Lyme Borreliosis Infection as a Cause of Dilated Cardiomyopathy

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Abstract: The relatively low percent of patients affected with the cardiac form of Lyme borreliosis is difficult to diagnose, especially if the disease manifests itself in ways other than atrio-ventricular blockade. The advanced stage of Lyme carditis manifesting as dilated cardiomyopathy is a special case of this affliction. The authors of this report present clinical experience with an attempt to support the working hypothesis about involvement of Lyme borreliosis infection in the development of dilated cardiomyopathy. The patients were clinically examined thoroughly with special attention to the cardiovascular system. In addition to the basic clinical methods, the following procedures have been employed: dynamic Holter's electrocardiography, exercise ECG test, coronarography, and myocardial biopsy. From laboratory methods pertaining to the detection of Borrelia, ELISA method, Western blot, PCR, electron microscopy and histopathological analysis were used. In all three cases, clinical and laboratory findings provided the evidence of the borreliosis infection involvement in the development of dilated cardiomyopathy.

Introduction

Cardiac involvement in the course of Lyme borreliosis (LB) occurs rarely in comparison with the skin, joints and nervous system involvement. It amounts less than 4% out of all patients in the European countries. However, cardiac Lyme disease belongs to the most diagnostically challenging [1–3] diseases. According to U.S. literary data, there is predominance of the patients presenting with AV blockades, while in our country there is apparent predominance of patients with manifestations of various frequent arrhythmias. In this report, we would like to pay our attention to the form which belongs to the rarest, to the dilated cardiomyopathy (DCMP).

The Austrian authors drew attention to the possible causative relation between Lyme borreliosis infection and DCMP for the first time in 1990 [4]. Two years later, the reports aimed at detection of Borreliosis infection (BI) in 42 patients with confirmed DCMP were published. In 9 out of them the positivity of serological investigation was detected and the treatment with cephalosporins was recommended. In 6 patients treated this way, the ejection fraction (EF) returned to normal values after 6 months, in 2 patients some improvement was observed and only in 1 patient there was no response.

Borrelia infection as an etiological agent in chronic cardiac failure was proved by the same research team [5, 6, 7, 8]. The situation can be somehow aggravated by the difficulty of morphological detection of the infectious agent [9]. However, it is necessary to say that there has not been so far any unambiguous agreement in Lyme borreliosis infection being a real etiological factor of DCMP [10, 11].

We would like to contribute to this discussion by the experience with 3 patients who developed clinical picture of myocarditis or dilated cardiomyopathy.

Interim experience with 2 out of these three patients was formerly published [12, 13].

Methods

The female patients underwent the complete internal or cardiological examination which in addition to the physical examination included following methods: standard 12-lead electrocardiographic examination using Hewlett Packard Pagewriter apparatus, ECG Holter monitoring performed by apparatus Philips M3 731A system 16672 using recording unit Digitrak Plus 24. Echocardiographic examination was performed using apparatus Sonos 2000 by means of 2D mode, pulsed and continuous Doppler technique and Doppler colour flow mapping. The examination was done in the standard views, size of heart chambers and ascending aorta were measured, volume and systolic function of the left ventricle by biplane-ellipse method and by Simpson method were measured, morphological evaluation and Doppler examination of all valves and of the flow in right upper pulmonary vein were carried out and evaluation of pericardium was performed.

Exercise stress tests were performed by means of stationary bicycle Ergoline ergo-metrics 800S using method of continuous incremental load with 25-Watt starting load and incremental workload every 3 minutes. Coronarographic examination was carried out by standard procedure using apparatus Siemens Coroscope with access via right femoral artery to both coronary arteries in usual views, ventriculography of the left ventricle was performed in the right oblique view. Tomographic examination and all biochemical laboratory analyses were done in the Institute of Clinical Biochemistry and Laboratory Diagnostics (attested by a certificate) of the First Medical Faculty, Charles University in Prague. Examination by ELISA method, Western blot, PCR a Bb detection in biological material were performed by National reference laboratory for Lyme borreliosis (Národní referenční laboratoř pro lymeskou borreliózu), cooperating with WHO and working within National Institute for Public Health in Prague (Státní zdravotní ústav v Praze), using the following procedures:

Plasmid DNA was recovered with the GenElute Plasmid Miniprep kit (Sigma-Aldrich com., Germany). Filter barrier pipette tips and dedicated sets of pipettors were used. PCR was used with the Czech isolates B. garinii and B. afzelii strains 192M and Kc90 and with B31, H13, and BITS control strains with primer sets described by Marconi and Garon (23) and with primers for OspA or OspC genes described elsewhere (24). Multiplex PCR was done as has been described (17). PCR reagents from the Qiagen Taq PCR Master Mix Kit (Qiagen GmbH, Hilden) or from the Gene Amp kit (Roche Diagnostics, GmbH, Germany) were used as recommended by suppliers. PCR amplification was performed with a PTC 200 Peltier Thermal Cycler as described previously. Mix contained 2.5 U of HotStart Taq DNA polymerase (QIAGEN), 200 uM of each

dNTP, 2,0 mM MgCl2 and 1,0 μM forward and reverse LD+ primer 5'-ATGCACACTTGGTGTTAACTA-3', LD- primer 5'-GACTTATCACCGGCAGTCTTA-3' and 0,8 μM forward OspA primer R+ 5'-TGGATCTGGAGTACTTGAAGGCG-3', and reverse primer R- 5'-AGTGCCTGAATT CCAAGCTGCAGT-3', water for PCR (Roche) and 20% of template DNA with concentration of 1–3 μg/1ml.

We used also real-time PCR (rt-PCR) for detection of species-specific DNA in heart tissue. Rt-PCR protocol with the Light Cycler FastStart DNA Master SYBR Green 1 kit (Roche Diagnostics, Mannheim, Germany) was used as recommended. We used 20-μl reaction volume in a glass capillary which each contained 2 μl of SYBR Green I mix, 2.4 μl $MgCl_2$ (4 mM), 1 μl of each primer (3–5 μM), 3 μl of the template DNA and water for rt-PCR. Control DNA was added in different dilution (1:10 – 1:1 mil). Annealing and melting temperatures in different rt-PCRs were dependent on primers. Fluorescence of the melting curve was measured continuously by heating the product to 95° C, cooling it 20 min to 58° C at 20° C/s and then heating it at 0.1 °C/s to 95° C.

Electron microscopy: Tissue samples were fixed in 4% paraformaldehyde with 1.5% glutaraldehyde in 0.1 M cacodylate buffer, washed in cacodylate buffer, postfixed with 1% OsO4, dehydrated and embedded into Epon812 or Lowicryl K4M resin as has been described elsewhere. Semithick and semithin sections were cut using Ultracut LKB equipment and stained by the modified Bosma technique with amylase pre-treatment and AgNO3 stain. Thin sections were stained with uranyl acetate and lead citrate (UALC) and examined under the Jeol 200 CX electron microscope.

Immunohistochemical staining was performed on Lowicryl embedded tissues using streptavidin-biotin-gold or biotin-peroxidase system and the following monoclonal antibodies (Mab) against flagellin (H9724), OspA (H5332) by the method described by [14].

Western blots. Western blotting was performed as previously described. Briefly, a whole cell sonicates of 192M or Kc90 strains were subjected to sodium dodecyl sulphate- polyacrylamide gel electrophoresis and transferred overnight to nitrocellulose membrane (Nm). The membrane strips were incubated with 1:200 dilutions of sera after blocking with gelatine, then washed, and incubated with goat anti- human IgG, IgA and IgM conjugated to alkaline phosphatase. The strips were than washed and developed with substrate (nitrotetrazolium blue solution, Bio-Rad).

Case report No. 1

A 43-year-old female with insignificant past medical history

1993/8: insect bite at the ankle of left lower extremity with reddish coloration and the consequent development of suppurative focus accompanied by swelling. 3 week lasting outpatient therapy by a surgeon.

Epidemiological history: She is not aware of tick bite, but she has been spending her weekends for many years regularly in the epidemiologically unfavourable regions of the central Bohemia.

1994/12: she was referred to the angiological outpatient department because of 6 months lasting oedema of the right ankle joint accompanied by skin rash. Erythema migrans (EM) was suspected and confirmed by biopsy. The patient was treated with amoxycillin (200 mg daily *for* 3 weeks).

1995/6: on check-up found exertional breathlessness (NYHA III), on ECG atrial fibrillation with rapid ventricular response, echocardiographically proved heart dilation – cardiac form of LB was suspected and the patient was hospitalized.

From further examinations

Normal findings: ESR, blood count + differential count, microscopic and biochemical examination of urine, bilirubin, ALT, AST, GMT, ALP, cholesterol, triacylglycerols, glycaemia, ASLO, CRP, 24 hr creatinine clearance, total protein, protein electrophoresis, 24 hours ECG Holter monitoring, coronarography.

Pathological findings: Average value of ELISA method of IgM antibodies = 358 during the years 1995–2004 (minim. = 153, maxim. = 776), average value of IgG class = 2.095 (minim. = 1042, maxim. = 4832) with persistent positivity of WB IgM and persistent negativity of WB IgG.
(Normal level: IgM 900, IgG 700; Border values: IgM 900–1000, IgG 700–900; Positive values: IgM > 1000, IgG > 900)

6. 6. 1995: ECG: atrial fibrillation with rapid ventricular response, HR = 180/min.

Repeated ECG record: sinus rhythm, HR = 67/min. electrical axis + 13 degrees PQ = 0.16 QRS = 0.09 QTc = 0.48, evidence of LV hypertrophy, flat negative T aVL, biphasic T in V1–5, no focal changes.

6. 6. 1995: Chest X-ray: mitral configuration of the heart with mild bilateral dilation. Congestion in the pulmonary circulation, predominantly central type. Smooth diaphragm contours, sharp and clear angles, adequately wide aorta.

6. 6. 1995: Echocardiogram: advanced dilation of both ventricles with severe systolic dysfunction of the left ventricle (LV), estimated ejection fraction of LV (EF LV) about 15% (examined during HR = 150/min.) with global hypokinesis.
Dilation of both atria, mitral regurgitation grade II–III, tricuspid regurgitation grade II–III. Pulmonary hypertension with right ventricle pressure = 50–55 mm Hg.

21. 8. 1995: Repeated echocardiogram end-diastolic diameter LV 6.4 cm, End-systolic diameter 5.2 cm. EF LV = 37–41% (sinus rhythm during examination).

8. 1. 1997: end-diastolic diameter of LV = 6.1 cm, end-systolic diameter = 4.4 cm, EF LV = 48–52%

23. 6. 1995: Endomyocardial biopsy (specimen No. 1).

The finding does not rule out clinical diagnosis of DCMP. In one specimen there are two foci corresponding with focal "borderline" myocarditis, in other sections the foci corresponded to focal "classical" myocarditis. Those 2 foci are not of the same age, in one of them there is as tendency for organization. Amyloid is negative.

6. 8. 1995: Endomyocardial biopsy (specimen No. 2)
Immunofluorescence: Very weak focal positivity of IgG in interstitium. C3, IgA and IgM are negative. In the interstitial tissue, there is exudate and infiltrate consisting mainly of neutrophil leukocytes and lymphocytes, tiny foci of fibrosis. Borreliae are in the close surroundings of fibroblasts. The muscle cells are edematous with damaged actin of the fibrils.
Apparent transversal sections of the Borreliae, containing the cross sections of flagellal and typical extracellular vesicles in the surroundings are observed. Borreliae are localised extracellularly in close adhesion to the endothelial cell. Destruction of the cell membrane is apparent (Figure 1).

20. 6. 1995: Spirometry: vital capacity in the lower range of normal values. Mild obstruction of the small airways. The finding is compatible with diagnosis of cardiomyopathy.

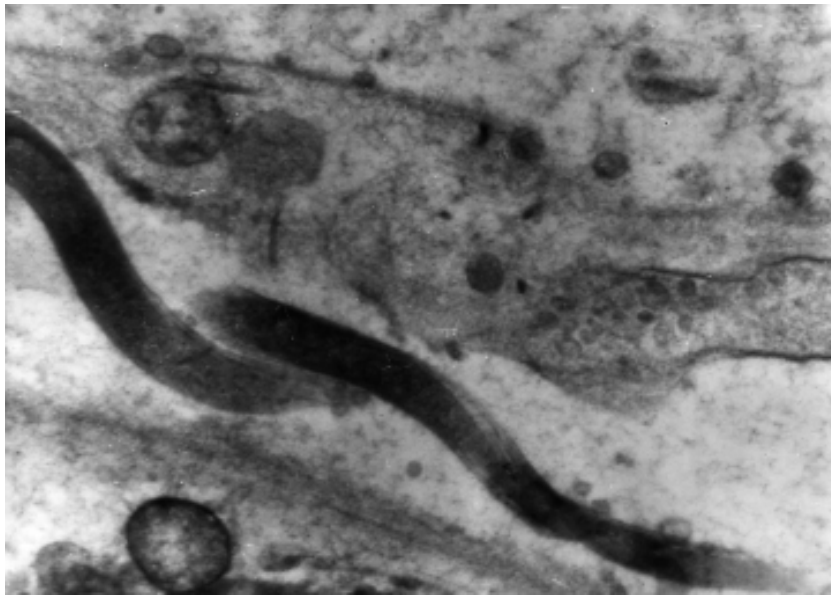

Figure 1 – Myocardium (No. 28905): Spirochete 20 μm long and 0.25 μm thick lying between the myocardial fibres. Spirochetal flagellal are seen under thin outer envelope. Uranyl acetate-lead citrate staining: magnification × 49 300, Bar 1 cm represents 0.3 μm.

The course of the disease

In the female patient with erythema migrans, a skin rash associated with Lyme disease was present along with severe systolic dysfunction of LV accompanied by exertional dyspnoea NYHA III and atrial fibrillation with rapid ventricular response. After heart rate deceleration and starting the therapy with ACE inhibitors, clinical and echocardiographic improvement was achieved. Due to the presence of myocarditis (confirmed by histology), corticosteroid therapy had been started, and after receiving confirmation of Borreliae in the myocardium, the initial therapy with amoxycillin was extended with parenteral administration of Rocephin (cephalosporin) with a total dose of 28 g. In the first year of follow-up, relatively frequent but short-time lasting episodes of atrial fibrillation, and frequent ventricular and supraventricular tachycardia were detected. Annual follow-ups during 8 years demonstrated quite normal ECG recordings (standard ECG and Holter monitoring).

1998/8: Echocardiogram: non-enlarged LV, EF = 49–52%, borderline size of the left atrium, hemodynamically insignificant mitral regurgitation.

2004/9: Echocardiogram: non-enlarged left ventricle, EF = 50%, mild dilation of the left ventricle (found on volume measure, nevertheless the depth parasternally remains normal), hemodynamically insignificant mitral regurgitation. Small calcification in aortal valve with insignificant regurgitation.

Case report No. 2

52-year-old female, suffering from asthmoid bronchitis with polyvalent allergy since childhood (to Sulfamethoxazol, Staphylococci and cold).

In 1990 and 1995, total endoprothesis implantation of the hip due to dysplasia on the basis of congenital luxation, in 1995 infectious mononucleosis. Suffering from back pain for many years, probably linked with the changes of the spine axis because of hip joint replacement. No other serious diseases.

Epidemiological history

1999/7: Three times she had a tick-bite with consequent EM and treated with amoxycillin (20 days). Skin involvement disappeared but later the patient developed breathlessness provoked by usual physical activity, with palpitations occurring episodically. On examination there was anteroseptal ischemia and concurrent positivity of ELISA Lyme IgM.

1999/10: The patient was hospitalized due to acute myocarditis of LB etiology (exposure to ticks, positivity of antiborrelial antibodies) with manifestation of hypokinetic LV. Chronic obstructive lung disease with moderate airway obstruction presented as comorbid condition. After the treatment with antibiotics Rocephin (cephalosporin) and Sumamed (azithromycinum), the patient was discharged in good health condition and referred to the out-patient department for LB.

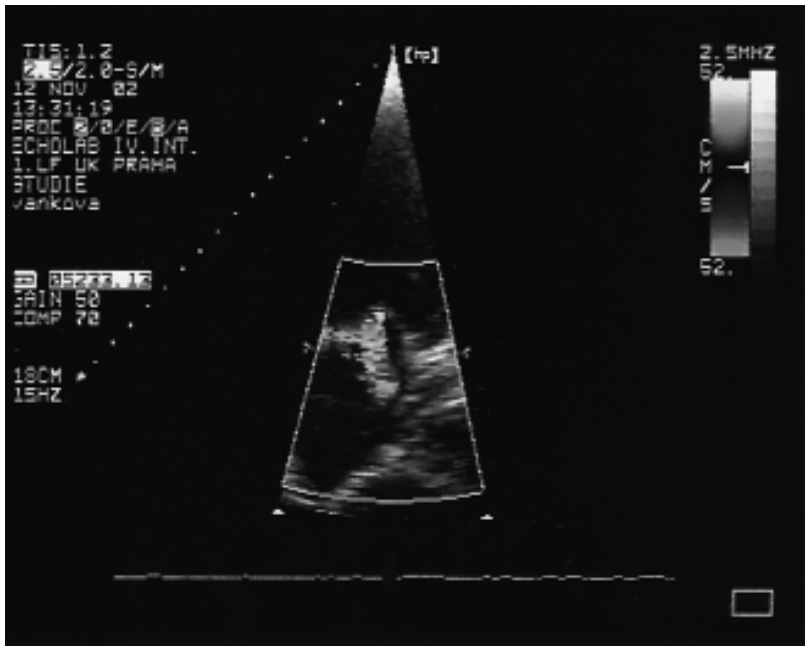

Figure 2 – Pulsed Doppler of the pulmonary vein elevated left ventricular filling pressure.

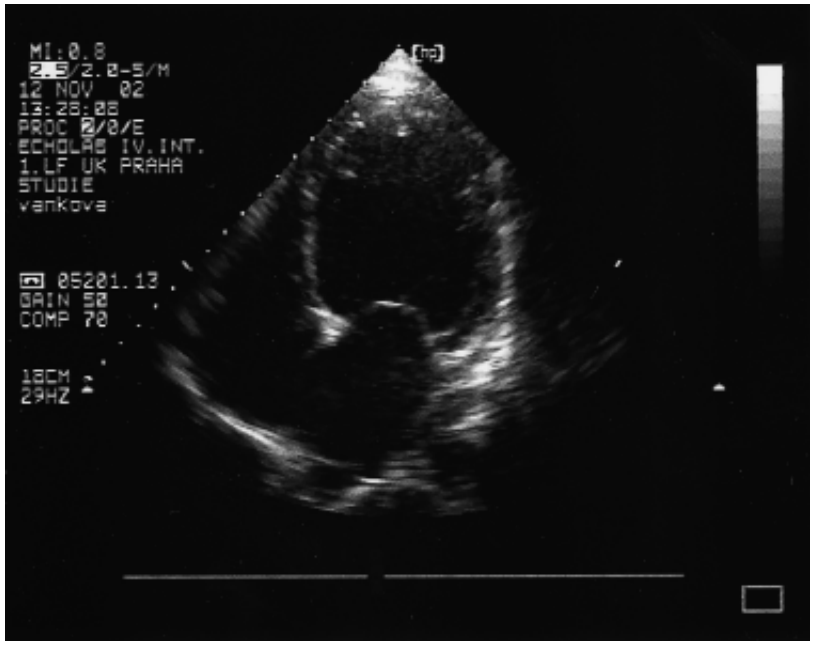

Figure 3 – Mild mitral regurgitation.

2000/11: repeated echocardiogram: non-enlarged LV, systolic function is slightly decreased because of diffuse hypokinesis. Impairment of relaxation on transmitral flow.
Subsequent transesophageal echocardiography: hyperkinetic filliform formations on the aortic valve with ultrasound characteristics resembling Lambl's excrescences. Impairment of relaxation on transmitral flow without increase of LVDEP. Systolic function within lower range of normal values. On exercise stress test no heart-related chest pain and no manifestation of coronary insufficiency.
2002/5: Almost no breathlessness, no complaints (she rode a bike for 30 km in the spring).
2002/7: the onset of severe dyspnoea during minimal exercise. Because of objective findings (see examination) she became a candidate for orthotopic heart transplantation (OHT).
2003/5: OHT performed.

Investigations
Normal findings: BSR, blood count + differential count, electrolytes, bilirubin, ALT, AST, ALP, GMT, cholesterol, HDL, LDL, CRP, CK,-MB, troponin, thyroid hormones INR, APTT, TT, fibrinogen, D dimer, AT III.
Pathological findings: GMT, LDL cholesterol, TG.
1. 10. 1999: ECG: sinus rhythm, HR=80/min, flattening of T II., III. aVF, negative T waves in V 1–4, LBBB.
12. 11. 2002: On echocardiography severe dilation, extreme systolic and severe diastolic dysfunction of LV (EF = 11.8%). Mural fixed thrombus in the apex of LV 30×12 mm. Prolaps of the posterior cusp of the mitral valve with insignificant regurgitation – II./IV. grade. Doppler signs of severely decreased cardiac output in aorta (Figures 2, 3).
Average value of the ELISA method for antibodies of class IgM = 708 (minim. = 323, maxim. = 1389) in the course of the years 1999–2004, average value of class IgG = 1036 (minim. = 636, maxim. = 1349), with permanent positivity of WB IgG and permanent negativity of WB IgM.
15. 5. 2003: Myocardial biopsy (PCR):
Detection of the agent: Borrelia burgdorferi sensu lato genome: suspected Borrelia burgdorferi sensu lato plasmid: positive.
Result of the test: positive.

Case report No. 3
Female, 60 years, with no significant past medical history.
1978–1990: Rapid palpitations from time to time, usually linked with over-exertion.
2001/9: Examined due to recurring palpitations. Normal findings.

2002/11: Recurrence of frequent palpitations.
2003/2: Worsening of health condition after virosis, with exertional dyspnoea and palpitations. She was examined in detail and suspected DKMP was concluded. Etiology of Lyme borreliosis was suspected because of positive finding of antiborrelial antibodies.
2003/5: Marked worsening of the condition, resting dyspnoea and palpitations. After starting treatment with Tritace (Ramiprilum), Digoxin (Digoxinum), Verospiron (Spironolactonum), Furon (Furosemidum), Warfarin (Warfarinum natricum) 5 mg 1×1 there was alleviation of symptoms.
Epidemiological history: Weekends spent in the endemic regions for Lyme borreliosis (Poběžovice, Horšovský Týn), tick in *2002/7*. No eruption of erythema migrans. Repeatedly bitten by the crane flies.

Clinical findings (only pathological findings)
BP 120/70 HR 68/74
Heart: normal heart rate, irregular heart rhythm with small peripheral pulse deficit, conspicuously silent heart sounds. Lower extremities: varices of 1. degree of the left calf.

From further examinations
16. 5. 2003: ECG: atrial fibrillation – fibriloflutter HR = 89'.
16. 5. 2003: Holter ECG: atrial fibrillation with average HR = 105/min., during the night HR approximately 100/min. Symptomatic palpitations are consistent with ECG detection of atrial fibrillation with rapid ventricular response about 180/min., linked with slight exercise.
16. 5. 2003: Holter BP : average BP per 24 hrs = 130/78 mmHg (Max. 151/97 mmHg).
Average HR from 6.00 till 18.00 = 130/81 (dBP > 90 mmHg = 16.7%).
Average BP from 18.00 till 6.00 = 120/80 mmHg.
19. 5. 2003: Echocardiogram: non-enlarged LV with significantly decreased systolic function, with diffuse hypokinesis, maximum on the inferior wall, EF=33–39%. Borderline left atrium size. Trace mitral and tricuspid regurgitation. Filling pressure of LV is probably increased at rest.
12. 8. 2003: Echocardiogram: non-enlarged LV with decreased systolic function, due to diffuse hypokinesis with maximum on the inferior wall, EF = 35–50%. Borderline left atrium size. Trace mitral and tricuspid regurgitation.
21. 5. 2003: Thallium tomography: normal heart perfusion scan during sufficient exercise (up to 125 W), no symptoms of AP and no ischemic ECG changes, atrial fibrillation is present.
15. 6. 2003: Selective coronarography: normal coronarographic finding (the investigation was performed on account of myocardial biopsy).
Average value of ELISA method for antibodies of IgM class = 379 (minim. =

273, maxim. = 504) during the years 2003–2004, average value for IgG class = 353 (minim. = 272, maxim. = 433) with permanent positivity of WB IgM and permanent negativity of WB IgG.

25. 6. 2003: PCR: Borrelia burgdorferi sensu lato genome: posit.
Borrelia burgdorferi sensu lato plasmid: posit.
Myocardial biopsy: negative cultivation.

5. 8. 2003: Chest X-ray: Borderline heart size, adequate vascular pulmonary markings. Sclerotic thoracic aorta, normal width of mediastinum. No infiltration and no focal opacities in pulmonary parenchyma. Mild emphysema. Smooth diaphragmatic contours, with steep, clear angles. Bone structure of the thoracic skeleton is regular.

10. 3. 2005: Echocardiogram: non-enlarged LV with good systolic function, no signs of focal impairment of kinetics, EF = 55–60%. Borderline left atrium size. Trace mitral and tricuspid regurgitation. Normotension in pulmonary artery.

Discussion

Cardiac involvement in Lyme disease manifests itself usually during 4 to 8 weeks, although manifestations during the time interval ranging from 4 days till 10 months have been noted. Vieyeers relates the first cardiac manifestation of LB to the time of the tick bite and emphasizes that these signs mostly occur early, appearing after about 10 days. They may also occur late in the course of 4 months.

Validity of this assertion is limited, because a considerable number of the patients (about 2/3) do not know or are unaware of previous tick bite [15].

Our roughly 16 years experience with patients followed-up for Lyme carditis showed that the more favourable course of the disease was seen in more than 90% of cases in the initial phase of the disease and also later in the disease, which approximately corresponds with literary data [16, 17, 18]. 15 of 20 patients have intermittent complaints. Follow-up examinations are performed by our department twice a year and include a standard medical examination, Holter ECG monitoring, serological tests and possibly additional examination in case the patient has complaints that might originate from circulatory system. There are some symptoms, however, of which the origin cannot not be satisfactorily elucidated.

These symptoms include palpitations (without conclusive ECG correlate during Holter monitoring), chest pain at rest, and in some of the patients, shortness of breath not induced by exercise. With exception of Steere, who found vague, short-lasting stabbing chest pain in some of his patients, this experience is not mentioned by other reports or discussions [19]. Clearly, among these patients are not included persons, in whom other illnesses could be the cause of the above-mentioned complaints. These include patients with

ischemic heart disease, with disorders of thyroid gland or patients with hypertension.

A portion of our patients may have an ECG illustrating various frequent extrasystoles. When evaluating recurring palpitations, it is necessary to take into account the prevalence of arrhythmias that increases with age. It relates both to frequency and to variability of myocardial ectopic activity. It is proven that the prevalence of ventricular arrhythmias increases already from the third decade of life.

Similar to the occurrence of VES, there are much uncertainties regarding variability and reproducibility of ventricular electrical instability. There are numerous reports drawing our attention to the limitations of VES reproducibility in the course of a day. The fact that more than 40% electrophysiological trials have failed to bring reproducible ECG findings, shows the necessity of variability testing when it is necessary to objectivize. Awareness of all above-mentioned limitations of VES variability and especially with respect to their prevalence in older people highlights the difficulty of differential diagnostic procedure pertaining to the confirmation of Borrelia etiology and heart involvement.

A quite favourable impression of satisfactory prognosis of the patients with Lyme carditis is undoubtedly influenced by the reports about fatal courses of the disease in some patients with LB. Marcus describes the case of 88 year old man with babesiosis who died unexpectedly in a hospital. The autopsy showed pancarditis with diffuse lymphoplasmatic infiltration and with Spirochaetae in the myocardium. Serological examination performed before the death confirmed the suspicion of the presence of Bb. The author concludes that the patient's sudden death was caused by an atrioventricular blockade or a malignant arrhythmia [19]. The next fatal case of LB was reported in a farm worker in England. The autopsy confirmed pericarditis, focal myocarditis and noticeable interstitial and endocardial fibrosis [20].

From 1994 till 2004, the authors treated 3 patients with DCMP. In each of them the participation of Bb in the development of this advanced form of LC was confirmed. The ages of the patients at the beginning of the study were 43, 54, 58 years, respectively. Two female patients suffered from the cutaneous form of LB, erythema migrans (EM) and all of them were treated with antibiotics in the early stage. The initial investigations included the complete cardiological examination along with complete laboratory screening of antiborrelial antibodies by ELISA method and Western blot and PCR in National Reference Laboratory for LB in National Institute for Public Health (Státní zdravotní ústav) in Prague.

Clinical and objective findings, including direct proof of Bb in myocardium (case report No. 1) and the presence of Bb by ELISA methods, Western blot, PCR in two patients (case report No. 2, 3) confirmed the unequivocal participation of LB infection in the development of dilated cardiomyopathy with absence of ischemic heart disease and other possible etiological agents. This necessitated the

performance of orthotopic heart transplantation in one of the female patients (Case report No. 2).

Conclusion

The presented findings have been consistent with participation of Borrelia infection in heart involvement as it was published in many studies formerly, even if this theory has not been always unanimously accepted.

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