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Lyme borreliosis, an etiological factor in sensorineural hearing loss?

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Abstract The incidence of Lyme borreliosis was studied prospectively in 165 patients with acute idiopathic sensorineural hearing loss. The prevalence of positive levels of antibodies against *Borrelia burgdorferi* was sixfold higher in patients with sensorineural hearing loss than in the general population in Finland. Four patients fulfilled the criteria for Lyme borreliosis. No specific risk factors were found with which to predict the occurrence of Lyme borreliosis among patients with hearing loss. In logistic regression modeling the poor outcome of hearing loss was best explained by advanced age, high-frequency or flat-type hearing loss, and absence of positive levels of antibodies against *B. burgdorferi*. Although the causal relationship between Lyme borreliosis and sensorineural hearing loss is difficult to verify, we suggest that Lyme borreliosis is a rare but potentially treatable cause of sudden deafness. We propose that in endemic areas antibodies against Lyme borreliosis should be determined in patients with idiopathic sensorineural hearing loss.

Keywords *Borrelia burgdorferi* · Lyme borreliosis · Cranial neuropathy · Sensorineural hearing loss

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Introduction

Idiopathic sudden sensorineural hearing loss (SHL) is a loss of hearing that develops during a period not exceeding a few hours or is present on awakening. In the vast majority of cases sudden SHL is unilateral. The annual incidence of sudden SHL appears to increase with advancing age and is reported to be between 5 and 20 cases per 100,000 population [3].

Viral infections [35], autoimmune disease [21], vascular insults [1] and labyrinthine membrane rupture [11, 34] have been suggested as causes of sudden SHL. In approximately two-thirds of patients sudden SHL has a natural tendency to heal spontaneously [20]. The prognosis of sudden SHL is influenced by several factors, including the shape of the audiogram (low- and middle-frequency hearing losses heal better), age of the patient (the elderly have a poorer prognosis) and the presence of vertigo (vestibular symptoms indicate impaired recovery) [3, 17]. The longer the hearing loss persists, the poorer is the return to normal hearing [3, 20]. Several viral and bacterial infections [14], including lues [13], are recognized causes of sudden SHL. *Treponema pallidum*, the causative agent of lues, and *Borrelia burgdorferi* belong to the same eubacterial order Spirochetales. These two spirochetes not only share many morphological features and antigenic properties, they also induce many similar clinical findings. These similarities include the staged progress of the symptoms, the rapid spread of the pathogen into the central nervous system [6, 19], focal vasculitic lesions [2], and various neurological abnormalities, including cranial nerve dysfunctions [29].

The vestibulocochlear nerve is involved in fewer than 5% of cranial neuropathies in patients with Lyme borreliosis (LB) [29]. LB seems to affect the cochlear part of the nerve more often [31], but the vestibular part can also be involved [10, 25]. Reik [30] has reported the occurrence of sudden SHL in patients with both early and late LB. Serological evidence of LB has also been reported in about one-fifth of patients with sudden SHL [9, 15]. Ad-

ditionally, four of ten patients with vertigo and serological evidence of LB; four had sensorineural hearing impairments [32].

The aim of the present study was to evaluate the incidence of LB among patients with sudden SHL in Finland, the characteristics of the hearing loss and other neuro-otological symptoms of these patients.

Materials and methods

Patients

A total of 230 consecutive patients with sudden SHL were treated prospectively in the Department of Otolaryngology, Helsinki University Central Hospital, between 1 January 1993 and 31 December 1994. The study protocol was reviewed and approved by the research ethics committee of the Department. Forty-five patients with sudden SHL related to other causes, such as trauma, Menière's disease, and vestibular schwannoma were excluded. The audiological follow-up data of a further 20 patients were missing, so that data of 165 patients with 168 episodes of sudden SHL were available for further analysis. In the three patients with bilateral sudden SHL each ear was evaluated separately. Demographic data from each patient, including age, gender, ear involved, presence of tinnitus or vertigo, and the delay from the onset of symptoms to the recording of the initial audiogram were recorded in a self-administered questionnaire at the time of the first visit (Table 1). The initial and follow-up audiograms defined air and bone thresholds. The shapes of the initial audiogram (up-slope, down-slope, flat, or middle frequency) were also recorded.

Serology

Antigen for the measurement of serum antibodies against *B. burgdorferi* flagellin was obtained from a commercial kit (Dako, Glostrup, Denmark), which included plates for an enzyme-linked immunosorbent assay that were coated with the endoflagellum of *B. burgdorferi*. The sera were diluted serially in threefold steps for the test and applied to the plates for overnight incubation. The bound antibodies were detected by biotin-labeled goat anti-human IgM or IgG (Zymed, Los Angeles, Calif., USA) and streptavidin alkaline phosphatase (Zymed). An end-point titer was obtained at an optical density determined by a cutoff control provided with the kit. The titer limit for a positive IgG antibody level was 500 and for positive IgM was 2500. These cutoff levels conformed with the level of the mean +3 standard deviation for a reference population living in central Finland [33].

Antibodies in the cerebrospinal fluid (CSF) were studied by the same method as the serum antibodies starting from dilution 1–3. To demonstrate the intrathecal antibody production the ratio between IgG antibody titers in the CSF and serum were compared with the corresponding ratio of total IgG concentration. If the calculated ratio of the CSF was more than twice as high as that of the serum, IgG antibodies to *B. burgdorferi* in the CSF were considered to be synthesized intrathecally. The CSF was also examined for cells, protein, albumin, IgM, and IgG, and the IgG index [18] was calculated. A *T. pallidum* hemagglutinin assay (TPHA, Porton Cambridge, Newmarket, UK) was used to exclude lues.

Table 1 Demographic and clinical characteristics of the 165 patients with sudden hearing loss (*NA* not available)

	Patients with definite LB (n = 4)	Patients with probable LB (n = 16)	Seronegative patients (n = 145)[a]
Male/female	1/3	5/11	75/70
Mean age (years; range)	37.8 (8–56)	48.2 (14–81)	50.9 (14–87)
Side of hearing loss			
Right (%)	2 (50)	6 (37)	70 (48)
Left (%)	2 (50)	10 (63)	72 (50)
Bilateral (%)	0	0	3 (2)
Delay (days; range)[b]	23.5 (7–50)	32 (1–120)	6.3 (0–180)
Type of hearing loss (%)			
Up-sloping	1 (25)	2 (12)	21 (14)
Middle-frequency loss	0	0	17 (11)
Down-sloping	1 (25)	11 (69)	53 (36)
Flat-type	2 (50)	3 (19)	57 (39)
Tick bite (%)	1 (25)	5 (31)	NA
Tinnitus (%)	3 (75)	13 (81)	118 (80)
Vertigo (%)	3 (75)	7 (44)	44 (30)

[a] Includes three bilateral cases in which each ear was evaluated separately

[b] Mean delay between the onset of hearing loss and the initial audiogram

Polymerase chain reaction

DNA was extracted from the serum specimens by InstaGene DNA extraction matrix (Bio-Rad Laboratories, Hercules, Calif., USA). Following this 200 µl of the matrix was added to 100 µl of serum and incubated at 56 °C for 30 min. The specimen was then mixed for 30 s, incubated at 100 °C for 8 min, mixed briefly and centrifuged at 13,000 rpm for 3 min. Then 5 µl of the supernatant was used in the polymerase chain reaction (PCR) amplification.

The target of the PCR amplification was a segment of the gene encoding the 41-kDa flagellin of *B. burgdorferi*. The primers were modifications of those described by Picken et al. [12, 27]. The primers used included sequences (5′–3′) CTGCTGGCATGGGAGTTTCT (128–147), TCAATTGCATACTCAGTACT (857–838), AAGGAATTGGCAGTTCAATC (271–290), ACAGCAATAGCTTCATCTTG (560–541) and GCATTTTCAATTTTAGCAAGTGATG (767–743). Oligonucleotides were synthesized by an automatic DNA synthesizer (Model 391 PCR-Mate DNA Synthesizer; Applied Biosystems, Foster City, Calif., USA) based on phosphoamidite chemistry. The PCR mixture contained 50 mM KCl, 10 mM Tris-HCl (pH 8.8), 1.5 mM $MgCl_2$, 0.1% Triton X-100, 200 µM deoxyribonucleotides (Pharmacia P-L Biochemicals, Milwaukee, Wis., USA), 20 pmol of each oligonucleotide primer, 1 U polymerase (DynaZyme, Finnzymes, Espoo, Finland), and purified DNA. The reaction volume was 50 µl, and a total of 40 cycles was carried out in a thermal cycler (HB-TR1; Hybaid, Middlesex, UK). The temperatures were 94 °C for 1 min (denaturation), 50 °C for 1 min (annealing) and 72 °C for 1.5 min (extension). After amplification 20 µl of the reaction mixture was run in a 1.5% or 2% agarose gel. After staining with ethidium bromide and destaining with water the PCR products were visualized and photographed under ultraviolet light.

Rigorous measures were undertaken to avoid carry-over contamination and contamination caused by amplicon. The pre- and post-PCR stages of the process were carried out in physically separate rooms and by separate technicians. Each PCR run included a positive control containing DNA extracted from reference strain B31 of *B. burgdorferi* sensu stricto (ATCC 35210). Every fifth or sixth tube of each run was used as a negative control and was subjected to all sample treatment procedures.

Audiological evaluations

Pure-tone audiometry was recorded at frequencies of 0.125, 0.250, 0.5, 1, 2, 4, and 8 kHz for both ears (Madsen OB822, Madsen Electronics, Denmark). The outcome data included the pure-tone averages (PTA) of hearing thresholds of 500, 1000, 2000, and 4000 Hz and the PTA recovery percentage, which was calculated as a ratio between PTA improvement and the initial PTA as: [(initial PTA–final PTA)/initial PTA] × 100. The percentage PTA im-

provement included the PTA of the opposite ear as reference: [(initial PTA–final PTA)/(initial PTA–opposite ear PTA)] × 100. In addition, recovery of hearing was ranked into four categories: complete [final PTA better than 10 dB hearing level (HL) or equaling that of the uninvolved ear)], good (final PTA less than 40 dB HL or more than 50 dB HL improvement from the initial audiogram), fair (final PTA worse than 40 dB HL, but at least a 30 dB HL improvement), and poor [20]. During follow-up a Nicolet compact auditory electrodiagnostic system (Nicolet Spirit; Nicolet Instrument, Madison, Wis., USA) was used for measuring the brainstem auditory response of the patients with a permanent hearing deficit. The stimuli were transduced by TDH-39 earphones.

Magnetic resonance imaging

Magnetic resonance imaging enhanced with gadolinium or computed tomography of the posterior fossa area was performed for patients for whom the brainstem audiometry suggested retrocochlear pathology.

Criteria for the diagnosis of Lyme borreliosis

In addition to positive levels of serum antibodies against *B. burgdorferi*, the diagnosis of definite LB was based on (a) history of erythema migrans and/or (b) a positive PCR test. Erythema migrans was defined as an expanding erythematous lesion with a diameter of at least 5 cm. Erythema migrans in our patients was verified by history after showing photographs of typical erythema migrans lesions to the patients, but actual lesions were not seen by a physician. The group with probable LB included seropositive patients not fulfilling the diagnostic criteria for LB, where the seronegative group included patients without serum antibodies against *B. burgdorferi*.

Treatment of sensorineural hearing loss

During the present study there was no consistent therapy program for the patients with sudden SHL in our Department. The therapy given included either a single intramuscular corticotrophin-releasing hormone dose, peroral prednisone (1 mg/kg) for 2 weeks with diminishing doses, miscellaneous peroral medication, rest in bed for 1 week, or no treatment.

Treatment of Lyme borreliosis

Patients with definite LB were treated with intravenous ceftriaxone (100 mg/kg per day) for a maximum dose of 2.0 g per day) for 2 weeks.

Statistical analysis

The χ^2 test performed with StatView 4.5 software (Abacus Concepts, Berkeley, Calif., USA) and the analysis of variance and logistic regression test performed with S-Plus 4 software (MathSoft, Seattle, Wash., USA), were used for the statistical methods.

Results

Laboratory findings

Of the 165 patients with sudden SHL 20 (12%) had positive levels of antibodies against *B. burgdorferi*, which is six times more common than in the general population in our area. Nine of them had IgM antibodies only, another nine had IgG antibodies only, and two had both IgM and IgG antibodies. The geometric mean levels of the IgM and IgG antibodies of seropositive patients were 2.0-fold (range 1.1–4.4) and 1.6-fold (range 1.1–2.2) higher than the cutoff limit, respectively. The sera of 11 patients of the 20 seropositive patients were tested by *Borrelia* PCR, which was positive in two cases. Seronegative patients were not tested. The *T. pallidum* hemagglutinin assay was negative in the sera of all 13 of the patients studied.

The CSF was analyzed in 3 of the 4 patients with definite LB (2 men, 1 women; age range 37–56) and in 9 of the 16 patients with probable LB (2 men, 7 women; age range 40–69). None of them had positive levels of antibodies against *B. burgdorferi* in the CSF; also the *Borrelia* PCR of the CSF was negative in all cases. The protein, albumin, IgM, and IgG concentrations, the IgG index and the leukocyte count were normal for all the CSF specimens.

Patients with definite Lyme borreliosis

Two of the four patients with definitive LB (a 48-year-old man and a 7-year-old girl) had untreated erythema migrans, one 30 days and the other 180 days before the onset of hearing loss The other two had a positive PCR result from their sera. One of the four patients with definite LB recalled a previous tick bite and two had arthralgias concurrent with sudden SHL, but none of them had a frank arthritis. Three of the patients had both vertigo and tinnitus at the onset of symptoms.

Hearing, tinnitus, and vertigo

Two patients with definite LB, five from the probable LB group and two from the seronegative group came to our institution after more than 30 days from the onset of sudden SHL. Because at the time of the initial audiogram these cases were already in a convalescent and stable phase, they were omitted from the statistical analysis of our outcome parameters.

The mean PTA in the initial audiogram in the affected ears varied between 4 and 119 dB HL (Table 2). Four patients with an initial PTA less than 10 dB HL had previous audiograms confirming sudden SHL. There was no signif-

Table 2 Recovery according to the grading of the 165 patients, including three bilateral cases, with sudden hearing loss

Improvement	Patients with definite LB (n = 4)		Patients with probable LB (n = 16)		Seronegative patients (n = 145)	
	n	%	n	%	n	%
Complete	3	75	3	19	29	20
Good	1	25	10	62	67	45
Fair	0	–	0	–	9	6
Poor	0	–	3	19	43	29

Table 3 Audiological parameters of 156 of 165 patients with sudden hearing loss (nine patients initially evaluated in the convalescent phase were excluded)

	Patients with definite LB (n = 2)[c]	Patients with probable LB (n = 11)[d]	Seronegative patients (n = 143)[e, f]
Mean initial PTA (dB HL)	12.5	45.3	58.0
Mean final PTA (dB HL)	7.5	31.1	34.6
Mean PTA difference (dB HL)[a]	5.0	14.3	24.0
Recovery percentage (%)[b]	28.6	33.4	44.6
Improvement percentage (%)[b]	80.0	42.2	66.0

[a] Initial PTA–final PTA
[b] For the equation, see text
[c] Two patients initially evaluated in convalescent phase excluded
[d] Five patients initially evaluated in convalescent phase excluded
[e] Includes three bilateral cases for which each ear was evaluated separately
[f] Two patients initially evaluated in convalescent phase excluded

icant difference in the mean initial PTA levels between the patient groups (Table 3). The mean PTA difference (difference between the initial and final PTA) varied between 0 and 118 dB HL. It was highest in the seronegative group and lowest in the definite LB and probable LB groups (P = 0.005). The mean PTA recovery percentages reflecting the absolute final improvement in hearing loss did not reveal any significant differences between the groups.

The graded recovery tended to be more often complete for the patients with definite LB (75% vs. 19% and 20%), but the difference was not significant (P = 0.21) and may have been biased by the relatively mild hearing loss in LB group. The percentage PTA improvement, which is measured using the opposite ear as reference for recovery, was also best in the seronegative group; however, the difference between the probable LB and seronegative groups was not significant (P = 0.07).

There were no significant differences in the occurrence of vertigo and tinnitus between the groups, although vertigo was less prevalent in the seronegative group than in the other groups.

Seasonal distribution of hearing loss

The occurrence of sudden SHL was evenly distributed throughout the year in all the groups. However, there was a slightly increased incidence of sudden SHL in early spring (March–April) and late autumn (October–November; Fig. 1).

Treatment and recovery of the patients with Lyme borreliosis

All four patients with definite LB received parenteral ceftriaxone for 2 weeks. One of the patients received another course of ceftriaxone 9 months after the first course because of relapsing symptoms, including hearing loss and vertigo. The arthralgias of two patients initially responded well to the antimicrobial therapy, but the joint symptoms of these patients recurred later without any laboratory evidence of a relapse of borrelial infection.

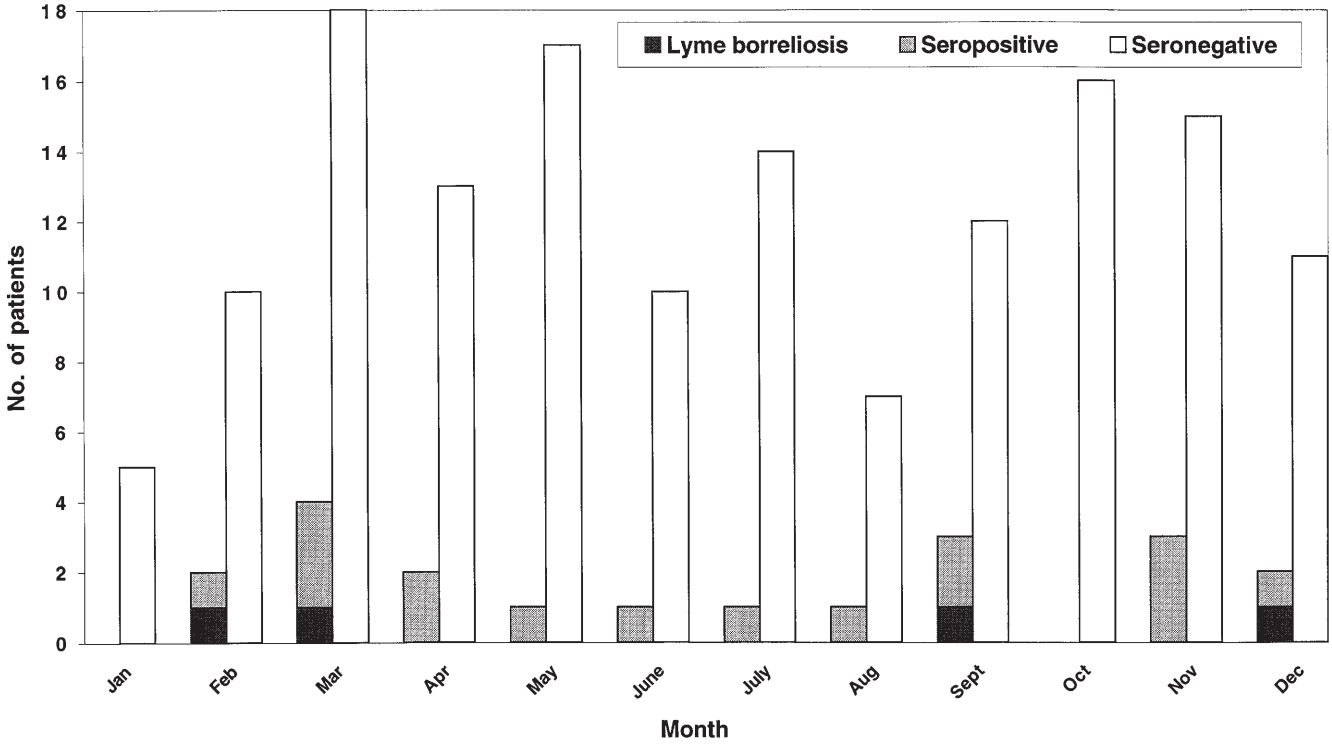

Fig. 1 Seasonal distribution of the 168 cases of sudden deafness

In addition to the patients with definite LB, four patients from the probable LB group received a 14-day course of ceftriaxone. There was no significant difference in the audiological outcome between patients in the definite LB and the other two groups or between the patients with and without antimicrobial medication.

Factors influencing the outcome of hearing loss

The χ^2 test showed no significant differences in outcome between seronegative and seropositive patients. Logistic regression was used in order to find a model to explain the outcome of sudden SHL. The explanatory variables selected for the modeling were the advanced age of the patient, seropositivity against *B. burgdorferi* and the shape of the audiogram (high-frequency hearing loss as reference). For the best model all selected variables were needed to explain the outcome of the hearing loss. The odds ratio (OR) for poor outcome was 0.7 (95% CI 0.5–0.9) for age per 10 years, 7.8 (1.6 –38) for low-frequency hearing loss, 1.2 (0.6–2.6) for flat-type hearing loss, 10 (1.2–84) for middle-frequency hearing loss (hearing loss types compared with high frequency hearing loss) and 3.4 (0.9–13) for seropositivity. These OR values correspond to the minimum (P = 0.23) and maximum (P = 0.99) probabilities of the patients to recover from their hearing loss.

Since serological material was collected prospectively, it was possible to calculate the probabilities corresponding to the OR values. Patients with the best probability to recover from sudden SHL (P = 0.99) had a combination of age less than 30 years, middle-frequency hearing loss and positive levels of antibodies against *B. burgdorferi*. On the other hand, patients with the poorest probability of recovering (P = 0.23) were older than 80 years and had high-frequency hearing losses and no antibodies against *B. burgdorferi*.

Risk of Lyme borreliosis

An attempt was made to evaluate the risk of LB for patients with various clinical signs and findings by cross-tabulating data (Table 1). However, in the χ^2 test, there were no significant differences in the occurrence of clinical signs and findings in the patient groups. Vertigo was more common in the definite LB and probable LB groups, but this difference was not significant. Thus no risk factors were found to predict the occurrence of LB in patients with sudden SHL.

Discussion

In the present study we found that 4 of 165 patients (2.4%) with sudden SHL had definite LB. We believe that LB is a rare but recognizable cause of sudden SHL. Borreliosis can be present with sudden SHL or sudden SHL may be part of the clinical findings due to LB [16, 22, 28, 36] The causal relationship between sudden SHL and the underlying spirochetal infection is difficult to verify, however. The published series concerning LB in patients with sudden SHL are too small and altogether limited in number.

The prevalence of seropositivity against *B. burgdorferi* in our patients with sudden SHL was six times higher than the prevalence of seropositivity in the general population in our area. The prevalence of seropositivity against *B. burgdorferi* in over 2000 patients with vertigo in our Department was 2%, which is at the same level as the prevalence of seropositivity in the normal Finnish population [25]. In accordance with our results, some previous studies have shown a connection between sudden SHL and the presence of positive levels of antibodies against *B. burgdorferi* [8, 10, 22, 31]. If not supported by other positive laboratory findings or typical clinical signs, a positive serological finding alone does not confirm the causal relationship between sudden SHL and LB.

Intrathecal production of antibodies against *B. burgdorferi* is a definite evidence of Lyme neuroborreliosis. The lack of pathological CSF findings in our patients raises doubt of causal relationship between sudden SHL and LB in these patients. Pathological CSF findings in patients with cranial nerve affections are frequent, which is also supported by our own findings in children with LB-related facial paralysis [26]. There is, however, a subgroup of patients in LB patients with localized cranial nerve dysfunctions without CSF pathology. This has been reported in both North American [7, 24, 30] and European patients with facial paralysis [4]. Because early LB has a tendency to be limited spontaneously, the occurrence of CSF pathology is a matter of timing of the CSF sample. This is also one possible explanation for the lack of CSF abnormalities in our series. In the early course of neurological LB the probability of pathological CSF findings is higher [23]. In future studies it is important to diagnose and test sudden SHL patients with LB as early as possible to find possible definite signs of Lyme neuroborreliosis and to more clearly show a causal relationship between sudden SHL and LB.

Sudden SHL generally has a rather good prognosis. Approximately two-thirds of patients improve without specific treatment [5, 20]. Because of the high spontaneous recovery rate it is not easy to determine the efficacy of treatment on patients with sudden SHL. In addition, even prospective studies may be biased and prone to interpretive error because not all patients can be studied at the same stage of the disease [14]. A few case reports have shown a beneficial effect of antimicrobial treatment on the recovery of sudden SHL in patients with LB [28, 36]. In our study antimicrobial treatment did not, however, affect the audiological outcome of patients. To demonstrate the role of LB in patients with sudden SHL and the effect of antimicrobial medication on recovery, further studies are required with larger series of patients with definite diagnoses of LB.

Our analysis of the audiological results in our patients showed no typical characteristics of sudden SHL caused

by LB and no risk factors to predict the occurrence of LB in these patients. Data analysis revealed slight differences between our groups, but the number of patients in the definite LB group was too small to allow any significant differences to be determined.

Our present study indicated that positive levels of antibodies against *B. burgdorferi* were associated with better recovery, as were a young age and low or middle-frequency types of hearing loss. Although the causal relationship between seropositivity and sudden SHL remains elusive, seropositivity in our study seemed to be linked to a favorable outcome of sudden SHL.

Our study provides further evidence that sudden SHL may be caused by LB. Special attention must be paid to the careful assessment of a patient's medical history, with special emphasis on clinical signs and symptoms of LB. In the case of a positive history of Lyme borreliosis further investigations of serum and CSF for LB are needed. Further studies with better methods for the diagnosis of LB and larger series of patients are still needed to clarify the causal relationship between hearing disorders and LB.

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