

Difficulties faced by doctors in an infectious diseases clinic

Lyme LDA conference September 12th 2015



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Overview

- Radboudumc Lyme-disease department
- Practical experience
- Assessment of Lyme disease
- Treatment
- Antibiotic strategies and how to deal with symptoms (i.e. pain, neurocognitive complaints, sleepdisorders)
- Borrelia testing
- Guidelines in the Netherlands
- Patient cases
- (More) research



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Radboudumc outpatient department

- Lyme borreliosis (LB) expertise center
- National Reference clinic in the Netherlands
- Collaboration with other hospitals; o.a. AMC (Amsterdam)
- About 2000 referrals a year; 500 new patients/year
- Capacity problem

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Radboudumc outpatient department

- 500 medical advices to GPs or medical specialists
- Low access to outpatient department for people with high risk profession (i.e. foresters)

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Background

Bacterium: *Borrelia burgdorferi*
(*B. burgdorferi*, *B. afzelii*, *B. garinii*)



— *B. burgdorferi*
— *B. afzelii*
— *B. garinii*
..... other

5

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Erythema migrans EM



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Surveillance data the Netherlands

GP consultations

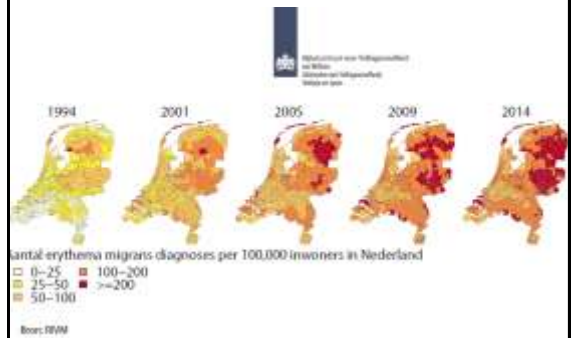
- for tickbites
 - 1994: 33000
 - 2001: 65000
 - 2006: 73000
 - 2009: 93000
- For Erythema migrans
 - 1994: 6500
 - 2001: 13000
 - 2006: 17000
 - 2009: 22000



Hofhuis et al. 2015

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Geographics of EM per 100.000 inhabitants (NL)



Surveillance data UK

- Since 1997, over 6,900 cases of Lyme-borreliosis (LB) reported.
- Increase of mean annual incidence rates for laboratory-confirmed cases
 - 1997-2000: 0.38
 - 2002: 0.64
 - 2010: 1.64 cases per 100,000 total population
- Between 1,000 and 2,000 additional cases of LB occur each year

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Particularly high population of ticks in UK

Exmoor

the New Forest and other rural areas of Hampshire

the South Downs

parts of Wiltshire and Berkshire

parts of Surrey and West Sussex

Thetford Forest in Norfolk

the Lake District

the North York Moors

the Scottish Highlands

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Early symptoms of Lyme-borreliosis

- Flu-like symptoms:
 - o tiredness (fatigue)
 - o muscle pain
 - o joint pains
 - o headaches
 - o high temperature (fever),
 - o chills
 - o neck stiffness
- Paralysis of the facial muscles, typically only on one side of the face (Bell's palsy).
- Other nerve pains

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Late symptoms of Lyme-borreliosis

- Joint: Pain and swelling in the joints
- Nervous system: numbness, pain in limbs, facial paralysis, memory problems and difficulty concentrating
- Headache Inflammation of the membranes surrounding the brain and spinal cord (meningitis)
- sensitivity to light or sound
- heart problems: inflammation, cardiac arrhythmia

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Patients seen in Radboudumc

•Mostly persistent symptoms
after LB defining disease; EM, ACA, neuroborreliosis.

Or

- Patients with long-term symptoms like in LB
- Early LB patients are currently seen in research setting

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Dilemma

Patients with long-term symptoms like in LB:

Possibilities:

- Proven LB
- Probably LB
- Possible LB
- No LB
- Other diagnosis

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Patients with long-term symptoms like in Lyme-borreliosis

Medical history

Physical examination

Blood tests (general and serology)

Scans not useful in most cases (useful to exclude other diagnosis)

Consultation of i.e. rheumatologist, neurologist, dermatologist

Exclusion of other diagnosis

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Treatment (1) antibiotics

doxycycline
(minocycline; penetration in CSF)

amoxicillin

claritromycin or azitromycin

ceftriaxone iv

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Treatment (2)

Combination with plaquenil (hydroxychloroquine)

doxycycline + plaquenil

claritromycin/azitromycin
+ plaquenil

*DontaMed Sci Monit 2003;9(11):P1136-1142. Radboudumc

Disadvantages/ side effects of treatment

- General: diarrhoea
- Doxycycline: photosensitivity
- Azithromycin/clarithromycin: pharmacological interaction with other medication
- Plaquenil: eye problems
- Amoxicillin: allergic reaction/rash

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How to deal with ongoing symptoms?

Cause of ongoing symptoms:

- persistent infection?
- tissue damage/scar tissue?
- auto immune phenomenon?

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Chronic pain

joint and muscle pain

- painkillers,
- paracetamol
- NSAID; naproxen, celecoxib
- hydroxychloroquine

nerve pain

- gabapentin
- duloxetine
- anti-epileptics
- or anti-depressants

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Other persistent complaints

Insomnia

Depression

Loss of energy/chronic fatigue

Consultation of a rehabilitation physician

Clinics for convalescence

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Dutch guideline Lyme borreliosis

- CBO- guideline (diagnosis and treatment) 2013
 - (CBO : institute to improve quality in patient care)
- LCI-guideline (prevention)
 - (national centre for coordination of infectious disease)



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Erythema migrans



Tickbite and positive IgM seroconversion



Baseline

After 2 weeks

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Acrodermatitis chronica atrophicans (ACA)

Borrelia tests

- Serology
- Immunoblot
- PCR (polymerase chain reaction)
- Immunology tests
- LTT
- culture

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Antibody testing

- Serology
 - Antibody tests; IgM and IgG
 - IgM = early antibody (within few weeks)
 - IgG = late antibody (within months)

Immunoblot (native Euroimmune)

- More specific
- Results show antibody against specific part of bacteria

Regular False positive IgM (cross reactivity with other antibodies or diseases)

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Differences between Antigen tests

Table 2
Agreement between ELISAs for detecting IgM and/or IgG and immunoblot (Euroimmun)

ELISA method	ELISA method	Immunoblot	Agreement	Agreement	Agreement	Agreement	Agreement	Agreement
Immunoblot	Immunoblot	0.97	0.98	0.98	0.98	0.98	0.98	0.98
Immunoblot	Immunoblot	0.97	0.98	0.98	0.98	0.98	0.98	0.98
Immunoblot	Immunoblot	0.97	0.98	0.98	0.98	0.98	0.98	0.98
Immunoblot	Immunoblot	0.97	0.98	0.98	0.98	0.98	0.98	0.98
Immunoblot	Immunoblot	0.97	0.98	0.98	0.98	0.98	0.98	0.98
Immunoblot	Immunoblot	0.97	0.98	0.98	0.98	0.98	0.98	0.98
Immunoblot	Immunoblot	0.97	0.98	0.98	0.98	0.98	0.98	0.98
Immunoblot	Immunoblot	0.97	0.98	0.98	0.98	0.98	0.98	0.98

Ang et al Eur J Clin Microbiol Infect Dis. 2011 Aug; 30(8): 1027-1032.

Other tests

- PCR
 - Against DNA of bacteria
 - Difficult
 - Can be positive due to errors in lab or 'dirty' lab
 - Not useful in all tissue (skin, fluid or tissue from joint)

LTT
lymphocyte transformation tests

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Case

- 35 year old female
- 3-4 years ago tick bite
- No EM
- Now 2 years complaints of fatigue, flu-like symptoms, myalgia
- Swelling of knee
- Arthritis of knee
- IgG positive in blood
- PCR positive in joint fluid
- Treatment: doxycycline
- Later claritromycine + hydroxychloroquine

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Case

- 45 year old male
- Forest worker
- Skin laesion
- tick bites, no EM



- IgG positive
- Skin biopsy: PCR borrelia negative
- Histology: ACA

- Treatment: doxycycline, azithromycin + hydroxychloroquine

- Retrospective: Complaints of joints, muscles, fatigue gone after antibiotics

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Case

- 50 year old male
- For years numbness in feet
- Burning sensation in limbs
- Joint pain and stiffness
- tick bites, no EM

- IgG positive
- CSF: no inflammtion
- EMG: nerve damage due to previous inflammation

- Treatment: doxycycline, azithromycin + hydroxychloroquine

- Complaints remain

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Most Cases

- Tick bite unknown
- EM unknown
- Symptoms of fatigue, arthralgia, myalgia, problems with memory and concentration, sleep disorders, numbness of fingers/feet, burning sensations in limbs, dizziness, chronic pain, headache
- Negative serology
- Blood tests (anaemia, kidney, liver, vitamins ect: all normal)
- Next step??

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Research Radboudumc

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- Basic immunology (Lab) research
- Diagnostic tests
- Surveillance in professionals with high risk for LB
- Clinical research:
 - PLEASE study (short versus long treatment in persistent LB)
 - LymeProspect study

Vaccination (Amsterdam)

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PLEASE study

- Long versus short term treatment
- Open label 2 weeks ceftriaxon
- Followed by 12 weeks
 - Placebo
 - Doxycycline or
 - Hydroxychloroquine and clarithromycin

Serology tests
Immunology tests
Neurocognitive tests
Physical functioning

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Surveillance in professionals with high risk for LB

- Serology and immunoblot each year
- Questionnaires for LB suspected symptoms
- Low access to outpatient dept (telephone, visit)
- Lab research

In summary

- High incidence of positive tests
- Low incidence of Lyme-disease symptoms or disease burden
- Not always seroconversion from IgM to IgG; persistent IgM with or without IgG without Lyme disease

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LymeProspect Background

- 5-20% of patients with acute LB have persistent physical symptoms after treatment

Causes unknown:

- Microbiological
- Genetics
- Immunological
- Clinical
- Environment
- Cognitive aspects
- Behaviour

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Overview

- Prospective observational cohortstudy (ZonMw)
- 2000 patients with Lyme-borreliosis
- Follow-up 1 year: blood samples and questionnaires about health

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Aim of study

How many patients with persistent symptoms after treatment?

What are determinants for development of these symptoms?

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Inclusion

Cases & controls (n=2000)

- Patients with erythema migrans: before treatment

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Inclusion

- Patients with acute disseminated manifestation of LB (n=500)
 - Neuroborreliosis / Lyme-arthritis / ACA

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Determinants

Determinants	Tests
Microbiological	Serology PCR, culture (blood, skin) other tick-borne pathogens skin microbioma
Immunologic and genetic	Cellular immune response, RNA DNA
clinical and environmental factors	Medical history (CRF) and physical examination antibiotic bloodlevels
Neurocognitive functioning	Online questionnaires (i.e. SF-36)

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Additional

- 300 patients with similar symptoms;
- Symptoms of myalgia, arthralgia, neurocognitive symptoms (memory, concentration), fatigue.
- started < 1 month after tickbite with negative serology
- With/without
- positive alternative (not validated/accepted) LB test LB

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Secondary outcomes:

1. Long-term effect on health of early localised, early disseminated and late disseminated Lyme-borreliosis
2. Compare persistent symptoms in proven and non proven LB patients
3. Future: more individually advice in diagnosis and treatment strategies

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Thank you for the invitation

Questions?

