Lyme Borreliosis – Waiting for Lyme Carditis?

A long-term prospective study

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Abstract: A long-term prospective study of patients with confirmed non-cardiac form of Lyme disease (n=221) over a mean follow-up period of 40.6 months is reported. The study revealed no case of Borrelia-related cardiac involvement developed after several years in patients who had received antibiotic therapy in the early period. Therefore, these patients do not need follow-up by a cardiologist.

Key words: Lyme borreliosis – Lyme carditis – Antiborrelial antibodies

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Introduction

Lyme borreliosis (LB) is a tick-borne infectious disease caused by Borrelia burgdorferi (Bb). The disease may evolve up to a picture of multiorgan failure. It poses a medical challenge on account of its variable course, difficulty in diagnosing it, and often persisting problems after appropriately instituted causal antibiotic therapy [1, 2]. Because of its epidemic to endemic incidence (a total of 3677 cases were reported in the Czech Republic in 2003), it drew attention of not only microbiologists and epidemiologists but also, most importantly, of clinicians and it is becoming a society-wide issue in many industrialized nations.

It occurs all over the world, endemically in nature. In our geographic zone, LB is most frequent anthropozoonosis.

As the main carriers are ticks capable of Bb transmission, the site of the occurrence is the main determinant of the risk for LB [4]. The infection rate of ticks with Bb is high; the studies conducted in the Czech Republic have shown region-specific infection rates ranging from 1.9 to 22% [3]. The invasion of the body by Bb is associated with activation of cellular and humoral immunity [4, 5]. However, it is a well-known fact that even completely health individuals may have positive antiborrelial antibody levels [6].

The course of LB can be divided into several stages, although another sequence of disease patterns may also be present in some cases. The classification of clinical stages of LB, as proposed by Asbrink, has been accepted and is still in use [12]. Cardiac complications, referred to as Lyme carditis (LC) appear in the early stage of disease dissemination [12]. The incidence of cardiac manifestations in LB patients is reported to be 8% in North America and up to 4% in Europe [8, 9, 10].

Proper diagnosis depends mainly on clinical findings, with notifications of the incidence of LB employing primarily the diagnostic criteria developed by the U.S.-based Centers for Disease Control and Prevention [11]. The evaluation is based exclusively on objective clinical criteria of involvement of the organ system and on laboratory confirmation of infection. It should be noted that the above criteria are not those used to establish the diagnosis in a specific patient but criteria for report on the numbers of patients, which is not always necessarily the same. Proper use of serologic tests is another prerequisite for establishing a correct diagnosis.

Cardiac complications include various degrees of atrio-ventricular blocks in 77%, bundle branch blocks or intraventricular conduction disorders in 13%, myopericarditis in 16%, and congestive heart failure in 13% [12, 13]. However, another survey gives an incidence of 19% for conduction disorders, 10% for

Lyme disease Czech Republic

1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
4062	6300	4192	2470	2138	2722	3847	3547	3658	3677	3243

myocarditis, 5% for left ventricular failure, and 69% of patients were included in a group with palpitations; 21% required hospitalization [14]. The condition apparently does not involve the valvular system; however, a case report was published [15]. Fatal cases have also been reported, but not adequately supported in all cases [16]. Gasser published two cases of coronary artery aneurysm related to Bb infection [17].

Experiments with mice have been carried out to develop models allowing the study of cardiac involvement in the course of Lyme disease [18, 19]. $CD4^+$ T lymphocytes have also been shown to play a role in the development of the pathological process initiated by immune mechanisms in knockout mice with Bb-caused myocarditis and arthritis [20]. However, a role of lymphocytes is not indispensable in the early stage of cardiac involvement, and a direct response by macrophages to Borrelia into cardiac tissue has been demonstrated [21].

Over the year 1987 through 1992, the team carrying out research into LB in our department identified, in its outpatient clinic, a total of 62 patients with an established LC out of the more than 100 patients suspected to have the condition. However most of those with the diagnosis beyond any doubt, had had cardiac problems from the beginning, or had LC already in the early stage of LB. Still, in keeping with sporadic literary reports, we noted that there are the patients not developing cardiac involvement until long after the acute stage of LB; with the cardiac involvement taking both the form of conduction system disorders (sinoatrial and, primarily, atrioventricular blocks) and the form of dilated cardiomyopathy [22, 23].

Another question yet to be answered and the resulting uncertainty relates to information on the unreliability of interpretation of serologic results and information on inadequate efficacy of antibiotic therapy with commonly used regimens.

All these facts taken together made us conduct a prospective study designed to furnish clear and consistent information whether the patients with the acute stage of LB treated with antibiotics may later develop cardiac involvement and, if so, at what time interval.

To date, no prospective study has been published in this respect. The only three studies whose results have been published are retrospective ones analyzing the medical records of patients who had previous LB [24, 25, 26]. The results of the above studies were not reported until 1997, 1998, and 2000, respectively, that is, not until several years after our study had been launched.

Aim of study

The main goal of our study was to establish,

1) Whether patients with the non-cardiac form of LB in the acute stage, treated with antibiotics, may later develop cardiac involvement with Bb. If so,
2) At what time interval and in what forms,

3) To determine the relationship between the late cardiac complications and the antibiotic regimen in the early stage and the potential for their therapeutic modulation.
4) The last goal defined before start of the study was to describe the dynamics of antiborrelial antibody levels in the affected patients.

Patients

A total of 221 strictly consecutively chosen (after exclusion of patients with known heart disease) patients (152 women and 69 men with a mean age of 44.77 years at inclusion) were included in the study (Table 1). The following relative organ involvement was present in the probands: skin 100%, joints 54.8%, fatigue syndrome 52.0%, ocular involvement 15.4%, nodal syndrome 14.5%, facial nerve paralysis 6.8%, and another neural condition 5.4%. A tick in the pre-disease history was reported in 61.1%. The patients were most often treated with a tetracycline-family antibiotic, in 64.3%, penicillins in 44.3%, cephalosporins in 17.2%, macrolides in 16.7%, and chloramphenicol in 0.9% of cases.

Methods

Patients were included into the study and remained on follow-up during the period from January 1, 1993 through June 30, 2000 (7.5 years = 90 months). In all patients the diagnosis of LB with non-cardiac localization was established beyond any doubt. As a rule, the criteria of the U.S.-based Centers for Disease Control and Prevention for erythema migrans (EM) (as assessed by a physician) had to be met, with clearly positive antiborrelial antibody levels determined thereafter. The individual referring physicians investigated the antibodies in local laboratories using procedures commonly used. Given the inter-laboratory differences, we do not report the absolute values obtained, but only positive/negative values. All other antiborrelial antibody level determinations were performed using ELISA exclusively by the National Reference Laboratory for LB CEM at the State Health Institute in Prague as a center cooperating with the World Health Organization.

After giving their informed consent, patients completed their medical history questionnaire with an emphasis on heart disease (as a potentially exclusive criterion; another heart disease or left ventricular dysfunction in the early stage) and on epidemiology. The possible exposure to a tick and the presence, be that of professional or a recreational purpose, in the endemic region was also established.

Table 1 – Average age of the patiens

Average age in patients with erythema migrans (years)	44,7
Minimum (years)	16,0
Maximum (years)	79,9

Those included were examined on a regular basis (at an approximately six-month interval) for the potential development of cardiac involvement. If another heart disease was diagnosed, the

probands were excluded from the study; if Bb-based cardiac involvement had developed, this would have meant the endpoint of the study.

Standard 12-lead electrocardiogram was obtained, and 24-electrocardiographic Holter monitoring, bicycle stress test, transthoracic echocardiography were performed, blood samples collected for antiborrelial antibody level determination, Na^+, K^+, Cl^-, and T_3, T_4 and TSH hormone analysis, and physical examination was performed by a cardiologist in all patients regardless of the symptomatology (i.e., even in asymptomatic patients).

In the presence of potentially cardiac symptoms (subjective or objective), the patients were examined using routine algorithms. Emphasis was particularly placed on exclusion/confirmation of coronary disease due to atherosclerosis as the most frequent heart condition in adult individuals.

Under the study protocol, whenever a cardiac symptom was found, the patient was to have another bicycle stress test which, if positive in terms of myocardial ischemia, was to be followed by thallium stress myocardial scintigraphy which, again, if positive or in the presence of an echocardiographic pattern of dilated cardiomyopathy, was to be followed by selective coronary angiography.
Right ventricular endomyocardial biopsy was obtained in patients with normal finding.

The incidence of cardiac symptoms always with the time point of their first manifestation from eruption of erythema migrans and subsequent exclusion of coronary atherosclerosis and/or another heart disease, were thus determined.

Subjective cardiac symptoms included palpitations which the patients complained of (decreasing the quality of their lives) and chest pain (with no other apparent reason).

Our definition of objective cardiac symptoms included new onset of atrial fibrillation, sino-atrial blocks, atrio-ventricular blocks, fascicular and bundle blocks, ectopic ventricular activity and, possibly, signs of electric ventricular instability. Statistical description and evaluation of ventricular ectopy were undertaken using the classification by Lown [27] aware as we were of all its pitfalls (specifically its almost zero value in determining its severity, i.e., prognosis of patients with ventricular ectopy without a structural heart disease). Apart from ECG criteria, these included the echocardiographic picture of pericardial effusion and signs of left ventricular dilation suggestive of dilated cardiomyopathy.

The study endpoint was defined under the study protocol in compliance with the U.S.-based Centers for Diseases Control and Prevention, literary data, and our own experience as *the development of AV block of a higher degree or the development of dilated cardiomyopathy in the absence of another heart disease and in the presence of evidence for borrelial activity* (ideally by direct evidence of the presence of Bb in the myocardium using electron optical visualization, PCR from blood or, indirectly, by means of antiborrelial antibody level determination using ELISA and borrelial antigens using Western blot.

Identification of any of the above objective cardiac symptoms served as an indicator of the possible development of heart disease, and provided the basis for the ensuing diagnostic procedure.

The mean period of follow-up of the probands was 40.6 months with a maximum of 94.2 months, minimum of 0.0 months, standard deviation 26.5, and median 42.9 months.

Results

New significant *palpitations* occurred in 53 patients (24%) at a mean 21.6 months from erythema migrans; *chest pain* in 37 patients (16.7%) at a mean 21.9 months post EM.

Electrocardiographic findings. Sino-atrial block occurred in two patients (0.9%). First-degree atrio-ventricular was identified in four patients (1.8%), second-degree atrio-ventricular block in one female patient (0.45%); no third-degree atrio-ventricular block was detected. Anterior fascicular block was identified in two patients (0.9%), right bundle branch block in 11 probands (5.0%); there was no case of posterior fascicular block and left bundle branch block. One female patient with sino-atrial block (with a maximum pause of 2750 ms), second-degree atrio-ventricular block, and paroxysmal atrial fibrillation was implanted a DDD pacemaker. Selective coronary arteriography and endomyocardial biopsy were not undertaken because of the absence of signs of

Table 2 – Incidence of ECG findings

			Interval from EM [months]			
	n	%	Min.	Mean	SD	Max.
Sino-atrial block	2	0.9	62.2	67.0	6.8	71.8
First-degree atrio-ventricular block	4	1.8	8.1	46.0	26.1	67.6
Second-degree atrio-ventricular block	1	0.45	–	71.7	–	–
Third-degree atrio-ventricular block	0	0	–	–	–	–
Anterior fascicular block	2	0.9	2.7	4.1	1.9	5.4
Posterior fascicular block	0	0	–	–	–	–
Left bundle branch block	0	0	–	–	–	–
Right bundle branch block	11	5.0	0.3	21.0	19.3	53.2
Atrial fibrillation	2	0.9	20.5	31.2	15.2	42.0
Atrial flutter	0	0	–	–	–	–
Lown 2 – frequent ventricular extrasystoles (> 30/h)	9	4.1	0.6	25.0	25.7	74.2
Lown 3a – multifocal ventricular extrasystoles	44	19.9	0.1	27.4	23.0	68.6
Lown 3b – bigeminy, trigeminy	18	8.1	0.1	20.6	17.7	57.8
Lown 4a – coupled ventricular extrasystoles	22	10.0	0.1	23.8	20.3	63.1
Lown 4b – ventricular tachycardia	8	3.6	0.4	31.2	22.0	55.9
Lown 5 – R/T phenomenon	2	0.9	15.2	32.0	23.7	48.7

myocardial ischemia during bicycle stress test and antiborrelial antibody negativity. Her condition was diagnosed as sick sinus syndrome. The other patients were not further examined given the insignificance of the findings.

New atrial fibrillation was identified in two patients (0.9%); no atrial flutter was detected. Given the absence of any other cardiac involvement and antiborrelial antibody negativity, the patients were not further examined.

The incidence, frequency, and type of ventricular ectopy are defined by the classification developed by Lown. Lown type 2 (frequent ventricular extrasystoles) was noted in nine patients (4.1%), Lown type 3a (multifocal ventricular extrasystoles) in 44 patients (19.9%), Lown type 3b (bigeminy, trigeminy of ventricular extrasystoles) in 18 patients (8.1%), Lown type 4a (coupled ventricular extrasystoles) in 22 patients (10.0%), Lown type 4b (ventricular tachycardia) in eight patients (3.6%), and Lown type 5 (R on T phenomenon) in two (0.9%) (Table 2). As a rule, non-sustained ventricular tachycardia with a maximum of eight contractions was involved in all patients with recorded ventricular tachycardia. Given the absence of any other cardiac involvement and antiborrelial antibody negativity, the patients were not further examined.

Echocardiographic findings. Pericardial effusion developed in four patients (1.8%) during follow-up. In three cases, the condition was newly described yet "still physiological" pericardial effusion, while moderate effusion was present in one case. The latter was a patient with a recent history of "virosis" who showed spontaneous remission of the finding and had negative antiborrelial antibodies. His condition was diagnosed as benign viral pericarditis. Given the absence of any other cardiac involvement and antiborrelial antibody negativity, the patients with pericardial effusion were not further examined. There was no progression of left ventricular dilatation to the picture of dilated cardiomyopathy.

During the follow-up, eight patients (3.6%) had a positive result of **bicycle stress test**. Thallium stress myocardial scintigraphy was performed in all patients with an inconsistent finding on bicycle ergometry and, also, in all those whose positive results were based on the chest pain yet without electrocardiographic signs of myocardial ischemia. In these patients, impaired myocardial perfusion was demonstrated in one case (0.45%).

Table 3 – Incidence of coronary atherosclerosis

			Interval from EM [months]			
	n	%	Min.	Mean	SD	Max.
Positive ergometry (indicative of ischemia)	8	3.60	0.2	10.0	19.2	56.9
Positive myocardial scintigraphy	1	0.45	–	12.0	–	–
Pathological coronary arteriography = CHD	2	0.90	2.6	4.2	2.2	5.8

Selective coronary arteriography was then performed in four patients, with two (0.9%) shown to have coronary atherosclerosis (Table 3). The other two had endomyocardial biopsy, as defined by the protocol, with Bb not demonstrated in the samples. No clear-cut antiborrelial antibody positive results were seen in these patients.

Aim re 1): *Borrelia-based cardiac involvement was not demonstrated in any of the 221 patients over a mean follow-up period of 40.6 months, who had previously had LB and were treated with antibiotics in the early stage.*

Because of the negative answer to the first, basic question, that is, failure to demonstrate Borrelia-based cardiac involvement in patients who had previously had LB and were treated with antibiotics in the early stage, aims re 2), 3), and 4) became irrelevant.

Discussion

The present study is an absolutely original approach, not yet published in the relevant literature, to the issue of so-called late complications of the early stage of LB in cardiology.

Studies published to date suggest that cardiac complications develop in LB patients [7, 28] in the early stage of the disease. Furthermore, it is beyond any doubt that LB may activate its manifestations (non-cardiac in particular) at a very long interval (years) after the onset of the disease. It has been speculated whether reactivation of latent infection, reinfection by Bb, or non infectious mechanisms are involved. Of the more recent hypotheses, mention should also be made of unrecognized concomitant infection caused by the bite of a tick Ehrlichia, Babesia, or other organisms [29, 30]. Our own experience indicates that, in patients untreated in the early stage, cardiac involvement by Bb may not develop until after several months (if not later) after infection by Bb [22]. This gave rise to the quite simple question whether Bb-caused carditis may also develop in the patients treated, in the early stage of Lyme carditis, with antibiotics.

Two approaches can be taken to get an answer to the above question; a *retrospective analysis of data from patients with previous Lyme borreliosis treated by antibiotics, and a prospective approach.*

The advantage of the former is that it allows evaluating and analyzing data from large groups of patients, yet it requires careful and detailed statistical reports on cases. The drawbacks include the retrospective nature of the procedure which is likely to be associated with some bias, at least in terms of the selection of parameters evaluated. This approach is also fairly demanding because of the need to form a control group and subsequent multivariant analysis. Still, only one, most valuable, study has been published by Sangha to date [24].

The latter is a prospective approach whereby patients with known Lyme borreliosis, treated by antibiotics in the early stage, are followed up, examined regularly by a cardiologist, and the development of cardiac involvement is being

looked for. However, this approach is time-consuming and also requires very careful exclusion of other causes of cardiac involvement.

Using the above approach we demonstrated, in keeping with the study by Sangha, that patients with Lyme borreliosis without cardiac involvement in the early stage, and treated properly by antibiotics do not develop Bb-caused cardiac involvement even after several years.

Our explanation for this finding is that all patients included in our study were treated by physicians experienced in the management of LB, who treated their patients by the appropriate antibiotic for an appropriate period of time.

It is a well known fact from other branches of medicine that there are patients who, despite some antibiotic therapy in the early stage of their disease, may develop late complications – usually neurological ones. As a result, the hypothetical question remains unanswered of the future course of patients with Lyme borreliosis who were "treated", in the early stage of the disease, for an inadequately short period of time. This possibility is suggested by some new concepts regarding the life cycle of Bb and its varying sensitivity to antibiotics over time.

Conclusion

In patients who had had treated Lyme borreliosis in the early stage with antibiotics, we did not demonstrate any cardiac involvement.

As a result, we conclude there is no need for a concern that patients with Lyme borreliosis treated with antibiotics in the early stage could develop cardiac involvement in the late stage, not even at an interval of several years. There is no need for such patients to be treated by a cardiologist.

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