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 (n = 150) diagnosed, by cerebrospinal fluid (CSF) analysis, with neuroborreliosis (NB) in Jönköping County, Sweden during 2000–2005. The number of NB cases increased from 5/100 000 to 10/100 000 inhabitants/year. In 17% of the patients, anti-*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. Post-treatment symptoms persisting for more than 6 months occurred in 13%, and the patients concerned were significantly older, had longer-lasting symptoms prior to treatment, had higher levels of *Borrelia*-specific IgG in CSF, and more often had radiculitis. The total cost of NB-related healthcare was estimated to be €500 000 for the entire study group (€3300 per patient), and the cost of social benefits was estimated to be €134 000 (€2000 per patient). CSF analysis is necessary for the diagnosis of NB, because some patients develop antibodies in serum later than in CSF. Early diagnosis of borreliosis would result in reduced human suffering and in economic gain.

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Introduction

In Europe, neuroborreliosis (NB) is the most common manifestation of disseminated borreliosis, occurring in 14–34% of all patients 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].

In Jönköping County, with an area of 10 475 km^2 and located in the south-east of Sweden (Fig. 1), borreliosis is known to be endemic. In December 2005, the county had 330 179 inhabitants. The prevalence of *Borrelia*-infected *Ixodes* ticks varies between 10% and 20% [9,10]. The incidence of human borreliosis in Jönköping County was reported to be 60 cases/100 000 inhabitants/year in 1992–1993 [1]. Of these cases, 10/100 000/year were considered to be NB.

The aims of this retrospective study were to: (i) monitor the incidence of NB during 2000–2005; (ii) study how NB symptoms relate to age; (iii) identify cases with specific antibodies in cerebrospinal fluid (CSF) but not in serum at diagnosis; (iv) search for possible clinical or laboratory markers associated with the risk of developing long-lasting post-treatment symptoms; and (v) address some economic aspects of NB in terms of cost of healthcare and social benefits [11].

Materials and Methods

Study population and case definitions

The population studied comprised all 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—see below, ELISA) or borderline levels (IgG, OD 0.19–0.39; IgM,

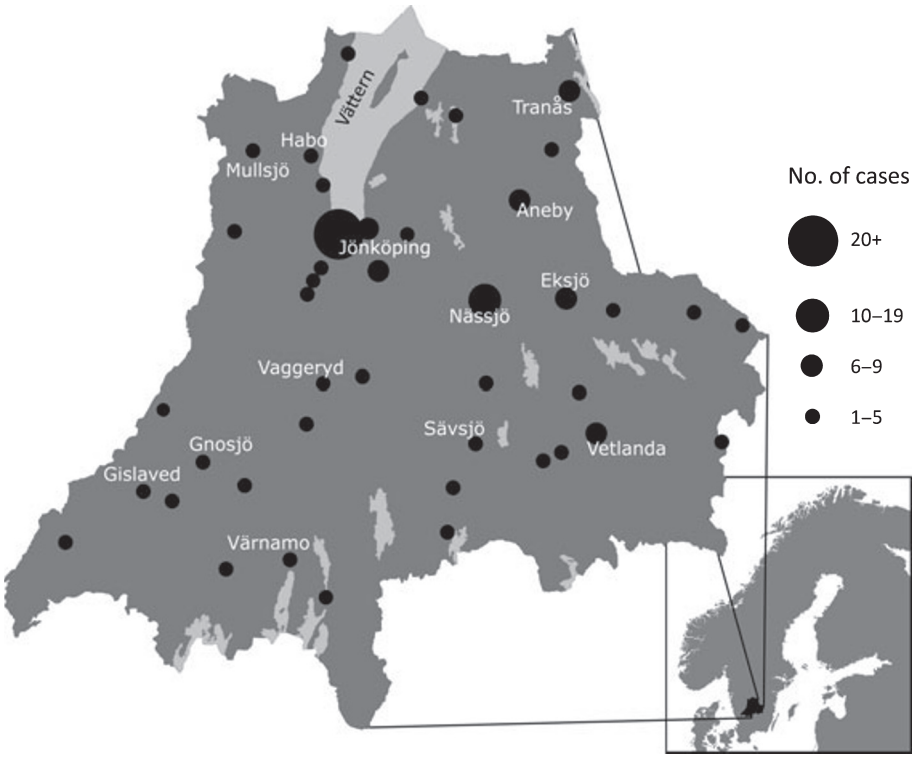

FIG. 1. Jönköping County, Sweden. Each spot refers to a site of domicile.

OD 0.16–0.39) (n = 157). All patients finally included (n = 150) had pleocytosis in the CSF, defined as >5 mononuclear cells (MNCs)/μL, except for four patients who had positive or borderline *Borrelia*-specific CSF IgG, a 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.

The four patients had a long history of illness (36 weeks to several years). One of them responded to antibiotic treatment, two responded only partially, and one did not receive any treatment. Seven of the 157 patients were excluded because of other obvious diagnoses (e.g. normal-pressure hydrocephalus, cerebellar infarction or *Varicella* encephalitis) and/or absence of pleocytosis. In these seven patients, 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 (Fig. 2).

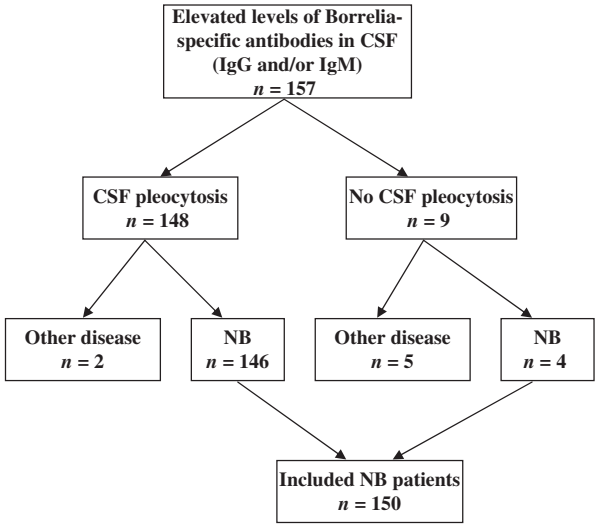

FIG. 2. Inclusion of patients with neuroborreliosis (NB). CSF, cerebrospinal fluid.

Laboratory methods

The Laboratory of Microbiology, Ryhov County Hospital, performed all *Borrelia* antibody tests, using the commercially available Lyme Borreliosis ELISA kit (2nd Generation) (Dako Cytomation A/S, Glostrup, Denmark). From January 2000 to August 2004, the *Borrelia*-specific antibody index was calculated as described by Peter [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)]/[*Rubella*-specific IgG in CSF (OD)/*Rubella*-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)]/[total IgG in CSF (mg/L)/total IgG in serum (g/L)]. A *Borrelia*-specific antibody index >2 was considered to indicate intrathecal anti-*Borrelia* antibody production detected with both methods.

Data collection

The study was approved by the Regional Ethical Review Board in Linköping. Permission 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.

Data on cost of healthcare 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 during 2000–2003, and NordDRG during 2003–2005 [13,14]. 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 the Spearman correlation. Trend analysis of incidence was performed using linear regression. The chi-square test was used for statistical analysis of categorical variables, and the Fisher's exact test was applied when expected counts were <5. Two-tailed tests were used, and p-values of <0.05 were considered to be 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/year (5–10/100 000 inhabitants/year) (Fig. 3). Ninety-three patients (62%) were men, and 57 (38%) were women (Table 1). The median age was 18 years, with a range from 3 to 87 years (Fig. 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 years

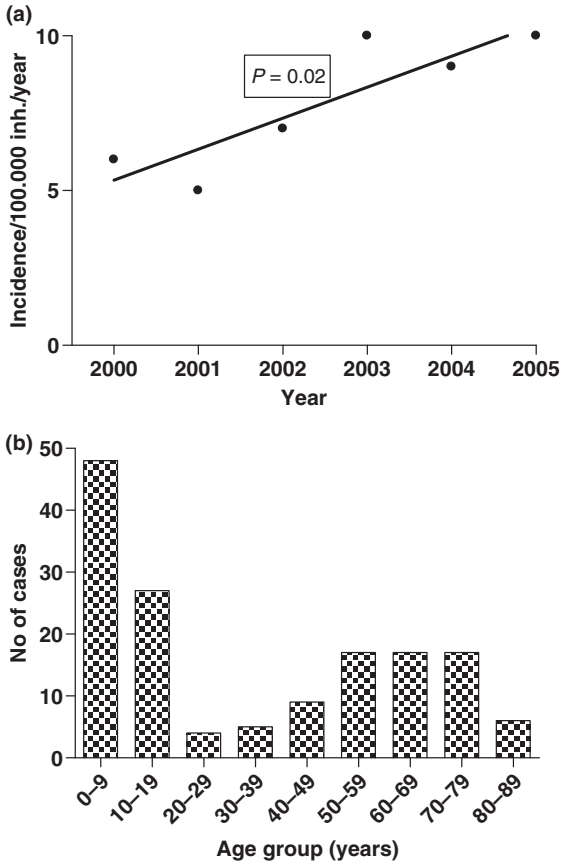

FIG. 3. (a) Number of cases with neuroborreliosis, verified by cerebrospinal fluid analysis, in Jönköping County, Sweden, 2000–2005. Trend analysis: p = 0.02. (b) Number of cases of neuroborreliosis in each age group.

(p 0.0001–0.031). Patients over 40 years of age reported muscle and joint pain, radiating pain, paresthesias, vertigo and concentration problems more often than patients under 40 years of age (p 0.0001–0.003). Patients under 40 years of age had symptoms of shorter duration prior to diagnosis than patients over 40 years of age (p <0.0001). A tick bite had been noticed by 32% of the patients, and 24% had an erythema migrans.

CSF pleocytosis was dominated by MNCs (median, 164 cells/μL; range, 0–1380 cells/μL). Increased levels of anti-*Borrelia* antibodies were found in CSF but not in serum in 25 (17%) of the patients at the time of diagnosis. These patients had symptoms with a median duration of 3 weeks (range, 1 day to 8 weeks). The CSF albumin/serum albumin ratio, as an indicator of blood–brain barrier damage, was elevated in 80% of the patients.

CSF lactate was elevated in 55% (range, 1.3–3.9 mM) and CSF glucose was low in 9% (range, 1.9–8.2 mM). Patients under the age of 40 years had higher cell counts in CSF than those over 40 years of age (p <0.0001).

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

Symptom[a]	Total	Sex		Age group (years)							
		M	F	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89
	n = 150	*n* = 93	*n* = 57	*n* = 48	*n* = 27	*n* = 4	*n* = 5	*n* = 9	*n* = 17	*n* = 17	*n* = 17	*n* = 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
Paresthesia	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 difficulties	5	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

M, males; F, females.
[a]Some patients reported several symptoms.

In general, no abnormalities were found in other routine blood laboratory parameters, i.e blood cell counts and creatinine, electrolyte, aminotransferase, alkaline phosphatase, bilirubin or lactate dehydrogenase levels. C-reactive protein was elevated (>10 mg/L) in six of 99 analysed patients, and white blood cell counts were elevated (>8.8×10^9/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 the CSF and a positive *Borrelia*-specific IgG index, but no pleocytosis, had a long history of illness (median, 64 weeks; range, 36 weeks to 6 years). They most frequently reported muscle and joint pain, paresthesia, 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 the patients with the most pronounced pleocytosis (CSF cell count of >284/μL, the upper quartile), which also correlated with age <40 years. This group had also significantly higher CSF albumin ($p < 0.0001$), CSF albumin/serum albumin ratios ($p < 0.0001$) and CSF lactate ($p < 0.001$), and lower CSF glucose ($p < 0.001$).

The patients were treated with oral doxycycline (63%), intravenous ceftriaxone (25%), benzylpenicillin (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 for whom the clinical course until recovery was clearly documented were classified according to the duration of post-treatment symptoms (Table 2). Significant differences in age distribution were found among all groups, except when group B was compared with 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 among the groups was *Borrelia*-specific CSF IgG, which was highest in group D. No significant differences were found among the groups regarding type of antibiotic treatment or duration of treatment.

Economic aspects

The total healthcare cost for the patients in the study group was estimated to be €500 000. The number of visits to a physician in an outpatient department was 490, the cost of which was estimated to be €130 000. The number of outpatient visits per individual varied between 0 and 10 (median, 3), and 79 patients (53%) were hospitalized (median, 5 days; range, 1–

TABLE 2. Duration of post-treatment symptoms in relation to sex, age and duration of symptoms before treatment

	Patient group[a], *n* = 106[b]			
	A *n* = 26	B *n* = 33	C *n* = 33	D *n* = 14
Males, no. (%)	16 (61.5)	25 (75.8)	21 (63.6)	6 (42.9)
Females, no. (%)	10 (38.5)	8 (24.2)	12 (36.4)	8 (57.1)
Age (years), median (range)[c]	8 (4–66)	12 (3–79)	22 (3–85)	56.5 (10–64)
Duration of symptoms before treatment (weeks), median (range)[c]	2 (0.1–8)	2.5 (0.5–6)	3 (0.1–36)	5.5 (2–77)

[a]Groups according to duration of post-treatment symptoms: A, 0–2 weeks; B, 2–4 weeks; C, 1–6 months; D, >6 months.
[b]106/150 patients (where data were available).
[c]Significant differences between groups, except between groups B and C regarding age.

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 lumbar puncture (%)

	Patient group[a], *n* = 106[b]			
Symptom	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
Paresthesia	4	15	33	57
Facial palsy	46	61	55	7
Other cranial nerve palsy	0	6	6	7

[a]Group A, 0–2 weeks; group B, 2–4 weeks; group C, 1–6 months; group D, >6 months.
[b]106/150 patients (where data were available).

60 days). The total number of days in hospital for the entire study group was 603. Diagnosis-related group weights varied from 0.3104 to 1.8067 (median, 0.7825). The estimated total cost of hospital care was €330 000, i.e. €4200 per patient. (For comparison, the estimated costs of hospital care were €2800 per patient for pneumonia, €2300 per patient for viral meningitis, and €5200 per patient for sepsis). Children under 8 years of age were often treated with ceftriaxone administered intravenously once daily by a nurse in primary healthcare. In this study, 509 ceftriaxone days were registered, resulting in an estimated cost of €38 000.

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 of sickness benefits was €4600 per patient. Temporary parental benefits were granted to the parents of 39 (51%) of the children (range, 0.25–19 days; median, 5 days). The estimated total cost of social benefits was €134 000 (€2000 per patient).

Discussion

The number of NB cases verified by CSF analysis increased from 5/100 000 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 approximately half as many as reported previously [1]. This discrepancy can be explained by the fact that we only included cases verified by CSF analysis, whereas Berglund *et al.* [1] included patients diagnosed with NB on the basis of either CSF findings or clinical symptoms and anti-*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, and for whom the diagnosis was based on symptoms and the presence of *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 in NB cases may be explained by greater awareness of *Borrelia* infections, both in the general population and among physicians. However, there might well be a real increase in NB cases, and there are several plausible explanations for this, i.e. a milder and more humid climate in the region [15,16] that may be favourable to the ticks [17,18], and increasing populations of fallow deer and wild boars in the county during the study period [19–23] (P. Kjellander, Grimso Wildlife Research Centre, Swedish University of Agricultural Sciences; January 2008, personal communication).

The data on clinical manifestations of NB, age and sex distribution, laboratory findings and the frequency of observed tick bites and erythema migrans are mainly in line with ear-

lier observations [24–27]. However, some particularly interesting findings should be pointed out. As many as 80% of the patients had an elevated CSF albumin/serum albumin ratio, an indicator of impairment of the blood–brain barrier. The highest IgG indices 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 cannot be excluded that an earlier pleocytosis had resolved 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 of >284 cells/μL (the upper quartile) most frequently reported symptoms of meningitis and distinct symptoms such as facial palsy and fever. Also, in their case, the median duration of symptoms before treatment was shortest. Patients under the age of 40 years had significantly higher MNC counts in CSF than patients aged over 40 years. 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, causing more distinct clinical symptoms, which in turn lead to 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 [28–32]. In contrast, older patients show a less pronounced inflammatory response, and they often present with more vague symptoms, which might delay diagnosis and treatment.

Our findings emphasize the importance of CSF analysis for the diagnosis of NB, as 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 cannot establish whether 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.

Post-treatment symptoms lasting more than 6 months were reported by 13% of the patients (14/106). The clinical and laboratory findings in the acute phase characterizing this patient group were advanced 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, paresthesia, vertigo and concentration disturbances.

NB has important economic consequences, in terms of both healthcare and social benefits. If an NB patient is diagnosed at an early stage of the disease, outpatient treatment with oral doxycycline for 10–14 days is sufficient in most cases [33]. Early treatment is associated with quick recovery and, consequently, a shorter period of sickness benefits.

There are, of course, limitations to this retrospective study, such as a presumable bias both in reported and in documented symptoms. It was not possible to obtain data on time to recovery for all patients. However, the data were available in a substantial number of cases and, furthermore, our data are in line with those of previous prospective studies [1], 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 to be relevant and important to follow the epidemiological development of NB in the future, as continuing changes in climate and the tick-feeding fauna are expected. Symptoms and CSF findings seem to differ between younger and older individuals, with a tendency for there to be more distinct clinical symptoms and a more pronounced inflammatory response in the central nervous system in the younger. As many as 17% of the NB patients in this study had *Borrelia*-specific antibodies detectable in CSF but not in serum at the time of the lumbar puncture, emphasizing the importance of CSF analysis for early NB diagnosis. The costs of healthcare 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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