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# Neuroborreliosis-an epidemiological, clinical and healthcare cost study from an endemic area in the south-east of Sweden



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#### Abstract

We studied retrospectively the medical records of all patients diagnosed with neuroborreliosis (NB) by cerebrospinal fluid (CSF) analysis in Jönköping County, Sweden, during 2000-2005 (n=150). The number of NB cases increased from 5 to 10/100,000 inhabitants/year. In 17% of the patients, *Borrelia*-antibodies were found in CSF but not in serum at the time of diagnosis. Facial palsy, headache and fever were frequent manifestations in children, whereas unspecific muscle and joint pain were the most commonly reported symptoms in older patients. Symptoms persisting more than six months post-treatment occurred in 13%, and these patients were significantly older, had longer duration of symptoms prior to treatment, higher levels of *Borrelia*-specific IgG in CSF and more often radiculitis. The total cost for NB-related health care was estimated to 500,000 EUR for the entire study group (3,300 EUR/patient), and the cost for social benefits to 134,000 EUR (2,000 EUR/patient). CSF analysis is necessary for NB diagnosis since some patients develop antibodies in serum later than in CSF. Early diagnosis of borreliosis would result in reduced human suffering and economic gain.

#### Introduction

In Europe, neuroborreliosis (NB) is the most common manifestation of disseminated borreliosis, occurring in 14-34 % of all cases with borreliosis [1-3]. The clinical course of NB is highly variable. In most patients antibiotic therapy leads to full recovery, but some patients experience residual or recurrent symptoms even after treatment [4-8].

Jönköping County, with an area of 10,475 km<sup>2</sup> and located in the south-east of Sweden (Figure 1), is known to be endemic of borreliosis. In December 2005, the county had 330,179 inhabitants. The prevalence of *Borrelia* infected *Ixodes* ticks varies between 10-20% [9,10]. The incidence of human borreliosis in Jönköping County was reported to be 60 cases/100,000 inhabitants/year in 1992-93 [1]. Out of these, 10/100,000/year were considered to be NB.

The aims of this retrospective study were to 1) monitor the incidence of NB during 2000-2005, 2) study how NB symptoms relate to age, 3) to identify cases with antibodies in cerebrospinal fluid (CSF) but not in serum at diagnosis, 4) search for possible clinical or laboratory markers associated with the risk of developing long-lasting post-treatment symptoms, and 5) address some economic aspects of NB in terms of cost for health care and social benefits [11].

#### Materials and methods

Study population and case definitions

The population studied comprised all the inhabitants in Jönköping County, from 2000 through 2005. Inclusion criteria were clearly positive CSF *Borrelia*-specific antibody levels (optical density (OD) >0.40 for both IgG and IgM) or borderline levels (IgG: OD 0.19-0.39 and IgM:

OD 0.16-0.39), n=157. All patients had pleocytosis in the CSF, defined as >5 mononuclear cells (MNC)/μL, except for four cases who had positive or borderline *Borrelia*-specific CSF-IgG, positive *Borrelia*-specific IgG-index (according to either one or both of the *Borrelia*-specific IgG-index calculation methods described below), and symptoms consistent with active NB. All four patients had a long history of illness (36 weeks to several years). One of them responded to antibiotic treatment, two only partially and one did not get any treatment. Seven of the 157 patients were excluded due to other obvious diagnoses (e.g. normal pressure hydrocephalus, cerebellar infarction or *Varicella* encephalitis) and/or absence of pleocytosis. In these seven cases the anti-*Borrelia* CSF antibodies were considered to be an indication of a previous NB infection or IgM cross-reactivity to another pathogen (e.g. *Varicella*). The number of patients included was 150, all of whom had elevated *Borrelia*-specific antibodies (IgG and/or IgM) in CSF and pleocytosis, except in the four cases mentioned above (Figure 2).

#### Laboratory methods

The Laboratory of Microbiology, Ryhov County Hospital, performed all *Borrelia* antibody tests, using the commercially available Lyme Borreliosis ELISA kit 2<sup>nd</sup> Generation (Dako Cytomation A/S, Glostrup, Denmark). From January 2000 to August 2004 the *Borrelia*-specific antibody index was calculated as described by Peter 1992 [12] with the modification that total IgG was substituted for *Rubella*-specific IgG. The formula used was: [(*Borrelia*-specific IgG in CSF (OD) / *Borrelia*-specific IgG in serum (OD))]. From September 2004, the laboratory used total IgG as reference molecule: [(*Borrelia*-specific IgG in CSF (OD) / *Borrelia*-specific IgG in serum (OD))]. A *Borrelia*-specific IgG in serum (OD))]. A *Borrelia*-specific

antibody index >2 was considered to indicate intrathecal anti-*Borrelia* antibody production with both methods.

#### Data collection

The study was approved by the Regional Ethical Review Board in Linköping. Consent to read the patients' medical records was given by the medical director of each department. The medical records were scrutinized retrospectively by one of the authors (A.J.H.) according to a standardized protocol.

Economy data on health care were obtained from the Departments of Economy and Information Technology, Ryhov County Hospital. Monetary values were assigned to each hospitalization using the classification systems according to Health Care Financing Administration—Diagnosis Related Groups (HCFA-DRG) during the years 2000-2003, and NordDRG during 2003-2005 (Fernstrom M. Vad är DRG? [cited 2008 January 10]; available from: <a href="www.socialstyrelsen.se">www.socialstyrelsen.se</a> and <a href="www.nordclass.uu.se">www.nordclass.uu.se</a>). Data on sickness and temporary parental benefits were provided by The Swedish Social Insurance Agency.

#### Data handling and statistics

Statistical analyses were performed using SPSS for Windows, version 15.0. To compare multiple study groups, the Kruskal-Wallis ANOVA test was performed, followed by the Mann-Whitney test as a post-hoc analysis. Correlations were calculated using Spearman correlation. Trend analysis of incidence was performed using linear regression. Chi<sup>2</sup> test was used for statistical analysis of categorical variables, and Fisher's Exact test was applied when expected counts were less than five. Two-tailed tests were used, and p-values <0.05 were considered significant.

#### **Results**

Number of cases/year

During the study period 2000-2005, the annual number of NB cases, verified by CSF analysis, increased from 16 to 32 cases a year (5 to 10/100,000 inhabitants/year) (Figure 3). Ninety-three patients (62%) were men and 57 (38%) were women. The median age was 18 years, with a range from 3-87 years (figure 3).

Clinical and laboratory findings prior to treatment

The reported symptoms and their frequencies are presented in Table 1. Facial palsy, neck pain, fever and fatigue were more common in patients under the age of 40 (p=0.0001-0.031). Patients over 40 reported muscle and joint pain, radiating pain, parestesias, vertigo and concentration problems more often than patients under 40 (p=0.0001-0.003). Patients under 40 had shorter duration of symptoms prior to diagnosis than patients over 40 (p<0.0001). A tick bite had been noticed by 32% of the patients, and 24% had an erythema migrans (EM). CSF pleocytosis was dominated by MNC (median 164 cells/µL, range 0-1380). Increased levels of *Borrelia*-antibodies were found in CSF but not in serum in 25 (17%) of the patients at the time of diagnosis. These patients had a median duration of symptoms of three weeks (range one day-eight weeks). CSF-albumin/S-albumin ratio, as an indicator of blood-brain barrier (BBB) damage, was elevated in 80% of the patients. CSF-lactate was elevated in 55% (range 1.3-3.9 mmol/L), and CSF-glucose was low in 9% (range 1.9-8.2 mmol/L). Patients under the age of 40 had higher cell counts in CSF than those over 40 (p<0.0001). In general, no abnormalities were found in other routine blood laboratory parameters, e.g. blood cell count, creatinine, electrolytes, aminotransferases, alcalic phosphatase, bilirubine or lactate dehydrogenase. C-reactive protein was elevated (>10 mg/L) in 6 of 99 analyzed patients and white blood cell count was elevated (8.8 x 10<sup>9</sup>/L) in 26 of 98 patients. There were no significant differences between men and women regarding laboratory parameters or duration of illness before diagnosis.

All four patients with *Borrelia*-specific IgG in CSF and positive *Borrelia*-specific IgG-index but no pleocytosis had a long history of illness (median 64 weeks, range 36 weeks-six years). They most frequently reported muscle and joint pain, parestesia, vertigo and concentration problems. Interestingly, the highest *Borrelia*-specific IgG-indices were found among these four patients (range 2.4-13.1).

Fatigue, fever >38°C, headache, facial palsy, neck pain and muscle and joint pain were most frequently reported in patients with the most pronounced pleocytosis (CSF cell count >284/ $\mu$ L, the upper quartile), which also correlated with age <40. This group had also significantly higher CSF-albumin (p<0.0001), CSF-albumin/S-albumin ratio (p<0.0001) and CSF-lactate (p=0.001) as well as lower CSF-glucose (p=0.001).

Patients were treated with oral doxycycline (63%), intravenous ceftriaxone (25%), benzylpenicilline (9%) or cefuroxime (1%) for 10-21 days, median 14 days.

#### Follow-up

At follow-up, 106 patients had completely recovered, but 44 still had symptoms at the last visit. The 106 patients where the clinical course until recovery was clearly documented were classified according to the duration of symptoms post-treatment (Table 2). Significant differences in age distributions were found between all the groups, except when comparing group B versus group C. Higher age was associated with longer duration of symptoms. The acute phase symptoms are presented in Table 3. The only laboratory parameter in the acute phase that differed significantly between the groups was *Borrelia*-specific CSF-IgG, which was highest in group D. No significant differences were found between the groups regarding type of antibiotic treatment or duration of treatment.

#### Economic aspects

The total health care cost for the patients in the study group was estimated to 500,000 EUR. The number of visits to a physician in an out-patient department was 490, the cost of which was estimated to 130,000 EUR. The number of out-patient visits per individual varied between 0 and 10 (median 3), and 79 patients (53%) were hospitalized, median 5 days (range one to 60). The total number of days in hospital generated by the entire study group was 603. DRG weights varied from 0.3104-1.8067, median 0.7825. The estimated total cost for hospital care was 330,000 EUR (4,200 EUR/patient). For reference, estimated costs for hospital care for pneumonia: 2,800 EUR/patient, viral meningitis: 2,300 EUR/patient, sepsis: 5,200 EUR/patient. Children under 8 years of age were often treated with ceftriaxone administered intravenously once daily by a nurse in primary health care. In this study, 509 ceftriaxone-days were registered, resulting in an estimated cost of 38,000 EUR. Of the adult patients aged 16-64 years, 26 (51%) received sickness benefits from the Social Insurance Agency (range 4-528 days, median 32 days). The mean cost for sickness benefits was 4,600 EUR/patient. Temporary parental benefits were disbursed to the parents of 39 (51%) of the children (range 0.25-19 days, median 5 days). The estimated total cost for social benefits was 134,000 EUR (2,000 EUR/patient).

#### **Discussion**

The number of NB cases verified by CSF analysis increased from 5 to 10/100,000 inhabitants/year during the years 2000-2005 in Jönköping County. The number of NB cases during the first part of the study period was 5-6/100,000 inhabitants, which is about half as many as reported earlier[1]. This discrepancy can be explained by the fact that we only included cases verified by CSF analysis, whereas Berglund et al. included patients diagnosed

with NB based on either CSF findings or clinical symptoms and *Borrelia* antibodies in serum. There are probably a number of patients who during this study period were treated with antibiotics for a suspected NB infection, in whom the diagnosis was based on symptoms and *Borrelia*-specific antibodies in serum. The true number of NB cases in the county can thus be assumed to be even higher than 10/100,000 inhabitants/year.

The increase of NB cases may be explained by better awareness of *Borrelia* infections both in the general population as well as among physicians. However, it might well be a real increase of NB cases, and there are several plausible explanations, i.e. milder and more humid climate in the region (Westermark L, Rummukainen M, Nivrén A. Vintrarna är varmare. 2007 December 19 [cited 2008 January 8]; <a href="www.naturvardsverket.se">www.naturvardsverket.se</a> and Alexandersson H. Klimat i förändring. 2006 [cited 2008 January 8]; <a href="www.smhi.se">www.smhi.se</a>), that may be favourable to the ticks [13, 14], and increasing populations of fallow deer and wild boars in the county in later years [15-18], (Svenska-Jagareforbundet. Arsrapport Viltovervakningen. 2005/2006 [cited 2008 January 15]; available from: <a href="www.jagareforbundet.se">www.jagareforbundet.se</a> and personal communication with Kjellander P, Grimso Wildlife Research Centre, Swedish University of Agricultural Sciences; January 2008).

Data on clinical presentation of NB, age and sex distribution, laboratory findings and the frequency of observed tick bites and EM, are mainly in line with earlier observations [19-22]. However, some particularly interesting findings should be pointed out. As many as 80% of the patients had an elevated CSF-/S-albumin ratio, as an indicator of impairment of the BBB. The highest IgG-indeces were found among the four patients with the longest duration of symptoms prior to treatment (9-78 months). These four patients had no pleocytosis, although it can not be excluded that an earlier pleocytosis had normalized by the time of the lumbar puncture, probably reflecting the natural course of the disease. They reported mainly unspecific symptoms.

Patients with a CSF MNC count >284 cells/μL (the upper quartile) most frequently reported symptoms of meningitis and distinct symptoms like facial palsy and fever. They also had the shortest median duration of symptoms before treatment. Patients under the age of 40 had significantly higher MNC count in CSF than patients over 40. The risk of developing long-lasting post-treatment symptoms increased with age. One could speculate that young individuals can mobilize a strong and rapid inflammatory response to the *Borrelia* infection, giving them more distinct clinical symptoms, which in turn leads to an early diagnosis and treatment, as well as effective elimination of bacteria. Accordingly, a strong initial inflammatory response has previously been demonstrated to be associated with good prognosis in borreliosis [23-27]. In contrast, older patients show a less pronounced inflammatory response and they often present with more vague symptoms, which might delay the diagnosis and treatment.

Our findings emphasize the importance of CSF analysis for the NB diagnosis, since 17% of the patients presented with elevated levels of *Borrelia*-specific antibodies in CSF but not in serum. Repeated sampling was not performed in our study, so we can not establish if these patients developed antibodies in serum later on. However, without a diagnostic lumbar puncture, these patients might have been misdiagnosed. Earlier studies [7], as well as our data, further indicate that the duration of symptoms before treatment might be of importance for the clinical outcome.

Symptoms lasting more than six months post-treatment were reported by 13% of the patients (14/106). The clinical and laboratory findings in the acute phase characterizing this patient group were: high age, long duration of symptoms prior to treatment, high levels of *Borrelia*-specific IgG in CSF, symptoms of radiculitis, especially radiculitis involving the lower

extremities, and unspecific symptoms, i.e. muscle and joint pain, vertigo, parestesia and concentration disturbances.

NB has important economic consequences, both in terms of cost for health care and social benefits. If a NB patient is diagnosed at an early stage of the disease, out-patient treatment with oral doxycycline for 10-14 days is sufficient in most cases (Medical Products Agency. Fastingoverforda infektioner. 1998;(9)2. [cited 2008 January 10]; available from: <a href="https://www.lakemedelsverket.se">www.lakemedelsverket.se</a>). Early treatment is associated with quick recovery and, consequently, shorter period with sickness benefits.

There are of course limitations to this retrospective study, such as a presumable bias both in reported and documented symptoms. Data on time to recovery were not possible to obtain from all patients. However, the data were available in a substantial number of cases and, furthermore, our data are in line with previous prospective studies [1], thus supporting the accuracy of the results.

In conclusion, the number of NB cases seems to have increased in Jönköping County during the years 2000-2005. It appears as relevant and important to follow the epidemiological development of NB also in the future, since continuing changes in climate and tick-feeding fauna are expected. Symptoms and CSF findings seem to differ between younger and older individuals, with a tendency towards more distinct clinical symptoms and more pronounced inflammatory response in the CNS in the younger. As many as 17% of the NB patients in this study had *Borrelia*-antibodies detectable in CSF but not in serum at the time of the lumbar puncture, thus emphasizing the importance of CSF analysis for early NB diagnosis. The costs for health care and social benefits related to NB are quite important, especially in patients with unspecific and long-lasting symptoms.

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## **Transparency declaration**

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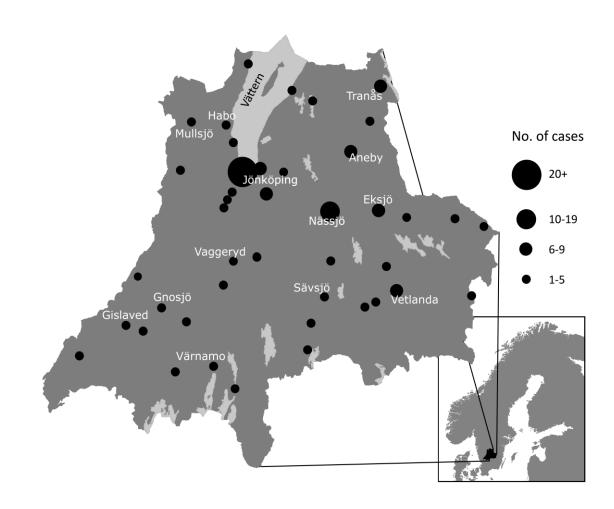


Figure 1.

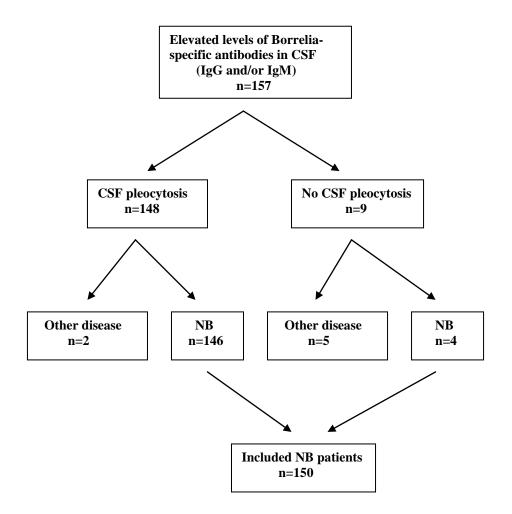


Figure 2.

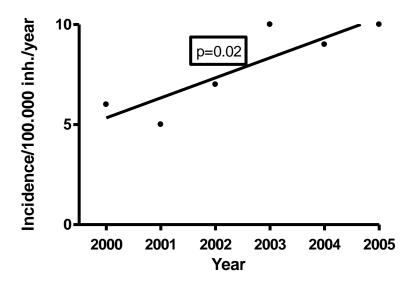


Figure 3, panel A.

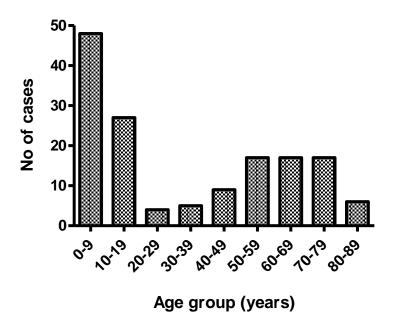


Figure 3, panel B.

Table 1.

Symptom*	Total	Se	exes	Age groups (years)								
	Total	M	F	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
n=	150	93	57	48	27	4	5	9	17	17	17	6
Muscle/ joint pain	54	54	54	31	26	75	40	89	88	71	82	83
Facial palsy	52	55	47	65	59	50	80	33	35	29	47	50
Fatigue	42	42	42	60	52	0	80	33	29	18	18	33
Headache	42	45	37	50	56	25	40	67	35	29	24	0
Neck pain	35	39	28	35	44	50	60	56	29	24	18	17
Parestesia	25	18	35	2	7	50	40	56	65	41	41	0
Fever	23	25	19	35	26	0	20	33	18	12	6	0
Radiculitis Leg	25	25	25	10	11	50	20	33	53	41	35	17
Arm	15	19	9	4	4	25	20	22	29	24	24	50
Trunk	13	17	7	0	4	0	40	33	41	12	29	0
Vertigo	12	7	21	2	11	0	20	11	24	18	24	17
Concentration difficultie	5 s	4	7	0	0	0	0	22	6	24	0	17
Other cranial nerve palsy	4	3	5	0	7	0	20	0	0	0	12	17

<sup>\*</sup>Some patients reported several symptoms. M=males. F=females.

Table 2. Duration of symptoms (A-D) in relation to sex, age and duration of symptoms before treatment.

		Patient groups, N=106*					
		A n=26	B n=33	C n=33	D n=14		
Males	number (%)	16 (61.5)	25 (75.8)	21 (63.6)	6 (42.9)		
Females	number (%)	10 (38.5)	8 (24.2)	12 (36.4)	8 (57.1)		
Age (years)**	median (range)	8 (4-66)	12 (3-79)	22 (3-85)	56,5 (10-64)		
Duration of symptoms before treatment (weeks)**	median (range)	2 (0.1-8)	2,5 (0.5-6)	3 (0.1-36)	5,5 (2-77)		

\* 106/150 patients where data were available.

\*\* significant differences between groups, except between group B and C regarding age.

Groups according to duration of symptoms post-treatment: A: 0-2 weeks; B: 2-4 weeks; C: 1-6 months; D: >6 months.

Table 3.

Symptom	Patient groups, N=106*							
	A n=26	B n=33	C n=33	D n=14				
Headache	58	42	36	43				
Fatigue	58	49	49	36				
Fever	31	30	15	14				
Neck pain	39	46	30	43				
Vertigo	0	6	9	29				
Concentration difficulties	0	0	6	14				
Radiculitis Leg	15	21	21	57				
Arm	4	12	9	29				
Trunk	8	3	9	36				
Muscle/ joint pain	35	42	61	86				
Parestesia	4	15	33	57				
Facial palsy	46	61	55	7				
Other cranial nerve palsy	0	6	6	7				

\* 106/150 patients where data were available. Group A: 0-2 weeks. Group B: 2-4 weeks. Group C: 1-6 months. Group D: > 6 months.

## **Legends:**

Figure 1: Jönköping County, Sweden. Each spot refers to site of domicile.

Figure 2: Inclusion of patients with neuroborreliosis (NB). CSF= cerebrospinal fluid.

Figure 3: Panel A: Number of cases with neuroborreliosis verified by CSF analysis in Jönköping County, Sweden 2000-2005. Trend analysis: p=0.02.

Panel B: Number of cases of neuroborreliosis in each age group.

Table 1: Frequency (%) of symptoms recorded at diagnosis of 150 patients with neuroborreliosis in relation to sex and age group.

Table 2: Patient groups according to time to recovery after start of antibiotic treatment.

Table 3: Patients categorized according to time to recovery after start of antibiotic treatment, in relation to symptoms with which they presented at the time of the lumbar puncture (%).