Lyme Borreliosis – A short overview about symptoms, diagnostic tests and therapies

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I, Armin Schwarzbach, have no personal or financial interest to declare: I have no financial support from an industry source at the current presentation. Actually, I am here as a private man to assist scientists, doctors and patients regarding questions for Lyme Borreliosis.
Borrelia burgdorferi: 15 million year old bacteria

WILD NATURE
Bacteria found in 15 million-year-old amber similar to Lyme disease

Published May 30, 2014
Associated Press

GRANTS PASS, Ore. — Fossilized bacteria found inside a tick encased in 15 million-year-old amber indicates the bacteria that cause Lyme disease were likely around long before there were humans to get the disease.

George Poinar Jr. is professor emeritus of entomology at Oregon State University. He bought the amber about 30 years ago in the Dominican Republic, while researching the ancient origins of diseases spread by ticks and mosquitoes.

He did not find the tick until five years ago, and when he cracked open the amber, saw the tick was full of millions of fossilized bacteria.

Poinar writes in the latest edition of the journal Historical Biology that the fossilized bacteria are similar in form to the bacteria causing Lyme disease.

The fossil record indicates homo sapiens has been around about 200,000 years.
The oldest patient 5300 years ago with Lyme Borreliosis: „Iceman“ Ötzi

Ötzi’s genome also hints at other health problems: Zink’s team found almost two-thirds of the genome of *Borrelia burgdorferi*, a bacterium that causes Lyme disease. Zink found no other telltale signs of Lyme disease in Ötzi’s preserved tissues, but he speculates that tattoos on the iceman’s spine and ankles and behind his right knee could have been an attempt to treat the joint pain that occurs when the condition goes untreated.”
Figure 13. Geographic distribution of pathogenic bacteria of *Borrelia burgdorferi* complex (pathogenic role of *Borrelia valaisiana* is highly suspected)
Pleomorphic forms and biofilm-like colonies of Borrelia burgdorferi in vitro

...pleomorphic B. burgdorferi should be taken into consideration as being clinically relevant and influence the development of novel diagnostics and treatment protocols...

Recent infection with Borrelia burgdorferi: Bulls eye rash / Erythema migrans

1. **Transmission of Borrelia during tick bites:** After 5 to 7 days, latest 7 to 10 weeks development of a **Bulls eye rash/Erythema migrans**

2. 20 % of infected patients develop a **feverish reaction** because of the penetration of Borrelia into the blood (only for a few days) („summer flu“)

3. Only 30-40 % of Lyme patients develop a Bulls eye rash

4. Only 30-40 % of chronic Lyme patients remember a former tick-bite
„Bulls eye rash“ (Stage I Lyme Borreliosis)
„Bulls eye rash“ (Stage I Lyme Borreliosis)
Multifocal Erythema Migrans

Erythema migrans
Multiple Form

Image Credit:
Dr Med S.A. Buchner MD
Dermatologist, Basil Universitatsspital
Stage I/II Acute Neuroborreliosis: Bells palsy (right side)
Stage II/III (acute/chronic): Arthritis left knee
Stage III: Acrodermatitis atrophicans Herxheimer
Laboratory results

Patient:               Date of birth:     08/09/1947 Date of testing:  07/08/2009

Antibodies (Humoral immune system)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borrelia burgdorferi-IgG-EIA</td>
<td>2.8 RU/ml</td>
<td>&lt;16</td>
</tr>
<tr>
<td>Borrelia burgdorferi-IgM-EIA</td>
<td>7.6 RU/ml</td>
<td>&lt;16</td>
</tr>
<tr>
<td>Borrelia burgdorferi-IgG-Blot</td>
<td>positive</td>
<td>Bands: OspC +, p41 +, VlsE-Bg +, VlsE-Ba +</td>
</tr>
<tr>
<td>Borrelia burgdorferi-IgM-Blot</td>
<td>positive</td>
<td>Bands: OspC-Bg +, OspC-Bb +, OspC-Ba +, p41 (+)</td>
</tr>
</tbody>
</table>

Interpretation:

The specific Borrelia burgdorferi-IgG/IgM-antibodies by immunoblot-technique (false-negative EIA !) are an indication for a humoral immune-response against Borrelia burgdorferi in blood.

Armin Schwarzbach M.D. Ph.D.
Doctor for laboratory medicine
• „In the case of ELISA, positive or borderline results were observed in only 24 patients (53.3%).“(Wojciechowska-Koszko et al., Feb. 2011)

• „32 patients had specific antiborrelial antibodies confirmed by using the westernblot in spite of negative ELISA...In patients with persisting difficulties it is necessary to use the westernblot test...It is probably due to the very low production of specific antibodies caused also by the status of immune-deficiency detected in all our patients.“ (Durovska et al., 2010)

• „The number of IgM- and/or IgG-positive ELISA results...ranged from 34 to 59%...Comparison of immunoblots yielded large differences in inter-test agreement...Remarkably, some immunoblots gave positive results in samples that had been tested negative by all eight ELISAs.“ (Ang CW et al., Jan. 2011)
Specificity and sensitivity of Borrelia antibodies by ELISA and Immunoblot

<table>
<thead>
<tr>
<th>Year</th>
<th>Author/Literature</th>
<th>Specificity/Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1993)</td>
<td>Schmitz et al. Eur J Clin Microbiol Infect Dis 12, 419-424</td>
<td>100% / 66%</td>
</tr>
<tr>
<td>(1996)</td>
<td>Ledue TB, Collins MF, Craig WY J Clin Microbiol 34, 2343–50.</td>
<td>100% / 44%</td>
</tr>
<tr>
<td>(2009)</td>
<td>Klemann W, Huismans BD. Umwelt-Medizin-Gesellschaft; 22(2) 132-138</td>
<td>- / 60%</td>
</tr>
<tr>
<td>(2010)</td>
<td>Schwarzbach A. (unpublished)</td>
<td>92% / 60% Blot</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- / 32-42% ELISA</td>
</tr>
</tbody>
</table>

• **Average** ~99% / ~43%
Borrelia antibodies by ELISA and immunoblot: Evidence based literature „false seronegativity“

Borrelia antibodies by ELISA and immunoblot: Evidence based literature „false seronegativity“

Borrelia antibodies by ELISA and immunoblot: Evidence based literature „false seronegativity“

Borrelia antibodies by ELISA and immunoblot: Evidence based literature „false seronegativity“

- Paul A. [Arthritis, headache, facial paralysis. Despite negative laboratory tests Borrelia can still be the cause]. MMW Fortschr. Med 2001 Feb 8;143(6):17.
- Ang CW, Notermans DW, Hommes M, Simoons-Smit AM, Herremans T. Large differences between test strategies for the detection of anti-Borrelia antibodies are revealed by comparing eight ELISAs and five immunoblots. Eur J Clin Microbiol Infect Dis. Published online: 27 Jan 2011
Evidence that an IgM Western blot response can last longer than 6 months in Lyme disease

“IgM levels rose during exacerbations and fell during remission” for 6 to 18 months after treatment of an EM rash. Steere, 1979

“56% of patients with early Lyme disease had detectable IgM responses to the spirochete 6 months later” Massarotti 1992

“Serum IgM levels correlated directly with disease activity (p = 0.025) Craft, Yale J Biol Med 1984

“Persistence of specific IgM antibodies may also be associated with more severe disease.” Craft, 1984

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Isolated IgM-persistence in chronic Lyme:
Evidence based literature

The spinal tap is poorly sensitive in chronic neurologic Lyme Borreliosis

27 subjects presenting with neurologic Lyme disease presenting to Tufts Univ. School of Medicine, Boston

1 of 27 with antibodies to Lyme disease

1 of 27 with abnormal spinal tap (7 white cells)

Logigian, Steere, 1990, NEJM

Copyright of this slide by Daniel J. Cameron MD MPH, USA
Cerbrospinal fluid (CFS): Evidence-based literature „false negative“

### Chronic Lyme Borreliosis symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power loss or reduction (mental/physical) at work, household, sport</td>
<td>&gt;99 %</td>
</tr>
<tr>
<td>Fatigue/ Drowsiness/Listlessness</td>
<td>&gt;99 %</td>
</tr>
<tr>
<td>Tingling/“Ants running”/Numbness/ „Needle burning“ or „burning“ skin-sensations</td>
<td>81 %</td>
</tr>
<tr>
<td>Neck pain/ neck stiffness</td>
<td>78 %</td>
</tr>
<tr>
<td>Shoulder pain</td>
<td>76 %</td>
</tr>
<tr>
<td>Headache/Dizziness</td>
<td>76 %</td>
</tr>
<tr>
<td>Changing, migrant joint pain (all joints are possible)</td>
<td>68 %</td>
</tr>
<tr>
<td>Changing, migrant muscle pain/“Rheumatism“/General weakness of the body</td>
<td>62 %</td>
</tr>
<tr>
<td>Feverish infection: in Stage I of Lyme disease as a sign for occurrence of borrelia-bacteria in blood</td>
<td>≈20 %</td>
</tr>
<tr>
<td>Mental strain/Depressions/Schizophrenia/Psychosis</td>
<td>62 %</td>
</tr>
<tr>
<td>Back pain/Sciatic pain syndrome</td>
<td>58 %</td>
</tr>
<tr>
<td>Sleeplessness with partly sweating/urge to urinate mostly between 2 and 4 o’clock at night</td>
<td>47 %</td>
</tr>
<tr>
<td>Sore throat/Tendence for general infections/HSV or EBV-Infections</td>
<td>39 %</td>
</tr>
<tr>
<td>„Burning eyes“/Overproduction of tears/Blurred vision/Double vision/Lightheadedness</td>
<td>28 %</td>
</tr>
</tbody>
</table>
Dr. Leo Joosten, Department of Medicine, Radboud University, Netherlands:

What solutions that are currently being pursued do you believe hold the most promise for diagnosing Lyme disease at a high confidence level? What tests currently available to the general public, other than the western blot test, do you believe provide a better degree of certainty?

“At the moment, there are cellular based tests on the market. **LTT and Elispot** are a few of these tests. These tests give us information about the cellular immune response towards *Borrelia* antigens. It seems that these tests will used in the future, apart from serological tests.”
Borrelia Elispot (T-Cell-Spot / IGRA: Interferon-Gamma-Release Assay)

... The ELISPOT assay showed ... a specificity of 82% in Neuroborreliosis...

Nordberg et al.: Can ELISPOT be applied to a clinical setting as a diagnostic utility for Neuroborreliosis?, Cells 2012, I, 153-167

... Borrelia antibody positive asymptomatic children (n=20), children with previous clinical LB (n=24), and controls (n=20). Blood samples were analyzed for Borrelia-specific interferon-gamma...by ELISPOT...We found no significant differences in cytokine secretion between groups...


... The sensitivity of ELISPOT is estimated at 84%, and the specificity is 94%...

... ELISPOT assays provide robust, highly reproducible data...

... ELISPOT can be retested for the acquisition of additional information in follow-up assays...

... the two assays systems (ELISPOT + CD57-cell count) compliment each other in the quest to understand T cell-mediated immunity in vivo....

Alzheimer Plaques can be Borrelia biofilms

Alzheimer plaques - google

Alzheimer plaques - Close Up

Borrelia Biofilm Units
Lyme Borreliosis: The great imitator?

20-30% of autistic disorders can be caused by Borrelia and 58% by Mycoplasma. (Bransfield et al.: Med Hypotheses. 2008; 70(5):967-74)

Multiple Sclerosis, Myelopathies, Polyneuropathies, brain tumor, encephalopathy. (Neurosurgery. 1992 May; 30(5): 769-73)


90% of chronic fatigue patients are Lyme positive. (Informal study by American Lyme Disease Alliance at www.lymealliance.org)

Most fibromyalgia patients are Lyme positive. (Rheum Dis Clin North Am. 1998 May; 24(2):323-51 & report of Lida Mattman, M.D.)

Borrelia can cause Parkinsonism. (Arch. of Path. & Lab. Med. 127(9):1204-6)

Pure Lyme dementia exists and has a good outcome after antibiotics. It is advisable to do Lyme serology in demented patients. (Blank et al.: Journal of Alzheimer’s disease, Volume 4/2014, 1087-1093)
Lyme Borreliosis: Antibiotics stage I (recent infection)

Stage I (recent infection)

Oral therapy (Duration: minimum until disappearance of “bull’s eye rash”, respectively of lymphocytic infiltration).

Doxycycline (from 8\textsuperscript{th} age)
Macrolides (Azithromycin, Clarythromycin)
Cefuroxime *
Amoxicillin *

(* for children under 8 years and pregnant women)
Antibiotics stage II/III Lyme disease

• Cefalosporines (Cefuroxime, Cefotaxime, Ceftriaxone)

• Penicillin G

• Macrolides (Azithromycin, Clarythromycin)

• Tetracyclines (Doxycycline/Minocycline)

• Metronidazole/Tinidazole
Controlled Studies of Persistent Lyme Borreliosis

- **Krupp et al. (2003):** Ceftriaxone IV for 4 weeks vs. Placebo: 64% showed improvement in fatigue, no improvement in cognition
  

- **Klempner et al. (2001):** Ceftriaxone IV for 4 weeks, then oral doxycycline for 2 months vs. Placebo: No improvement in fatigue or quality of life
  

- **Cameron (2008):** Oral amoxicillin for 3 months vs. Placebo: Retreatment was successful in 2/3 of patients with best initial quality of life
  

- **Fallon et al. (2008):** Ceftriaxone IV for 10 weeks vs. Placebo: Significant cognitive and physical improvement at 12 weeks.
  

Comments

- Exact duration of illness not stated (at least 6 months). Previously untreated patients did significantly better than controls in terms of fatigue improvement (69/ vs. 0%, p<0.01)

- Study criticized because patients had been sick an average of 4.7 years and had already failed similar treatment (inadequate treatment regimen).

- Average duration of illness 7.1 months. Quality of life worse than diabetes or heart disease

- Patients had been sick for an average of nine years and failed prior treatment. Cognitive relapse when treatment withdrawn
The great majority of Lyme patients present Erythema migrans (EM)

Exclusion of patients without EM in studies about chronic Lyme Borreliosis

Falsely high rate for estimated cases regarding the prevalence of EM

CDC: Surveillance criteria for Borreliosis, „not intended to be used in clinical diagnosis“

An Erythema migrans occurs in less than half of the cases

Patients without EM, but flu-like symptoms, fever, muscle or joint pain, paresthesia with or without antibodies are not included in the definition of stage I and studies

1: CDC Case Definitions for Infectious Conditions under Public Health Surveillance. Retrieved on 2006-03-15
CDC (USA) and

- „Present serological assays for Lyme disease have substantial limitations“
- Lyme disease is a clinical decision depending on symptoms and differential-diagnosis

Other opinions

- Serological tests, particularly important in the late stage of Lyme disease, are not reliable
- Lyme disease is a clinical decision depending on symptoms and differential-diagnosis
Persistent (chronic) Lyme disease is very rare.

Symptoms after a standardized therapy are „Post Treatment Lyme Disease Syndrome“ (PTLDS).

No possibility for a chronic persistence of B. b. by definition of symptoms.

Clinical definition as: CFS, RA, autoimmune disorders, fibromyalgia, psychosomatic and other „syndromes“.

Persistent symptoms mean bacterial persistence.

Delayed diagnosis and treatment lead to persistence.

PTLDS means persistence of Borrelia burgdorferi.

Longer treatment is necessary in persisting infections.

CFS, RA, autoimmune disorders, fibromyalgia, psychosomatic and other „syndromes“ can be caused by persistence of B. b.
CDC (USA) and

- No recommendation for long-term antibiotics because of no existence of chronic Lyme Borreliosis
- Some of the symptoms vanish after a standardized therapy in most patients spontaneously
- Borrelia-arthritis: “…we recommend to repeat treatment with another 4 week course of oral antibiotics or with a 2- to 4-week course of ceftriaxone iv”

Other opinions

- Persistent symptoms after a standardized therapy need longer antibiotics because of persistence of Borrelia burgd.
- Therapies cannot be standardized, but have to be individualized according to the development of symptoms during treatment
- Borrelia-arthritis: “…we recommend to repeat treatment with another 4 week course of oral antibiotics or with a 2- to 4-week course of ceftriaxone iv”
SUMMARY: CDC (USA) and
• Rigid, systematic approach for diagnosis and therapies
• No acceptance for persistence of B.b. infections
• Definition of PTLDS
• Symptomatic diagnosis and therapies
• Therapeutical success: Reduction of „major“ symptoms
• Symptomatic therapies for „minor“ symptoms

Other opinions
• Flexibility in the diagnostic and therapeutical approach
• Acceptance for persistence of B.b. infections
• No definition of PTLDS
• Basically long-term antibiotics for persistent B.b.
• Therapeutical success: Reduction of „major“ and „minor“ symptoms
• Avoid symptomatic therapies
Proposals

• Studies ELISA vs. Immunoblot and interassay standardization
• Studies short-term vs. long-term antibiotic treatment in chronic Lyme Borreliosis
• Need of in vivo studies about pleomorphic forms and biofilms
• Need of new antibiotics
• Teaching at medical universities about symptoms (standardized anamnesis), diagnosis and treatment options (including unsolved controversies in diagnosis and therapies)
• Basic courses for GPs about handling of tick-bites, symptomatology (standardized anamnesis), other TBD as differential-diagnosis
• Information for the population and health professionals by the health government etc. about prevention...
It's Lyme Time!

Protect Yourself Against Lyme Disease

1. Walk in the middle of trails, avoid sitting on logs and leaning on trees.
2. Wear a hat, tuck in hair, if possible.
3. Wear a long-sleeved shirt, fit at the wrist.
4. Wear shoes, no bare feet or sandals.
5. Wear long pants tucked into high socks or duct tape around pants.
6. Consider Deet for skin and permethrin for clothes.
7. Wear white or light-colored clothing to make it easier to see ticks.
8. Do tick checks immediately and 3 days after outdoor activity.
9. If you find a tick, remove it carefully and save it.
10. Ask your veterinarian about protection for your furry friends.