Neuroborreliosis: Challenges and experiences from Norway
London 250315

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Leader of the Norwegian National Advisory Unit on Tick-borne Diseases
Distribution Ixodes *ricinus* in Norway

Jore et al. "Multi-source analysis reveals latitude and altitude shifts in range of Ixodes ricinus at its northern distribution limit"
Parasites & Vectors 2011
Borrelia in Ixodes Ricinus in Norway (PCR) (Kjelland et al. 2010)

- 1130 nymfs, 449 adults, 230 larva

<table>
<thead>
<tr>
<th>Location</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farsund</td>
<td>31 %</td>
</tr>
<tr>
<td>Mandal</td>
<td>25 %</td>
</tr>
<tr>
<td>Søgne</td>
<td>23 %</td>
</tr>
<tr>
<td>Tromøy</td>
<td>22 %</td>
</tr>
<tr>
<td>Bb Afzelii</td>
<td>62 %</td>
</tr>
<tr>
<td>Bb Garinii</td>
<td>23 %</td>
</tr>
<tr>
<td>Bb sensu stricto</td>
<td>10 %</td>
</tr>
<tr>
<td>Mix</td>
<td>0.3 %</td>
</tr>
</tbody>
</table>
**MSIS**- the Norwegian Surveillance System for Communicable Diseases: incidence of disseminated borreliosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated borreliosis</td>
<td>273</td>
<td>288</td>
<td>248</td>
<td>256</td>
<td>315</td>
<td>321</td>
</tr>
<tr>
<td>Tick Born encephalitis</td>
<td>10</td>
<td>11</td>
<td>14</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>
## Borrelia Clinical Classification

<table>
<thead>
<tr>
<th>Early Localised</th>
<th>Early Disseminated</th>
<th>Late Disseminated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema migrans</td>
<td>Neuroborreliosis</td>
<td>Late neuroborreliosis</td>
</tr>
<tr>
<td>Lymfocytoma</td>
<td>Arthritis</td>
<td>Chronic arthritis</td>
</tr>
<tr>
<td></td>
<td>Carditis</td>
<td>Acrodermatitis chronica atropicans</td>
</tr>
</tbody>
</table>
Norwegian distribution of disseminated borreliosis (MSIS)

www.fhi.no
Risk of EM and disseminated disease after tick-bite in Norway and Sweden

STING study, EM study

4,67 EM/1000 inhabitants/year (Eliassen)

Sweden: 5 EM

Sting study 1546 ticks taken from bitten humans
428 carrying Borrelia
27 EM
2 neuroborreliosis
1 lymfocytoma

Fryland L, Wilhelmsson P, Lindgren PE, Nyman D, Ekerfelt C, Forsberg P.
Lyme arthritis in southern Norway - an endemic area for Lyme borreliosis

Inger Johanne W. Hansen, Dept. of Rheumatology, Sørlandet Hospital
Sølvi Noraas, Dept. of Microbiology, Sørlandet Hospital
Tone Skarpaas, Dept. of Microbiology, Sørlandet Hospital
Vivian Kjelland, Dept. of Research and Development, Sørlandet Hospital
and Dept. of Natural Sciences, University of Agder, Kristiansand S,
Glenn Haugeberg, Dept. of Rheumatology, Sørlandet Hospital.
Borrelia Arthritis, clinical appearance in Norway

21 cases in 5 years, incident rate of 2.7 in high endemic region:

<table>
<thead>
<tr>
<th>Diagnose</th>
<th>N=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite BA:</td>
<td>16</td>
</tr>
<tr>
<td>Possible BA:</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type artritt</th>
<th>N= 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoarthritis</td>
<td>20</td>
</tr>
<tr>
<td>Knee</td>
<td>18</td>
</tr>
<tr>
<td>Ankle</td>
<td>2</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>1</td>
</tr>
</tbody>
</table>
Neuroborreliosis definitions

• **Acute neuroborreliosis**: weeks to months after bite

• **Chronic neuroborreliosis**: More than 6 months after bite.

• ”**Post Lyme disease syndrome**” persistent symptoms after treated neuroborreliosis without signs of an active infection
### Diagnostic criteria neuroborreliosis

(Mygland et al. 2010 EFNS guidelines)

<table>
<thead>
<tr>
<th>Definite neuroborreliosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 3 criteria fulfilled</td>
</tr>
</tbody>
</table>

1. Typical neurological symptoms
2. Pleocytosis CSF spinal fluid
3. Intrathecal anti-Borrelia antibody production
Acute nevroborreliose (NB) clinical appearance in Norway Bannwarth syndrome

Meningitis
Radiating pain
Paresis and sensory symptoms
80% patients NB treatment study

Exclusion of neuroborreliosis

Symptoms more than 3 months and two different ELISA negative antibody tests in blood and spinal tap

No response of adequate treatment

Nederland diagnostic and treatment guidelines on borreliosis 2013

- Sensitivity of borrelia antibody tests:
  - Local infection: 50% sensitivity
  - <6-8 weeks duration of symptoms of disseminated neuroborreliosis: 80% sensitivity
  - > 8 weeks duration of symptoms of disseminated borreliosis: 98% sensitivity

(Hansen -81-91-92, Wilske -93, Goettner -05, Bacon-03)
Treatment neuroborreliosis Norway:

- Before treatment study: Ceftriaxone 2 g iv 14 days
- After: Peroral Doxycycline 200 mg for 14 days
- If suspected central nervous system infection: Ceftriaxone

Long term consequences after Lyme Neuroborreliosis (LNB)?

- Antibiotics: good effect on acute symptoms
- Complaints exist in 10-50% after treatment*
- Muscular pain, fatigue and altered cognition
- Cause of long term complaints not known
- Prolonged and repeated antibiotic treatment does not seem to help**

** Forsberg et al. SBU (Swedish Council on Technology Assessment) report 2013 Forsberg et al
The South Norwegian LNB cohort

- Aust- and Vest Agder county LNB treatment study 2004 - 2008*
- 50 of them came to a follow-up 30 months after treatment
- Patients brought their own control person matched for age, gender and educational level without a history of LNB

Aim of the Long term prognosis after nevroborrellosis study

Risk factors

Quality of life and fatigue

Neuro-psychological functioning
**Neurological findings and subjective complaints**

<table>
<thead>
<tr>
<th>Neurological findings n=14 *</th>
<th>Subjective symptoms alone n= 19**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiculopathy (n=6)</td>
<td>Fatigue (n=15)</td>
</tr>
<tr>
<td>Paresis arm/leg (n=4)</td>
<td>Memory loss (n=13)</td>
</tr>
<tr>
<td>Paresis face (n=3)</td>
<td>Attention problems (n=9)</td>
</tr>
<tr>
<td>Loss of sensation face (n=3)</td>
<td>Pain (n=7)</td>
</tr>
<tr>
<td>Tremor (n=2)</td>
<td>Paresthesias (n=7)</td>
</tr>
<tr>
<td>Reduced co-ordination (ataxia) (n=2)</td>
<td>Malaise (n=5)</td>
</tr>
<tr>
<td>Nystagmus(n=2)</td>
<td>** 14 more than 1 symptome</td>
</tr>
<tr>
<td>Reduced hearing (n=1)</td>
<td></td>
</tr>
<tr>
<td>Anisocoria (n=1)</td>
<td></td>
</tr>
</tbody>
</table>

*10 more than 1 finding

** 14 more than 1 symptom
Lyme neuroborreliosis reduces health related physical and mental quality of life 30 months after recommended treatment.
Fatigue and depression in LNB 30 months after treatment

<table>
<thead>
<tr>
<th>Test (range)</th>
<th>Patients n=50 Mean (SD)</th>
<th>Controls n=50 Mean (SD)</th>
<th>P-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression MADRS (0-60)</td>
<td>3.1 (4.9)</td>
<td>0.8 (1.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>Fatigue FSS (0-7)</td>
<td>3.5 (1.9)</td>
<td>2.1 (1.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Student t-test
Spinal fluid findings 30 months after LNB treatment

- Raised cell count: 10% (one person 6, one 7 and one 66 cells, normal less than 5-6 cells)
- High protein level: 28%
- Borrelia antibody production: 61%
- Oligoclonal bands: 43%

No signs of persistent infection
Conclusions

• Most patients recover after treated Lyme neuroborreliosis, long term complaints exist
• Reduced quality of life, fatigue and cognitive deficits
• Risk factors: Symptoms >6 weeks before treatment, more severe disease before treatment and non-recovery at 4 months
• No signs of active infection at 30 months
• Pain and depression are not the course
Course of long term complaints?

- Persistent Infection?
- Natural course?
- Co-infection?
- Tissue damage?
- Origin-hypothesis
- Psychological issues?
- Autoimmune?
- Immunological dys-regulation?
Why a national advisory unit for tick-borne diseases?

• Fear of serious consequences after tick-bite is common
• Poor knowledge and confusion about pathogens, diagnostics, treatment, prognoses among health professionals, politicians, media, patients
• Growing incidence of ticks and tick-born diseases
Norwegian National Advisory Unit on Tick-borne Diseases

Ministry of Health

The South-Eastern Norway Regional Health Authority

Sørlandet Hospital Board

Medical quality and safety department

NKFS
Groups of interest

- People suffering from acute tick-borne disease and people with persisting complaints after tick-borne diseases
- Healthcare professionals
- Politicians
- Media
- Norwegian population in general
Employees NKFS 2015

- Randi Eikeland (PhD, specialized in neurology)
- Harald Reiso (PhD, specialized in general medicine)
- Yvonne Kerlefsen (MSc in Biology)
National reference group NKFS

- Leader: Ingeborg Aaberge: Norwegian institute of public health, Immunology/microbiology
- Dag Tveitnes: Western Norway Regional Health Authority, Pediatrics
- Dag Hvidsten: Northern Norway Regional Health Authority, Microbiology/pediatrics
- Hilde Gran: General medicine
- Elling Ulvestad: The university of Bergen, Immunology/microbiology
- Rune Midgard: Central Norway Regional Health Authority, Neurology
- Vivian Kjelland: University of Agder, Molecular biology
- Carl Erik Semb: Norsk Lyme Borreliose-Forening
- Dag Berild: South-Eastern Norway Regional Health Authority/University of Oslo, Infectious diseases
- Randi Eikeland: NKFS, Neurology
- Yvonne Kerlefsen. Harald Reiso. NKFS
Counselling/ information

• To Systemize and distribute knowledge about tick-borne diseases
• To help to establish Clinical guidelines
• To organize symposia and teaching courses for health care professionals, patients, general public
• To Supervise and consult health care professionals, politicians, media and patients
• www.sshf.no/flått
• Flaattsenteret@sshf.no
Research and surveillance

• Establish and attend local/national/international research networks on tick-borne diseases
• Promote research and PhD candidates
• Supervision, literature services, contacts
• Contribute to the establishment of a national registry and bio-bank for Borrelia-serology
• Project leader of multi centre study on tick-born diseases BorrSci 2015-2020 (2 million £ founding)
My thesis is free for downloading at: http://hdl.handle.net/1956/5870

Thank you for your attention!

Picture: NRK Sørlandet