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Estimation of hearing impairment occurrence in patients with Lyme borreliosis – preliminary study

Ocena występowania zaburzeń słuchu u chorych na boreliozę z Lyme – badanie pilotażowe

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ABSTRACT

INTRODUCTION: Lyme borreliosis (LB) is the most common tick-borne human disease. The objective of the study was to carry out preliminary evaluation of the incidence of hearing impairments in LB patients.
MATERIAL AND METHODS: Audiometric tests were carried out on 66 patients with diagnosed LB (aged between 18 and 45 years). All the women and men were divided into two major groups: 1 – early, disseminated LB and 2 – late LB; among them subgroups of Lyme neuroborreliosis (LNB) were distinguished. The hearing organ was diagnosed on the basis of tonal audiometry, extended high-frequency tonal audiometry (up to 18 kHz), impedance audiometry and speech audiometry tests.
RESULTS: Abnormal results of the audiometric tests were recorded in 66.7% of patients. The statistical analysis indicates a significant role of borrelial infection (p = 0.017). Most of those were in patients suffering from late stages of the disease, both in patients with LB and LNB.
CONCLUSIONS: The study revealed the occurrence of hearing impairment of different degrees in more than one half of the patients with LB, especially in the late stages of the disease. The results indicate the necessity for further comprehensive studies, considering hearing and balance disorders in the course of LB, comprising larger groups of patients.

KEY WORDS

Lyme borreliosis, Lyme neuroborreliosis, hearing impairment

ABSTRACT

WSTĘP: Borelioza z Lyme (*Lyme borreliosis* – LB) jest najczęstszą chorobą odkleszczową u ludzi. Celem pracy było przeprowadzenie wstępnej analizy występowania zaburzeń słuchu u chorych na LB.

MATERIAŁ I METODY: Testy audiometryczne objęły 66 chorych z rozpoznaną LB, w wieku od 18 do 45 lat. Wszyscy badani (kobiety i mężczyźni) zostali podzieleni na dwie główne grupy: 1 – wczesnej, rozsianej LB i 2 – późnej LB; wśród nich zostały wyodrębnione podgrupy pacjentów z rozpoznaniem neuroboreliozy (*Lyme neuroborreliosis* – LNB). Diagnostykę narządu słuchu przeprowadzono na podstawie badań audiometrii tonalnej, audiometrii tonalnej rozszerzonej (o wysokiej częstotliwości do 18 kHz), audiometrii impedancyjnej i audiometrii mowy.

WYNIKI: Nieprawidłowe wyniki testów audiometrycznych stwierdzono u 66,7% badanych, a analiza statystyczna wskazała na istotny związek z zakażeniem *Borrelia burgdorferi* (p = 0,017). Większość stanowiły osoby z późną LB, zarówno bez, jak i z LNB.

WNIOSKI: Zaburzenia słuchu różnego stopnia występują u ponad połowy chorych na LB, zwłaszcza w późnych stadiach procesu chorobowego. Uzyskane wyniki wskazują na konieczność prowadzenia dalszych wszechstronnych badań uwzględniających uszkodzenie narządu słuchu i równowagi w przebiegu LB, obejmujących większe grupy chorych.

SŁOWA KLUCZOWE

borelioza z Lyme, neuroborelioza, zaburzenia słuchu

INTRODUCTION

Despite the progress achieved in diagnostics and therapies, Lyme borreliosis (LB) still remains a medical problem as an emerging, tick-borne infectious disease. The etiological factors are the bacteria of the *Borrelia burgdorferi* (*B. burgdorferi*) sensu lato genospecies complex. The transmission of infection results from a bite by an infected tick. Lyme borreliosis is a very common zoonosis throughout the northern hemisphere and the most prevalent tick-borne human disease in Northern America and Europe [1,2]. In Poland, the average incidence (2013 – 33.2, 2015 – 35.4 per 100 000 people) and the number of cases (2013 – 12 773 cases, 2015 – 13 624 cases) have remained for some years on a high level, with a tendency to a remarkable increase in the number of new diagnoses (2016 – 21 200 cases, incidence of 55.22 per 100 000 people) [3,4,5]. The Silesian region takes the leading position countrywide for the number of cases recorded (more than 1 600–1 700 new diagnoses each year, 2016 – 3 264 cases) and third place (after the Podlaskie and Warmińsko-Mazurskie regions) for the incidence of this spirochetosis [6].

Lyme borreliosis is a multi-stage and a multi-system condition. The incubation period, from infection to the onset of early stage manifestations, restricted to skin lesions – usually *erythema migrans* – lasts between some days and several weeks. It is estimated, however, that such early changes are not manifested in 20– –50% of infected individuals. Other organs and systems may become affected during the early, disseminated stage and during the late stage of this spirochetosis. The late symptoms of LB may as well appear after many months or years [1,7]. Apart from the skin symptoms, musculoskeletal manifestations, Lyme neuroborreliosis (LNB) and less frequently cardiac and ocular impairments [8,9,10], borrelial infection may also lead to hearing deterioration. It is supposed that in Europe alone, such pathologies may affect even 44–75% of patients [11,12]. During daily medical practice, a significant percentage of them report symptoms suggesting hearing disorders, impairing the patients' physical fitness and the quality of their life. On the other hand, the diagnostics of these symptoms may be performed without taking into consideration the relationship with *B. burgdorferi* sensu lato infection as about 40% of patients suffering from LB do not remember or did not notice any tick bite. In some patients, the symptoms may be poorly manifested with a long lasting, subclinical course of impairment.

The question of hearing disorders in LB has never been investigated in a comprehensive manner which would make it possible to draw reliable conclusions [11,13,14,15]. The world literature merely presents some descriptions of single cases and nearly all of them concern only evident sudden loss of hearing [16,17, 18,19].

The objective of the present study was a preliminary evaluation of the prevalence of hearing impairments in patients with LB.

MATERIAL AND METHODS

The study comprised patients with an established diagnosis of LB, following the valid standards and on the basis of the history taken to establish any tick bites and potential exposure to subsequent *erythema migrans*, the clinical picture and the routine two-tier laboratory testing algorithm to evaluate serum immunoglobulin (Ig) IgM and IgG antibodies against *B. burgdorferi* sensu lato using the chemiluminescence immunoassay (CLIA) method (set by DiaSorin, Italy), followed by the immunoblot (Western blot) serum confirmatory test (set by Mikrogen GmbH, Germany). In suspected LNB cases a routine diagnostic procedure was applied, including cerebrospinal fluid (CSF) tests, cases were confirmed based on the presence of lymphocytic pleocytosis, blood-brain barrier inflammatory impairment and *B. burgdorferi*-specific intrathecal antibody production (*B. burgdorferi* CSF/serum antibodies index). The CSF assays were preceded by an ophthalmological examination. Imaging of the central nervous system (MR – magnetic resonance) as well as neurological and otolaryngological consultation were performed to exclude other reasons for hearing disorders. In all the individuals syphilis and rheumatoid arthritis were excluded.

Audiometric tests were carried out in 66 patients (31 women and 35 men), aged from 18 to 45 years (mean age of females – 38.5 ± 6.2, males – 35.8 ± 8.9).

Depending on the disease stage, all the men and women were divided into two main groups: group 1 – early, disseminated LB and group 2 – late LB, indicating the etiology of *B. afzelii, B. burgdorferi* sensu stricto and *B. garinii* as well as considering the actual or probable time since infection. Among those, subgroups of patients with manifestations of LNB were distinguished, including cerebrospinal meningitis, facial nerve paresis or palsy and the Garin-Bujadoux--Bannwarth syndrome.

The inclusion criterion for audiometric tests was a type A tympanogram (middle ear pressure range ± 100 daPa, capacity 0.5–1.5 ml). The exclusion criteria comprised a history of head injuries, metabolic conditions, arterial hypertension, pathologies of the central nervous system other than neuroborreliosis, chronic otic conditions, an abnormal tympanogram (middle ear function) and individuals exposed to continuous and/or pulse noise or with previous hypoacusia. The hearing organ was diagnosed on the basis of tonal audiometry, extended high-frequency tonal audiometry (up to 18 kHz), impedance audiometry and speech audiometry tests. A pathological result was an auditory threshold above 30 dB for a given frequency.

The audiometric tests were carried out once, immediately following the established diagnosis of LB and prior to antibiotic therapy, except for patients with early LNB. In this group the tests were performed after an improved clinical condition had been achieved.

The audiometric tests were preceded by otolaryngological examination to exclude any possible contraindications for the procedure as well as any other factors which could affect the results. The audiometric tests made use exclusively of safe noise frequencies preventing any injury or impairment of the organ of hearing. They were performed as standard procedures with relevant safety precautions.

The results were statistically analysed. Verification of the dependence of hearing impairment occurrence on sex, clinical forms of LB and stages of the disease was evaluated by means of the Chi-square test. The accepted statistical significance level was $p < 0.05$. Taking into consideration the small number of participants in the sample, the p-value was calculated using the Monte Carlo simulation. The calculations also included Fisher's exact test and the Cochran-Mantel-Haenszel method. The analysis used the statistical software R* Core Team [20].

The study was approved by the Ethics Committee, Medical University of Silesia, resolution No. KNW/002/KBI/136/I/15 and the study follows the principles of the Declaration of Helsinki. Informed written consent was obtained prior to the study from all the enrolled patients.

RESULTS

The average time between infection and manifestation of early, disseminated LB, including LNB, was about 12.5 ± 3.4 weeks. The average time between infection and manifestations of late LB, including late LNB was about 1.3 ± 0.4 years, while the average time before specialistic medical assistance was sought was about 2.1 ± 0.8 years.

The incidence of early, disseminated and late LB, including LNB, structured by sex, is illustrated in Table I.

Table I. Groups of patients with Lyme borreliosis (LB) and Lyme neuroborreliosis (LNB)
**Tabela I.** Grupy chorych na boreliozę z Lyme (LB) i neuroboreliozę (LNB)

	Men n = 35 (53%)				Women n = 31 (47%)			
	group 1		group 2		group 1		group 2	
	early, disseminated LB	early LNB	late LB	late LNB	early, disseminated LB	early LNB	late LB	late LNB
n	1	3	22	9	0	1	26	4
%	1.5%	4.5%	33.6%	13.5%	0%	1.5%	39.4%	6.0%

The most common form of this spirochetosis in the evaluated men and women was late LB, while early and late LNB was manifested more frequently in men.

In the patients with early LNB the mean value of CSF lymphocytic pleocytosis was 867 ± 283 cells/μl, the CSF protein concentration 982 ± 453 g/L and the *B. burgdorferi* CSF/serum antibodies index 4.1 ± 2.2, whereas in the patients with late LNB: 132 ± 57 cells/μL, 684 ± 108 g/L and 2.9 ± 1.1 – respectively.

Analysis of *B. burgdorferi* sensu lato serotypes causing the disease in the evaluated patients showed the advantage of infections by *B. afzelii* and *B. burgdorferi* sensu stricto (Fig. 1).

Subjective hearing impairment was reported by 13 women (22.8%) and 15 men (26.3%). Diverse, mostly unilateral, pathologies showed up in the audiometric tests (in most cases in tonal audiometry as sensorineural hearing loss), were recorded in 21 women (unilateral or bilateral hearing loss of different degrees) and 23 men (in 1 individual unilateral deafness, unilateral or bilateral hearing loss of different degrees in other cases) – in total 66.7% of patients (Tab. II).
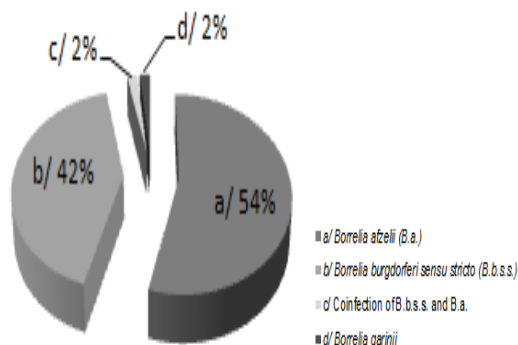
Fig. 1. Serotypes for *Borrelia burgdorferi* in evaluated patients.
Ryc. 1. Serotypy *Borrelia burgdorferi* u badanych chorych.

quently (among them 4 men with facial nerve paresis or palsy: 1 individual with early LNB, 3 individuals with late LNB and abnormal results of impedance audiometry), but without statistical significance. In the

Table II. Frequency of abnormal audiometric test results in patients with Lyme borreliosis (LB) and Lyme neuroborreliosis (LNB)
Tabela II. Częstość występowania nieprawidłowych wyników badań audiometrycznych u chorych na boreliozę z Lyme (LB) i neuroboreliozę (LNB)

	Men n = 35 (53%)				Women n = 31 (47%)			
	group 1		group 2		group 1		group 2	
	early, disseminated LB	early LNB	late LB	late LNB	early, disseminated LB	early LNB	late LB	late LNB
n	0	1	17	5	0	1	20	0
%	0%	1.5%	25.8%	7.6%	0%	1.5%	30.3%	0%

The majority of abnormal audiometric results were recorded in patients with late LB, without any clinical manifestations of LNB and did not depend on sex (Tab. III).

In the relatively small number of patients in the LNB subgroups, audiometric disorders appeared quite fre-

major number of cases (14 women and 13 men) disorders were recorded in individuals denying any hearing problems, as sub-clinical conditions, while in some, reporting hearing impairment, such disorders were excluded by the applied objective methods (6 women and 5 men).

Table III. Statistical analysis of relationships between abnormal audiometric test results and main clinical characteristic of evaluated patients
Tabela III. Analiza statystyczna zależności między nieprawidłowymi wy-nikami badań audiometrycznych i głównymi cechami klinicznymi badanych

Statistical analysis	Sex	LB manifestations	LB stage (early, disseminated or late)
Chi-square	0.030	9.498	1.731
p-value	NS	0.017*	NS
Yule's coefficient	0.021	NA	0.162
Contingency coefficient	0.021	0.355	0.160
Cramer's V coefficient	0.021	0.379	0.162

* total of men and women with late LB; NS – no statistical significance; NA – not available

DISCUSSION

The diversity and possible alteration of the ailments and manifestations in the course of LB appear to be a great diagnostic and clinical challenge, often bearing the burden of therapeutic obstacles [21,22]. This spirochetosis is able to mimic numerous pathologies, diverting the search for the causes in the wrong direction [23]. On the other hand, more attention is now being paid to the overdiagnosis of LB and its clinical masks, where other very grave conditions may be hidden under the picture of that disease [24,25,26]. The cause of such problems, very complicated and still requiring further research, are extremely complex pathogenic mechanisms associated with the infection transmission vectors, i.e. ticks, the properties of the transmitted microorganisms as well as the response of the immunological system of the infected body [27,28]. They include complex inflammatory and autoimmune processes affecting the target cells and organs [29,30, 31,32,33]. The course of the disease may be associated with HLA-DR molecules and depend on HLA-DRB1 alleles [34,35]. The pathomechanism of articular changes comprises adhesion mechanisms and interactions between bacteria, neutrophils and the epithelial cells [36], binding of borrelial lipoproteins to TLR-2 and to integrin $\alpha_3\beta_1$, with activation of metalloproteinases and elevated activity of lysosomal exoglycosidases, resulting in oxidative process balance disorders, oxygen stress and the release of proinflammatory cytokines and chemokines [37,38,39,40,41,42]. On the molecular level, persistence of the inflammatory, autoimmune process is fostered by molecular mimicry between OspA *B. burgdorferi* and the adhesive particle LFA-1α at the T-cell level [43]. A more intensive inflammatory process with a more severe Lyme disease is connected with the *B. burgdorferi* RST1 (OspC Type A) genotype [44]. Zajkowska et al. [45] demonstrated elevated concentrations of soluble ICAM-1, PECAM-1, VAP-1, E-selectin and VCAM-1 in the early, localized and disseminated late forms of LB. The studies by Grygorczuk [46] proved the role of *B. burgdorferi* in the apoptosis of the immunological system of cells, which leads to chronicization of an infection. Strle et al. [47] reported on the role of the TLR1-1805GG gene polymorphism as a risk factor of antibiotic resistant arthritis in the course of such spirochetosis, in the context of the role played in this process by cells similar to fibroblasts – synoviocytes of the hypertrophic synovial membrane.

Studies of the pathogenesis of LNB indicated the presence of lymphocytic infiltrates in cerebrospinal meninges in the brain tissue, in the spinal cord and in "*perineuritis*" type nerves, resulting in multiple axonal injuries of the nerve roots, ganglia and distal parts of the nerves. The histo- and anatomopathological changes may also comprise the blood vessels, in particular the arterial ones, effecting infiltrates in the vessel walls, obliteration of the vascular lumen or occlusive vasculitis [30,33,42,48]. The interaction of *B. burgdorferi* with the brain parenchyma results in the release of inflammatory mediators from glial cells and may be a reason for glial and neuronal apoptosis [49]. The spirochetes may also bring about a direct cytotoxic effect upon the nerve cells [22,42,50].

Some authors suggest the role of *B. burgdorferi* sensu lato in atrophy of the brain tissue and the formation of amyloid deposits leading to the disclosure of Alzheimer disease [51,52]. Similarities in the pathomechanisms of neurosyphilis and LNB are also worth noting [50,51]. Among the extensive symptomatology of the *B. burgdorferi* sensu lato infection, questions referring to hearing and balance organ disorders available in literature are scarce, except for several case studies [53,54,55,56]. Some of the publications present such disorders as the only manifestation of the infection, while others consider them concomitant symptoms of diverse forms of neuroborreliosis [57,58,59,60]. The studies of LNB addressing the question of cranial nerve injury, point first of all to paresis or palsy of nerve VII, while only some of them refer to the possibility of affected nerve VIII, not related to changes on subsequent levels of the auditory pathway or mechanisms coordinating the process of balance [48,61,62, 63,64].

Taking into consideration the structure of the organ of hearing and its pathways in the central nervous sys-

tem, the pathomechanisms of the disorders presented above may have a role in *B. burgdorferi* sensu lato infections lasting for weeks or years. The presence of bacteria can induce local inflammatory processes with structural and also vascular consequences in the involved tissues. Causal serotypes of *B. burgdorferi* sensu lato revealed in the evaluated patients were similar to the results of other Polish studies [65,66,67]. The incidence of hearing loss increases with age and in patients aged 19–44 years it is estimated to be 4.5–5% [68]. The present study demonstrated impairments of the auditory pathway in over one half the patients, especially associated with late LB. The results suggest a significant role of borrelial infection in hearing impairment (p = 0.017).

It should be noted that abnormal audiometric results were observed in a substantial share of individuals showing no clinical manifestations or changes revealed by laboratory tests indicative of LNB, which may suggest a significant role of processes also occurring in Lyme arthritis. In accepting this hypothesis, one cannot exclude the fact that in such patients the disease process also involves structures of the middle and inner ear. However, based on the pathomechanism of LB recognized to date, it should be expected that disorders of the hearing tract are revealed more frequently than in the performed tests, particularly in patients with affected nerve VII, also in the context of an anatomical, partly common pathway with nerve VIII and blood vessels supplying the organs of hearing and balance.

In a substantial number of patients reporting hearing deterioration, the condition of hearing disorders was not confirmed by objective measures. In such cases, one should take into consideration the relation between the affective disorders of a depressive or neurotic nature, manifested particularly in patients with late LB [69,70].

CONCLUSIONS

1. The study revealed the occurrence of hearing disorders in more than one half of the patients with LB, both in patients with and without LNB, especially in the late stages of the disease.
2. The results indicate the need for further comprehensive studies, with evaluation of the prevalence of balance impairment and tinnitus, involving larger groups of patients, to enable topodiagnostic investigations of disorders in the course of LB, evaluation of subclinical changes in the inner ear, the auditory nerve and the central pathways of the hearing and/or balance organs as well as possible confirmation by objective diagnostic methods of the present manifestations from the organs of hearing and balance, with monitoring of the post-treatment outcome and objective assessment of their cause-and--effect relationship with borrelial infection.

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DISCLOSURE OF INTEREST

The authors report no conflicts of interest.

Author's contribution

Study design – B. Oczko-Grzesik, G. Lisowska, M. Misiołek, A. Boroń-Kaczmarska, K.-F. Hamann
Data collection – B.Oczko-Grzesik, N. Rubicz, I. Kawecka
Data interpretation – G. Lisowska, B. Oczko-Grzesik, N. Rubicz, I. Kawecka
Statistical analysis – B. Oczko-Grzesik, L. Kępa
Manuscript preparation – B. Oczko-Grzesik, L. Kępa
Literature research – B. Oczko-Grzesik, L. Kępa

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