

CNS presentation of Lyme disease

From diagnosis to treatment



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What's the problem with
neuroborreliosis ?

Case report about a (virtual) observation of neuroborreliosis

- For example
 - A medical doctor in a university hospital somewhere in a capital of Europe between Paris and Berlin
 - Medical history 8th of november...
 - No fitness
 - Articular pain
 - Stress
 - Trouble of vision
 - Sensitive trouble
 - Disorientation
 - Misspeaking
 - Head ache
 - Difficulty with concentration
 - Similarity with me is not unintentional !!!

The question



Do you think that this doctor
could have neuroborreliosis ?

The answer

- If your reference is...

the net

- There is no doubt

He has
neuroborreliosis

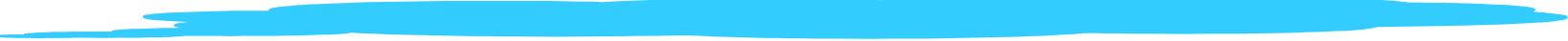
- If your reference are

scientific medical
publications

- there is no doubt

He does not have
neuroborreliosis

Why he does not have
neuroborreliosis ?



ILAD's diagnosis check list

Unexplained back pain



Forgetfulness, poor short term memory, poor attention
Disorientation: getting lost, going to wrong places

Speech errors- wrong word, misspeaking
Mood swings, irritability, depression

Anxiety, panic attacks

Psychosis (hallucinations, delusions, paranoia, bipolar)

Tremor



Neck creaks and cracks, stiffness, neck pain
Fatigue, tired, poor stamina
Insomnia, fractionated sleep, early awakening
Excessive night time sleep
Napping during the day
Unexplained weight gain
Unexplained weight loss
Unexplained hair loss
Pain in genital area
Unexplained menstrual irregularity
Unexplained milk production; breast pain
Irritable bladder or bladder dysfunction
Erectile dysfunction
Loss of libido
Queasy stomach or nausea
Heartburn, stomach pain
Constipation
Diarrhea
Lower abdominal pain, cramps
Heart murmur or valve
Joint swelling

Seizures

Headache

Light sensitivity

Sound sensitivity

Vision: double

Ear pain

Hearing: decreased

Increased

Increased

vertigo,

Off balance, "tippy" feeling

Lightheadedness, wooziness, unavoidable need to sit or lie

Tingling, numbness

or stabbing

shooting pain

Hypersensitivity

Facial pain

Dental pain

Persistent swollen glands

Sore throat

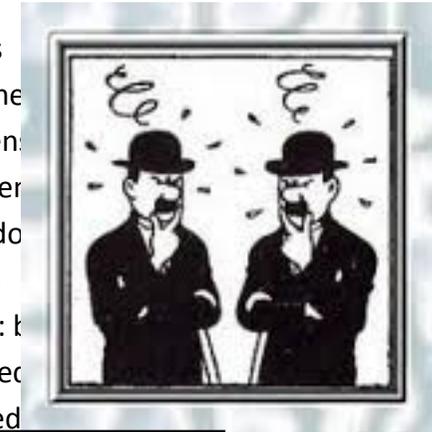
Fevers

Sore soles, esp. in the AM

Joint pain

Fingers, toes

Ankles, wrists



What do we need to make diagnosis of neuroborreliosis ?

- Symptoms
- Serological confirmation
- corner stones for diagnosis

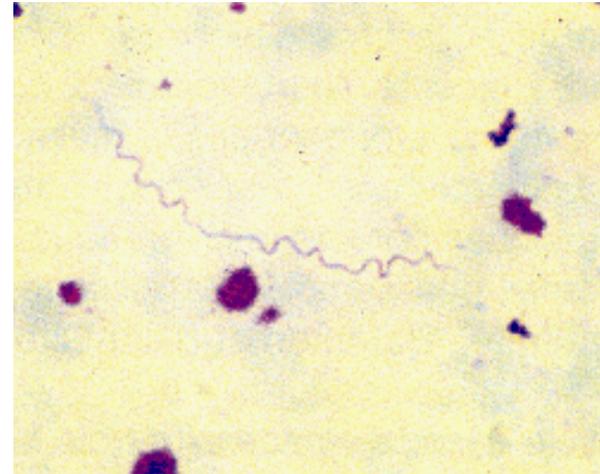
- symptoms are not specific,
- serology is neither reproducible, neither relevant of evolutive disease

- This lead to wrong diagnosis
 - All symptoms are considered
 - Serological testing are mis interpreted

- ... can we isolated the bacteria ?

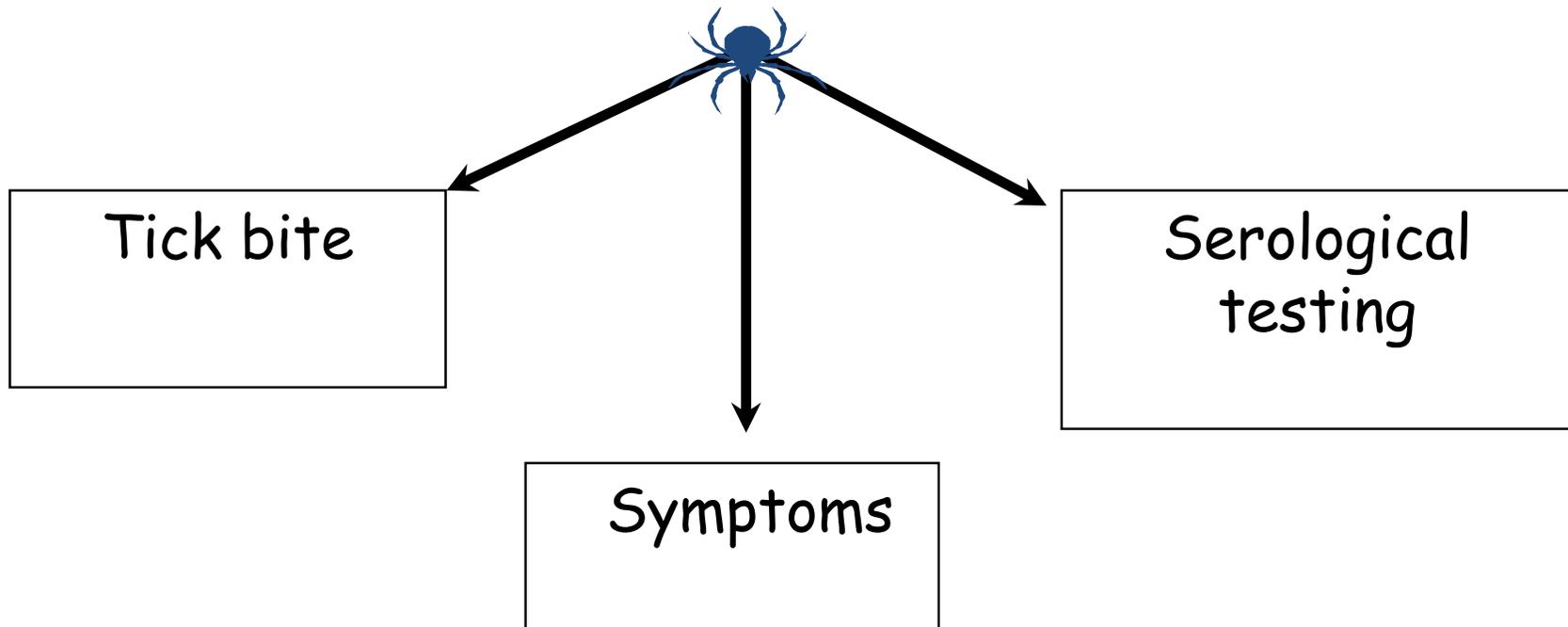
Lyme borreliosis microbiology

- Three main species
 - *B. burgdorferi sensu stricto*
 - *B. garinii*
 - *B. afzelii*
- Other species
 - *B. valaisiana*,
 - *B. lusitaniae*,
 - *B. spielmannii*.
- Epidemiology
 - *B. Burgdorferi* in United States
 - In Europe all species are present
 - Is it really the same disease ?



Lyme disease

the three steps of diagnosis



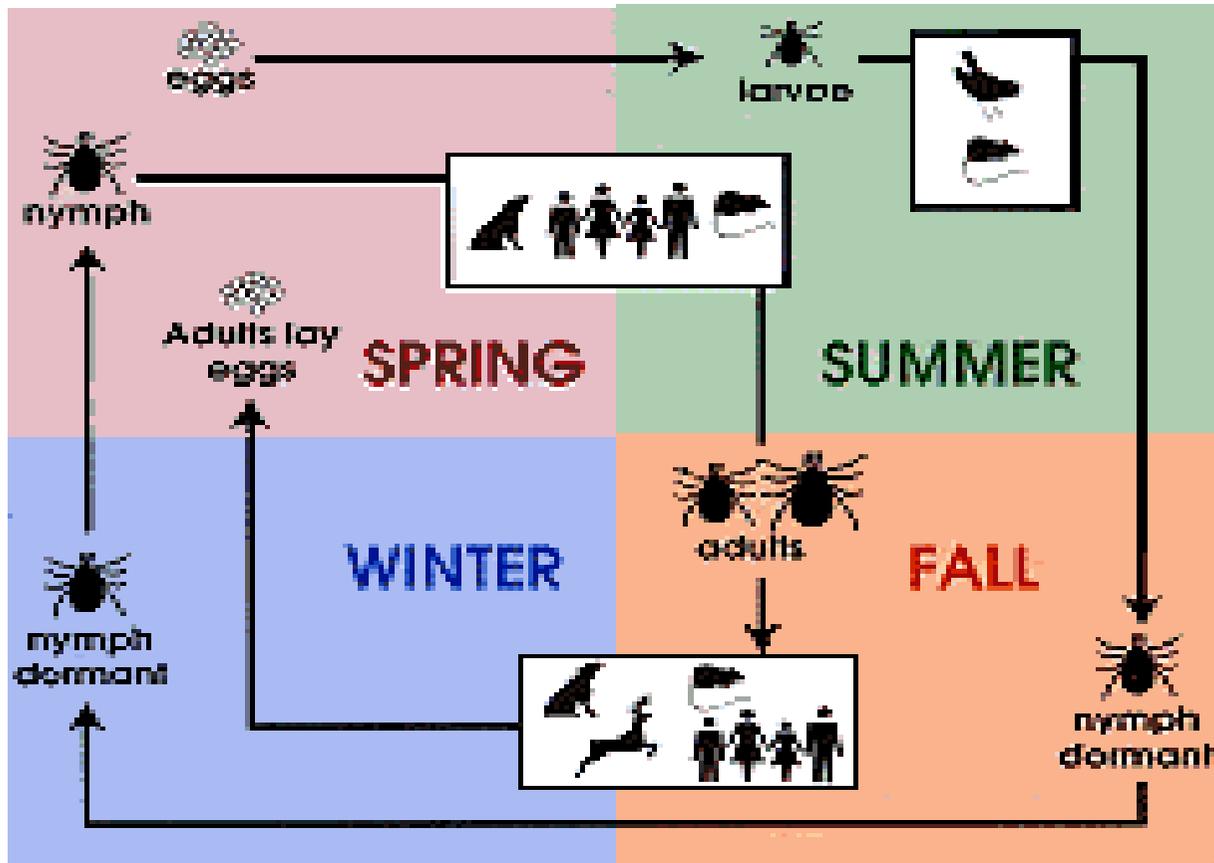
The tick in Europe : *Ixodes ricinus*



3 stages

- larva
- nymph
- adult (male and female)

2-Year Life Cycle of the Deer Tick



AUDF

Microbiological Epidemiology

- infestation rates of the ticks
 - 5 à 40 % according to the country
 - » larvae : 4,8 %
 - » nymph : 11,4 %
 - » adults : 7,4 %
- Seroprevalence in forestry workers
 - 10 to 35 %

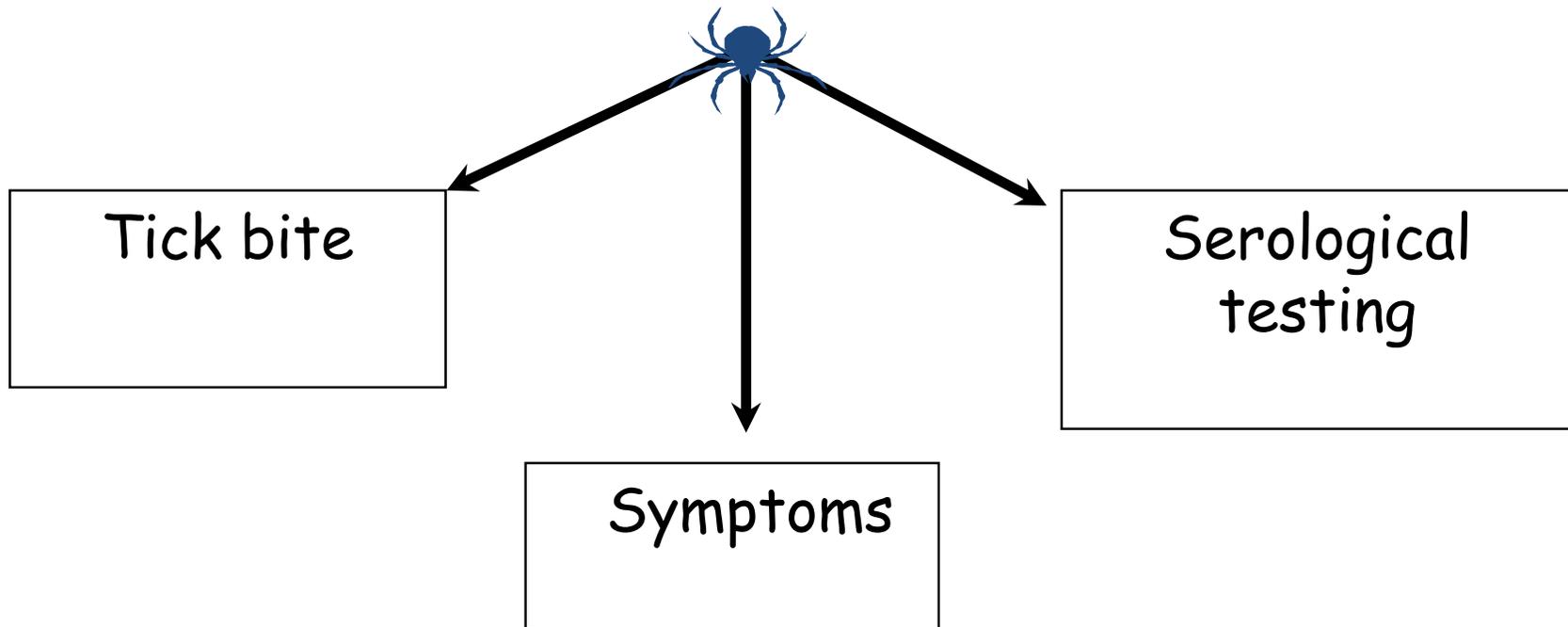


I. Ricinus in Europe



Lyme disease

the three steps of diagnosis



Symptoms of Lyme Borreliosis

historical features

- Skin manifestations known since more than 100 years
 - Afzelius in 1909 : *Erythema migrans*
 - Buchwald in 1883 : *Acrodermatitis chronica atrophicans*
- Neurological manifestations
 - Garin and Bujadoux in 1922 meningoradiculitis after tick bite
 - Also call : Bannwarth's syndrome
- Articular manifestations Steere in 1977 : Lyme disease
- Correlation between *Borrelia* and Lyme disease in 1982



Symptoms of Lyme borreliosis kinetic features

- Primary Lyme disease
 - Following some days to some weeks after tick bite 
- Early or Secondary Lyme disease
 - Approximately from three weeks to 3 months after tick bite
- Late manifestations 
 - More than several month evolution
- Post Lyme disease
 - Sequellae ?

Neuroborreliosis

At which stage ?

- Early manifestations
 - At the very least 3 weeks after tick bites
 - Sometimes before seroconversion
 - Mainly : facial palsy
- Secondary manifestations
 - Mainly radiculitis
- Late manifestations
 - Encephalopathy, myelitis
- Post Lyme disease
 - ...

Early LNB

- PNS manifestations.
 - most common manifestation in Europe : **meningoradiculitis** (Bannwarth's syndrome)
 - radicular pain (in 86% of the patients)
 - paresis (in 61%) especially facial palsy, less often the abducens or the oculomotor nerves, sometimes the abdominal wall or the limbs
 - typically exacerbates at night.
 - Headache (43%)
 - lymphocytic meningitis
 - other peripheral neurological manifestations (in 5-10% of the patients) : plexus neuritis and mononeuritis multiplex.

European national neurological societies guidelines.
Mygland et al. Eur J Neurol, 2010 ; 17 : 8-16

Early LNB



- CNS manifestations.
 - CNS involvement is rare,
 - Myelitis : poliomyelitis-like syndromes
 - Encephalitis : confusion, cerebellar ataxia, opsoclonus-myoclonus, ocular flutter, apraxia, hemiparesis or Parkinson-like symptoms,
 - acute stroke-like symptoms caused by cerebral vasculitis are rare and have been documented only in single case reports.

European national neurological societies guidelines.

Mygland et al. Eur J Neurol, 2010 ; 17 : 8-16

Late neuroborreliosis

- PNS manifestations.
 - mononeuropathy,
 - radiculopathy
 - polyneuropathy : a causative relationship between polyneuropathy and borrelial infection cannot be based on the sole detection of Bb specific antibodies in patients with polyneuropathy as those antibodies can also be found in 5-25% of healthy persons.

European national neurological societies guidelines.

Mygland et al. Eur J Neurol, 2010 ; 17 : 8-16

Late neuroborreliosis

- CNS manifestations.
 - cerebral vasculitis
 - chronic progressive Lyme encephalitis
 - encephalomyelitis with tetraspastic syndrome, spastic- ataxic gait disorder and disturbed micturition.

European national neurological societies guidelines.

Mygland et al. Eur J Neurol, 2010 ; 17 : 8-16

Neuroborreliosis an exemple in a recent therapeutic survey

J. Oksi, Eur J Clin Microbiol Inf Dis, 2007 ; 26 : 571-581

- Inclusion Criteria used :
 - lymphocytic meningitis,
 - cranial neuritis,
 - paresis,
 - radiculoneuritis,
 - Encephalomyelitis
 - Peripheral neuropathy (confirmed by ENMG)
 - Encephalopathy (confirmed by neuropsychiatric tests)
- Observed manifestations (n = 145)
 - Lymphocytic meningitis without radiculitis : 18
 - Meningoradiculitis : 27
 - Paresis 5
 - Encephalomyelitis : 4
 - Encephalopathy : 6
 - Facial paresis : 21
 - Sudden deafness : 6
 - Tinnitus 8
 - Other cranial nerve involvement : 13
 - Peripheral neuritis : 6
 - Other peripheral nervous system manifestations : 24
 - Headache without meningitis 39
 - Dizziness or vertigo 29
 - Transient global amnesia, epileptiform convulsions 1
 - Memory impairment 11

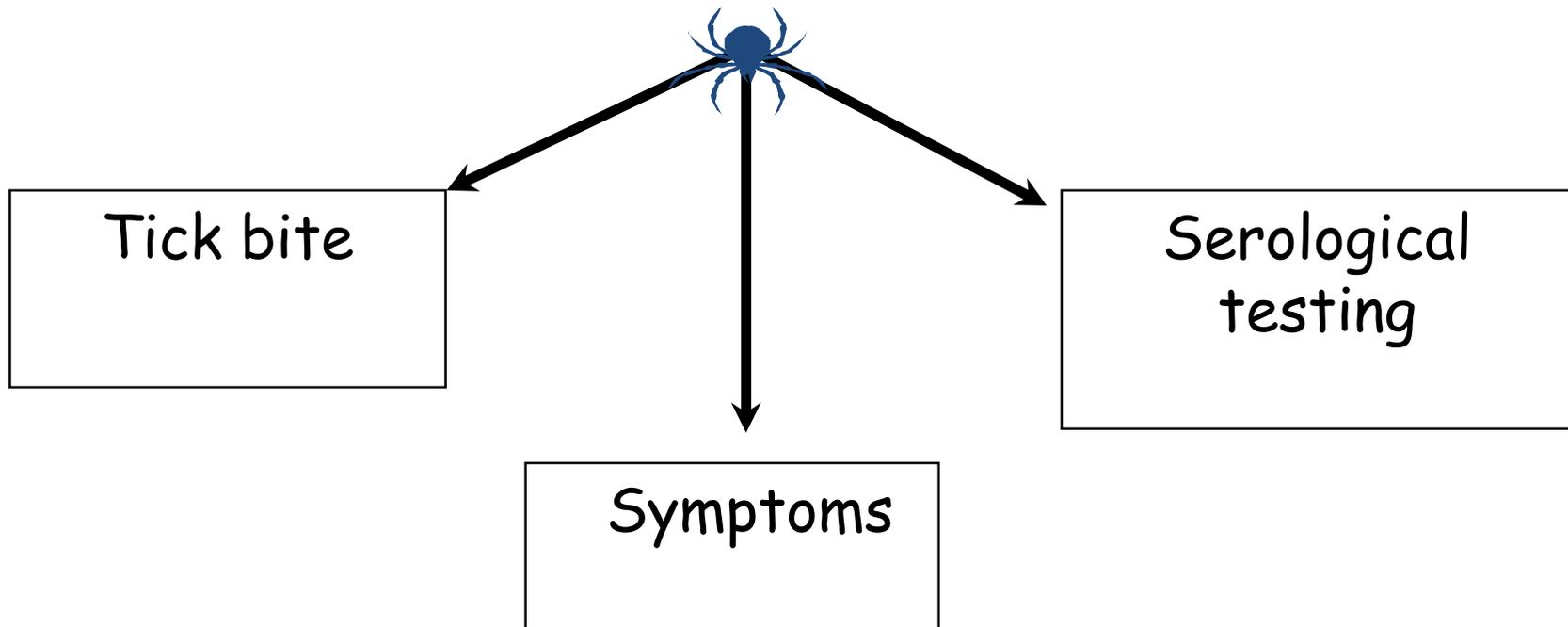
What do we need for the diagnosis ?

- Primary Lyme disease
 - Erythema migrans
- Secondary and late Lyme disease
 - Typical signs AND serological confirmations
 - *Borrelia* very rarely isolated into the tissue
- Neuroborreliosis
 - CSF analysis
 - Pleiocytosis : lymphocytic meningitis
 - Specific antibodies
 - intra thecal synthesis of specific antibodies
 - PCR *Borrelia* : very low sensitivity
 - *Borrelia* culture : very low sensitivity ; can be interesting in early neuroborreliosis



Lyme disease

the three steps of diagnosis



Diagnosis of neuroborreliosis serology testing

- Ab present 4 to 6 weeks after beginning of infection (first IgM, secondary IgG)
- Can stay
 - several months for IgM
 - Several years for IgG
- 💣 risk of false positive tests

Serology two-step approach

Screening test
ELISA



Used for serologic and
CSF testing

Confirmation test :
Western Blot



Lack of
standardisation
Interpretation in
CSF ???

ELISA



- neuroborreliosis
 - sensitivity 21 à 98 % according to the type of serology
 - specificity 69 à 99 % according to the type of serology
- A positive specific antibody response may persist for months or even years after successful treatment of the infection
- No follow-up of antibody titer

Western blot



- First antibodies in early borreliosis
 - IgM p 41
 - puis IgG p41
- American criteria
 - IgM : at least 2 among p24, p39, p41
 - IgG : at least 5 among p19, p21, p28, p30, p39, p41, p45, p58, p66, p93
- No european criteria
- Lack of reproductibility

CSF analysis



- Intrathecal synthesis of Bb antibody or specific CSF/serum antibody index
- ELISA
- Good positive predictive value



Diagnosis criteria

EUCALB case definition

Clinical case definition	Laboratory evidence: essential	Laboratory/clinical evidence: supporting
<p>In adults mainly meningo-radiculitis meningitis, +/- facial palsy rarely encephalitis, myelitis; very rarely cerebral vasculitis.□</p> <p>In children mainly meningitis and facial palsy.</p>	<p>CSF Pleocytosis and demonstration of intrathecal specific antibody synthesis</p>	<p>Detection of <i>B. burgdorferi</i> s.l. by culture and/or PCR from CSF.</p> <p>Intrathecal synthesis of total IgM, and/or IgG and/or IgA.</p> <p>Specific serum antibodies. Recent or concomitant EM</p>

European national neurological societies guidelines

- Definite LNB.
 - The following three criteria are fulfilled:
 - neurological symptoms suggestive of LNB (with other causes excluded);
 - CSF pleocytosis;
 - Bb specific antibodies in CSF (produced intrathecally).
- Possible LNB.
 - Two out of these three criteria are fulfilled.
- If criterion III is lacking; after a duration of 6 weeks, there has to be found Bb-specific antibodies in the serum.
- These criteria apply to all subclasses of LNB except for late LNB with polyneuropathy where the following should be fulfilled for definite diagnosis:
 - Peripheral neuropathy
 - Clinical diagnosis of ACA
 - Bb-Specific antibodies in serum.



Treatment of neuroborreliosis

Evidence based review

Antibiotic choice for neuroborreliosis



- High-dosage intravenous penicillin is an effective treatment for neuroborreliosis
 - Steere AC, et al. *Ann Intern Med* 1983; 99: 767-772.
- Ceftriaxone showed equivalence or a better efficacy at 2 g/day than penicillin.
 - Dattwyler RJ, et al. *Lancet* 1988; 1: 1191-1194.
 - Pfister HW, et al. *Arch Neurol* 1989; 46: 1190-1194.

Antibiotic choice for neuroborreliosis

- Ceftriaxone was effective in cases of neuroborreliosis where penicillin had failed, and can also be used in children with neurological involvement
 - Dattwyler RJ, et al. Ceftriaxone as effective therapy in refractory Lyme disease J Infect Dis 1987; 155: 1322-1324
- Among patients with Lyme encephalopathy, characterized by loss of memory, ceftriaxone is able to improve the clinical signs in some, but not all, cases
 - Logigian EL, : Successful treatment of Lyme encephalopathy with intravenous ceftriaxone. J Infect Dis 1999; 180: 377-383.

Doxyxyclin and neuroborreliosis

- Several studies show equivalent efficacy (200 mg/day, 3 weeks) compared to ceftriaxone and high-dosage intravenous penicillin
 - Karlsson M, et al.: Comparison of intravenous penicillin G and oral doxycycline for treatment of Lyme neuroborreliosis. *Neurology* 1994; 44: 1203-1207.
 - Dattwyler RJ, et al.: Ceftriaxone compared with doxycycline for the treatment of acute disseminated Lyme borreliosis. *N Engl J Med* 1997; 337: 289-294.
 - Dotevall L, et al. Successful oral doxycycline treatment of Lyme disease-associated facial palsy and meningitis. *Clin Infect Dis* 1999; 28: 569-574.
- In other studies, neurological complications occurred after doxycycline treatment,
 - poorly diffusion into the CSF ?
 - When dosage increased to 400 mg/day : equivalence to ceftriaxone
 - Borg R, et al.: Intravenous ceftriaxone compared with oral doxycycline for the treatment of Lyme neuroborreliosis. *Scand J Infect Dis* 2005; 37: 449-454.
- Oral doxycycline as efficient as intravenous ceftriaxone
 - inclusion criteria including patients with Bb antibodies in serum, without any other biological criteria
 - Ljostad *Lancet Neurology*, 2008 ; 7 : 6988-690.



Guidelines

Treatment of nervous system Lyme disease

- Halperin et al. Neurology, 2007 ; 69 : 91-102

Table 1 Antimicrobial regimens used in treatment of nervous system Lyme disease			
Medication	Adult dose	Pediatric dose	Classification
Oral regimens			
Doxycycline* (preferred)	100 (-200) mg BID	• 8 yo: 4 (-8) mg/kg/d in 2 divided doses; max 200 mg/dose	B
Amoxicillin (when doxycycline contraindicated)†	500 mg TID	50 mg/kg/d in 3 divided doses; max 500 mg/dose	C
Cefuroxime axetil (when doxycycline contraindicated)†	500 mg BID	30 mg/kg/d in 2 divided doses; max 500 mg/dose	C
Parenteral regimens			
Ceftriaxone	2 g IV daily	50-75 mg/kg/d in 1 dose, max 2 g	B
Cefotaxime	2 g IV Q8H	150-200 mg/kg/day in 3-4 divided doses; max 6 g/day	B
Penicillin G‡	18-24 MU/d, divided doses Q4H	200-400,000 U/Kg/d divided Q4H, max 18-24 MU/day	B

- †These two oral regimens are effective in non-nervous system Lyme borreliosis. There are no data demonstrating efficacy in neuroborreliosis but large numbers of patients have been treated with these regimens for other forms of Lyme disease without obvious subsequent onset of nervous system involvement. As such they may be an oral alternative in individuals who cannot take doxycycline.

European national neurological societies guidelines

Mygland et al. Eur J Neurol, 2010 ; 17

- Adult patients with Bannwarth syndrome
 - single 14-day course of antibiotics
 - Oral doxycycline or IV ceftriaxone or cefotaxime are effective and safe
 - Oral doxycycline (200 mg daily) for 14 days are equally effective
- Adult patients with early LNB with CNS manifestations
 - IV ceftriaxone (2 g daily) for 14 days



European national neurological societies guidelines



- Late Neuroborreliosis
 - Adult patients with peripheral neuropathy and ACA
 - oral doxycycline (200 mg daily)
 - IV ceftriaxone (2 g daily) for 3 weeks.
 - Adult patients with definite or possible late LNB with CNS manifestations
 - IV ceftriaxone (2 g daily) for 3 weeks.

Some specific situations

Facial palsy

- The Infectious Disease Society of America recommends the use of amoxicillin in absence of meningitis
- However, there is only a descriptive noncomparative study supporting this recommendation.
- So, the use of ceftriaxone or doxycycline, by analogy with the recommendations for other forms of neuroborreliosis (including peripheral neuropathy without meningitis), should be considered until more data can justify the use of oral amoxicillin.

Late stage neuroborreliosis

- There is no clinically evident benefit for long-duration treatments.
 - Klempner, N Engl J Med, 200; 345 :85-92
 - Fallon et al. Neurology, 2008 ; 70 : 992-1003
 - Krupp et al. Neurology, 2003 ; 60 : 1923-1930
- Only a 28-day ceftriaxone (2 g/day) treatment gave better results than a 14-day treatment, but without reaching a significant statistical difference in a non-randomized study
 - Dattwyler RJ, et al. Wien Klin Wochenschr 2005; 117: 393-397.
- And more recently ...

Late stage neuroborreliosis

- repeated IV antibiotic therapy for Lyme encephalopathy (persisting cognitive impairment after first treatment with ceftriaxone)
 - B.A. Fallon et al. Neurology, 2008, 70 : 992-1003
 - A randomized, placebo-controlled trial : Ceftriaxone vs placebo IV
 - Patients with Improvement of cognitive impairment at week 12 but no sustained effect at week 24
 - Pain and physical function was improved at week 24 in group with more severe signs
 - Inclusion criteria based on presence of antibody (ELISA and Western Blot tests)
- duration of antibiotic treatment in disseminated Lyme borreliosis
 - J. Oksi, Eur J Clin Microbiol Inf Dis, 2007 ; 26 : 571-581
 - double-blind, randomized, placebo-controlled,
 - oral adjunct antibiotics are not justified in the treatment of patients with disseminated LB who initially receive intravenous ceftriaxone for 3 weeks

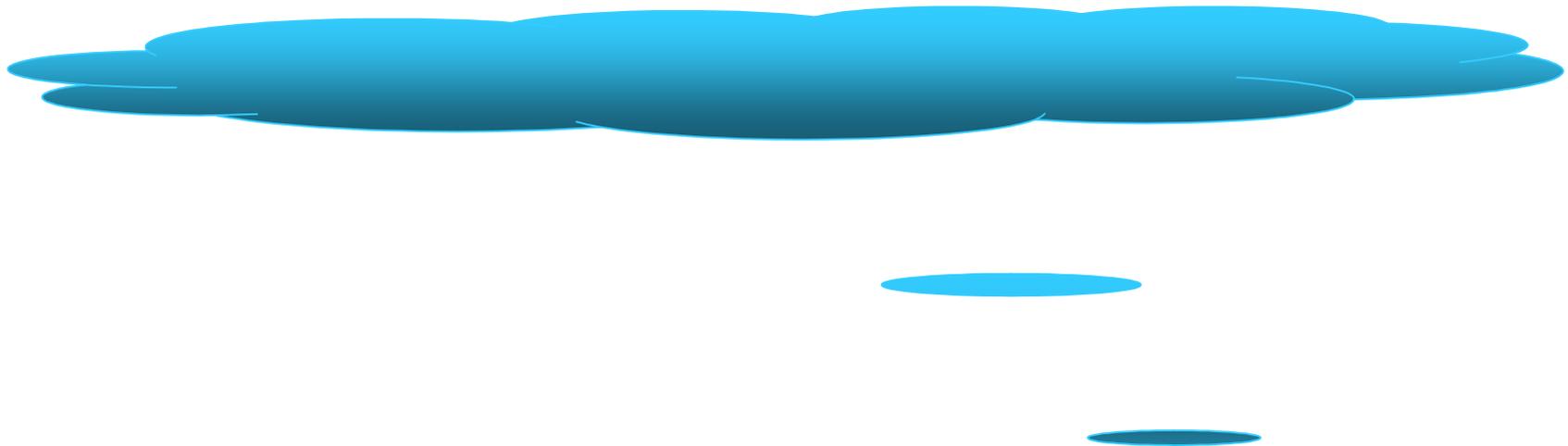
Follow up



- No correlation between recovery and serological results
 - Recovery criteria : regression of clinical symptoms
- **No Serology testing during follow up**



What do we know about
neuroborreliosis ?



Koch's postulate



- The microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy organisms.
- The microorganism must be isolated from a diseased organism and grown in pure culture.
- The cultured microorganism should cause disease when introduced into a healthy organism.
- The microorganism must be reisolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent.

The controversy

Advocacy of Lyme disease

P.G. Auwaerter et al., Lancet,
infection, sept 2011, vol 11 : 713 -718

The polemic



- Some patients « seem to foolishly believe that they understand everything there was to know »
 - Seth Kalichman author of « Denying AIDS » cited in the article of P.G. Auwaerter
- Lyme disease characteristics
 - Lot of subjective complaints like : fatigue, arthralgia, myalgia, headache, impaired concentration
- Laboratory testing
 - There are a lot of unvalidated laboratory testing
 - Non reproductive results
- Lot of patient think they have Lyme disease, even if they are healthy

Relationship between diagnosis and treatment



- Without diagnosis : low probability of treatment efficacy
- There is no gold standard for diagnosis of borreliosis : all diagnosis studies have lot of bias
- therapeutical studies : diagnosis is often not certain
- For physicians the main question is :
 - Shall I give an antibiotic to cure my patient ?
 - Which percentage of cure if serology is positive ?
 - Which percentage of cure if intra thecal synthesis is present ?

Relevance of the antibody index to diagnose Lyme neuroborreliosis among seropositive patients



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ABSTRACT

Background: No consensual criteria exist to diagnose neuroborreliosis. The intrathecal anti-*Borrelia* antibody index (AI) is a necessary criterion to diagnose neuroborreliosis in Europe, but not in the United States. Previous studies to determine the diagnostic value of the AI found a sensitivity ranging from 55% to 80%. However, these studies included only typical clinical cases of meningitis or meningoradiculitis, and none had a control group with CSF anti-*Borrelia* antibodies.

Methods: We studied a sample of 123 consecutive patients with clinical signs of neurologic involvement and CSF anti-*Borrelia* antibodies. We determined the AI for all patients and a final diagnosis was made. Patients were then divided into three groups (neuroborreliosis, possible neuroborreliosis, control).

Results: Thirty of the 40 patients with neuroborreliosis had a positive AI (AI sensitivity = 75%). Two of the 74 patients with another neurologic diagnosis had a positive AI (AI specificity = 97%).

Conclusion: The antibody index has a very good specificity but only moderate sensitivity. Given the lack of consensual criteria for neuroborreliosis and the absence of a "gold standard" diagnostic test, we propose pragmatic diagnostic criteria for neuroborreliosis, namely the presence of four of the following five items: no past history of neuroborreliosis, positive CSF ELISA serology, positive anti-*Borrelia* antibody index, favorable outcome after specific antibiotic treatment, and no differential diagnosis. These new criteria will need to be tested in a larger, prospective cohort.

Neurology® 2007;69:953-958

Aim of the study



- Evaluate the potential of antibody index in predicting neuroborreliosis
- Comparison of two groups of patients (all of them had serologic presence of Borrelia antibody) according to the diagnosis criteria for neuroborreliosis
- Response to ceftriaxone was associated with presence of intra thecal synthesis

Conclusion

Table 2 Proposed diagnostic criteria for neuroborreliosis

For a diagnosis of neuroborreliosis at least four of the following five items should be present:

- No past history of neuroborreliosis
- CSF anti-*Borrelia* antibodies
- Positive anti-*Borrelia* antibody index
- Favorable outcome after specific antibiotic treatment
- No other etiologic diagnosis

Conclusion



- Right diagnosis is important to cure neuroborreliosis
- Clinical symptoms are not specific enough
- Serology testing is often positive in endemic area
- CSF analysis can help to make right diagnosis

- Do you really think that I suffered from neuroborreliosis today ??