (nine men and 18 women, including four women infected professionally) presented a serological profile of IgM (+) IgG(-), 12 people presented IgM (+) IgG(+), and 43 presented IgM(-) IgG(+).

The exclusion criteria ruled out those with a positive test for rheumatic agents, acute-phase C-reactive protein, or anti-CCP, and those diagnosed with rheumatoid arthritis or lupus systematikus.

The additional inclusion criteria comprised patient age between 18 and 88, and no diagnosis of psychotic illness or severe cognitive impairment which may result in symptom overlap or measurement bias. The study was approved by the Medical University of Lublin Ethical Board. Informed consent was obtained from the participating subjects.

Methods

The participants completed a demographic survey including data on gender, age, residence area and marital status (Table 1). Administered immunological test results were within normal ranges for all subjects (rheumatoid factor – RF, cyclic citrullinated peptide antibodies – anti-CCP, acute-phase proteins – CRP and erythrocyte sedimentation rate – ESR). Fibromyalgia was primarily diagnosed using the *Criteria for the Classification of fibromyalgia of The American College of Rheumatology* (excerpt)²¹:

1. The history of widespread pain – recorded using the pain points protocol with a questionnaire definition, where pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. “Lower back” pain is considered lower segment pain.
2. Pain found to be present on digital palpation in at least 11 of the following 18 sites: Occiput (bilateral), Low

cervical (bilateral), Trapezius (bilateral), Supraspinatus (bilateral), Second rib (bilateral), Lateral epicondyle (bilateral), Gluteal (bilateral), Greater trochanter (bilateral), Knee (bilateral).

Digital palpation should be performed with an approximate force of 4 kg. For a tender point to be considered “positive”, the subject must state that the palpation was painful. Tender is not considered “painful”. Fibromyalgia is recorded as present if both criteria are satisfied. Widespread pain must have been present for at least three months.

Additionally, the psychological characteristics of the subjects toward Lyme borrelia were assessed with psychometric tests in an interview performed by a psychologist.

Anxiety

The State Trait Anxiety Inventory (STAI), developed by Spielberger, Gorsuch and Lushene, is a 40-item questionnaire indicating dispositional (20 items) and situational (20 items) feelings of worry and tension. A greater score is associated with higher levels of anxiety. The scale is reported to have good internal reliability coefficients (alpha-Cronbach values varying from 0.84 to 0.94) and is used internationally in clinical settings.²²

Depression

The self-reporting 21-item revised Beck’s Depression Inventory (BDI) was used to determine the occurrence and intensity of depressive symptoms such as feelings of being punished and guilt, worries, sadness, fatigue, suicidal thoughts, changes in sleep, appetite or decrease of interests in sexual behavior. The original version is reported to have good psychometric properties in clinical and non-clinical populations. The alpha-Cronbach value for the revised version was 0.86.²³ It has been widely used in psychological and medical research. The total score ranges from 0 to 63 points, with a higher score representing more common and stronger symptoms of depression disorder.

Statistical methods

The analyses were conducted using SPSS Statistics. All variables except the depression scale ($K-S = 1.55$; $p = 0.016$) were found to have a normal distribution. The chi-square test was used to compare the relationship between *erythema migrans* and fibromyalgia. The Student’s *t*-test for independent samples was used to compare anxiety level between patients with and without fibromyalgia. Similarly, the Mann–Whitney test was performed for determining depression levels. One-way ANOVA for independent groups followed by post hoc tests were conducted to compare the differences in anxiety and depression results among subjects with positive and negative IgM and IgG results. *p*-Values lower than 0.05 were determined to be significant, while *p*-values ranging from 0.05 to 0.09 were interpreted as suggesting a statistical tendency. A number of effect size measures was used, including ϕ for chi-square test, *r* for *U* Mann–Whitney test, Cohen’s *d* for *t*-test.

Table 1 Patient characteristics.

	N		Erythema migrans			
			No ECM	ECM	N	
Females	43(49.4%)	Fibromyalgia				
Males	44(50.6%)	No	42	27	69	$\chi^2 = 4.610$
Rural residence ^a	38(43.7%)	Yes	5	11	16	$p = 0.032$
Urban residence ^a	47(54.0%)	N	47	38	85 ^a	$\phi = 0.233$
Unknown residence	2 (2.3%)					
Occupational exposure	24(27.9%)					
	M	Mdn	SD	Min	Max	
Age	53.37	54	11.84	19.00	88.00	
State anxiety	43.18	44	10.33	19.00	70.00	
Trait anxiety	46.28	47	11.58	0.00	78.00	
Depression	14.56	12.50	9.36	2.00	47.00	

^a Missing data reported in 2 cases, ECM, erythema migrans; Mdn, median; SD, standard deviation; Min, minimum value; Max, maximum value; ϕ , measure of effect size for chi-square test.

Results

The severity of anxiety as a state (depending on the current situation) and anxiety as a trait (acquired behavioral disposition) was evaluated in Lyme borrelia patients who also presented with symptoms of fibromyalgia, and in whom physical examination had confirmed the presence of at least 11 of 18 tender points as described above. The findings were compared with those recorded in another group of patients without algetic symptoms, or those with algetic symptoms but with a negative result for the physical examination.

The data concerning exposure to bite, recognized tick-bite by patient and presence of *erythema migrans* did not significantly differentiate the studied groups with regard to the level of anxiety and depression. However, the presence of fibromyalgia was significantly different with regard to the appearance of erythema in the patient history (Table 1).

The Student's *t*-test revealed a significantly higher level of state anxiety in patients with algetic symptoms specific for fibromyalgia; while trait anxiety was similar in both groups (Table 2).

The results of the Mann-Whitney test indicate that the patients with fibromyalgia reported a higher level of depression symptoms ($M = 22.88$, $SD = 9.84$) than subjects without fibromyalgia ($M = 12.72$, $SD = 8.28$). However, the effect size was moderate ($Z = -3.903$; $p < 0.001$; $r = 0.426$).

Although the Western blot IgM test results did not differentiate patient anxiety, the IgM+ subjects were observed in general to have more severe depression symptoms ($M = 16.89$; $SD = 9.88$) than the IgM- subjects ($M = 12.13$; $SD = 7.96$), $t(83) = -2.417$; $p = 0.018$. A univariate analysis of variances for independent traits was performed to examine whether statistically significant differences were present with regard to depression, trait anxiety or state anxiety, depending on both IgM and IgG content (Table 3). The result revealed statistically significant differences with respect to the level of depression $F(2; 79) = 3.478$; $p < 0.05$, but no differences regarding state anxiety, $F(2; 80) = 0.854$; $p = 0.429$, or trait anxiety, $F(2; 80) = 0.626$; $p = 0.537$. Post hoc NIR tests found the only significant difference in the severity of

depression to be between IgM(+)/IgG(-) and IgM(-)/IgG(+) ($p < 0.05$): no such difference was found between these two and the two others. A higher level of depression was found in the IgM(+)/IgG(-) group than the IgM(-)/IgG(+) group. As the depression variable was not normally distributed, the non-parametric Kruskal-Wallis was used for further examination. The result of which confirmed the result of the ANOVA.

Discussion

The present study assesses the level of anxiety and depression in patients infected with *B. burgdorferi* to determine whether additional disorders and conditions, such as fibromyalgia, positive *B. burgdorferi* tests, types of Western-blot patterns (IgM and IgG) or recognition of tick bite exposure by the patient, were associated with different intensities of psychological symptoms.

The results suggest that a relationship may exist between the results of IgM and IgG tests, which allow relatively early infections to be differentiated from later ones, and the severity of depression, state anxiety and trait anxiety. Significantly higher levels of depression symptoms and higher levels of state anxiety, although not significant, were observed in the IgM+/IgG- group, including patients with early infection. These patients had no time to psychologically elaborate their diagnosis, to assess its meaning and consequences, and were not able to suffer any damage, such as neurological changes, due to the prolonged activity of *B. burgdorferi*.

The symptoms of depression are probably correlated with experiences of anxiety in the early stage of the disease, and are a typical defensive reaction before growth is observed.¹⁸ The increased level of anxiety mobilizes the individual to experience improvement and cope, while the presence of depressive symptoms may indicate a weak adaptation to new circumstances and feelings of apprehensiveness concerning loss of health, control or safety. Previous studies have also

Table 2 Anxiety in subjects with and without fibromyalgia.

	Fibromyalgia (n = 16)		No fibromyalgia (n = 69)		t	p	95% CI		d Cohen
	M	SD	M	SD			LL	UL	
State Anxiety	47.44	10.81	42.26	10.15	1.816	0.073	-0.494	10.847	0.504
Trait Anxiety	49.56	9.54	45.54	12.10	1.243	0.217	-2.418	10.471	0.345

M, mean; SD, standard deviation; CI, confidence interval, LL, lower limit, UL, upper limit; d Cohen, measure of effect size for the independent samples *t*-test.

Table 3 Depression and anxiety according to negative and positive Western blot tests.

	IgM(+)/IgG(-) n = 27		IgM(+)/IgG(+) n = 12		IgM(-)/IgG(+) n = 43		F	p
	M	SD	M	SD	M	SD		
Depression	17.93 _a	10.91	16.75	9.53	12.28 _b	7.76	3.478	0.036
State anxiety	44.93	10.02	40.33	11.06	42.84	10.44	0.854	0.429
Trait anxiety	44.30	14.09	48.67	12.22	46.50	10.02	0.626	0.537

M, mean; SD, standard deviation; IgM, immunoglobulin; IgG, immunoglobulin G. Note: averages not sharing a literal index differ at the level $p < 0.05$. Multiple comparisons: post hoc LSD (Fisher's least significant difference).

suggested the presence of mild depressive symptoms during the early stage of borreliosis.¹⁶

Patients whose serological test results indicated past infection demonstrated lower anxiety and depression scores, although they also demonstrated higher levels of state anxiety than patients with early infection. This could be the result of struggling with diagnosis and distress related to misconception of the illness, manifested as an increasing tendency toward anxiety and worry. Low indexes for mood disorders among patients with a longer duration of illness may also suggest that borrelia is not associated with psychological symptoms determined by changes in the central nervous system.

Our results suggest that neurological symptoms and changes in mental activities are non-specific, as no strong differentiation was found between groups: The only significant difference concerned depression. The sample size of this study can be a limiting factor in making generalizations, especially because epidemiological data from large populations indicates that IgG antibody level does not differ between healthy and infected people with regard to depression symptoms; however, these studies are not always based on an assessment of the clinical symptoms of depression.²⁴ The results of other works suggest that the prevalence of depression in Lyme disease is low and does not differ much from that of the general population. For instance, one study reported the prevalence of clinical depression to be 4% among a group of Lyme disease patients, with increased depression scores measured by BDI questionnaire in 40% of the same sample.²⁵ Similarly, Dersch et al.²⁶ report no significant differences in depression levels between patients with residual symptoms and healthy controls.

The participants of our study with fibromyalgia demonstrated higher levels of state and trait anxiety, which suggests they might be slightly more exposed to mental problems. An additional burden faced by a considerable number of patients with Lyme Neuroborreliosis is chronic

fatigue syndrome.²⁷ Our study confirms that fibromyalgia is associated with self-reported *erythema migrans* in the medical history.

Over the course of time, persistent somatic symptoms can affect the presence and maintenance of depressive symptoms in patients with borrelia. These include constant pain such as muscular and articular pains or headaches, prolonged complaints and physical restrictions,²⁸ as well as other consequences correlated with organ damage and inflammation of connective tissue.²⁹ Furthermore, the inflammatory processes in Borrelia infection may activate the response manifested by sickness behavior. Sickness behavior is considered to be an adaptive response that may have similar symptomatology to depression (i.e. anxiety, melancholic states). However, it serves a role in enhancing recovery by conserving energy.³⁰ The symptoms measured by BDI and STAI could be triggered both by depression and sickness behavior. Thus, the caution is needed when interpreting the results of this study.

The experience of chronic symptoms is related to perception of negative social impact of disease.³¹ Therapeutic interventions for depressive patients with borreliosis should take into account many factors, such as persistent physical complaints and environmental variables, and their negative influence should be reduced as far as possible. It cannot be ruled out that depression and anxiety symptoms may ameliorate as the disease progresses. Solomon³² reports that patients who experienced strong stress before infection with *B. burgdorferi*, had more chronic psychological complaints during the disease. A suggestion for future study could be identifying a group without preceding depression or anxiety in high risk population (exposure to tick bite) who may develop *B. burgdorferi* infection and following this cohort forward.

As well as occasional mood disturbances, borreliosis is believed to be sometimes accompanied by impairments in attention, memory or reduced speed of complex cognitive

processes, whose presence and severity might be expected to be controlled by early diagnosis and health education.³³

The species of spirochetes present in examined region may have a great influence on the degree of depression, and anxiety may result as a mood disturbance based on disease duration. While the most common species is *B. burgdorferi sensu stricto*, *Borrelia garinii* is also frequently observed; both are responsible for neuroborreliosis and articular-type symptoms. Species with less pathogenicity, such as *Borrelia spielmani*, are also found in the examined area, further complicating the already unclear picture of Lyme borreliosis and making diagnosis more difficult.¹⁶

Conclusions

1. A significantly higher level of depression and state anxiety is observed in early diagnosed *B. burgdorferi* patients with fibromyalgia than in those without.
2. *B. burgdorferi* patients characterized by IgM- and IgG+, suggesting far advanced infection in months, demonstrated the lowest levels of depression and anxiety.
3. A longitudinal study on depression and anxiety among patients with recent infections appears necessary to support the assumption that individuals treated medically for *B. burgdorferi* generally do not develop high levels of depression and anxiety in a long-term perspective.

Conflict of interest

The authors have no conflict of interest to declare.

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