Clinical characteristics of childhood Lyme neuroborreliosis in an endemic area of northern Europe

Abbreviated and running head title: Neuroborreliosis in children

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Abstract

Neuroborreliosis may be caused by different species of Borrelia burgdorferi (BB) and the clinical presentation of neuroborreliosis in children may differ between geographic areas due to occurrence of different BB genospecies. The aim of this study was to evaluate the clinical characteristics in children with neuroborreliosis in an endemic area of Scandinavia. During 1996-2006, children with suspected neuroborreliosis referred to Stavanger University Hospital were investigated by a standard procedure including a lumbar puncture. A total of 143 children were diagnosed with neuroborreliosis, and all cases were diagnosed from April to December. The most common clinical presentations were symptoms of mild meningitis (75%) and/or facial nerve palsy (69%). Radicular pain was present in only 10 children. In all but five children laboratory signs of meningitis were present. Erythema migrans preceded the neurological symptoms in only 27% of the children. In conclusion, we have found that in an endemic area of Northern Europe, meningitis is present in the majority of children with neuroborreliosis, and that symptoms of a mild meningitis or facial nerve palsy are the most common presentations.

Key words: Lyme borreliosis, children, facial palsy, meningitis, neuroborreliosis, symptoms.

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Lyme borreliosis is caused by different species of the spirochete Borrelia burgdorferi (BB) transmitted to humans by Ixodes ticks, and is a multisystem disorder with 3 clinical stages including dermatologic, neurologic and rheumatologic symptoms [1-4]. Neuroborreliosis is the neurological manifestation of systemic infection, and symptoms may include headache, mild neck stiffness or neck pain (meningismus), subtle encephalitis with cognitive difficulties, radiculoneuropathy (especially peripheral facial nerve palsy (FNP)), cerebellar ataxia or myelitis [2-5].

The clinical manifestations of neuroborreliosis in children differ between endemic areas. This may be due to the geographical distribution of various genospecies of BB which have different neurogenic properties [2,3,6]. Whereas neuroborreliosis in USA usually presents as a lymphocytic meningitis, studies have suggested that Bannwarth’s syndrome (meningopolyradiculitis) is the most common presentation of neuroborreliosis in Europe [2,6]. Furthermore, FNP in Lyme borreliosis seems to be more common in Europe than in the United States [6-9], and the symptoms in neuroborreliosis may differ between children and adults [5].

The south-western coast of Norway is an endemic area for BB infections. We recently reported that in this area as much as 65% of children with FNP had borreliosis, significantly higher than reported from some other endemic areas [1,9,10]. Furthermore, nearly all of these children had meningitis whereas others have reported a lower incidence of meningitis in children with FNP caused by borreliosis [11,12]. Consequently, it is possible that there is a wider variation in all neurological manifestations of childhood borreliosis between different endemic areas than is known at present.

The clinical picture of neuroborreliosis in children has been described in studies from USA and central Europe [1,3,6,13]. Fewer studies have evaluated the clinical characteristics of childhood neuroborreliosis in Scandinavia. The aim of this study was therefore to evaluate
the clinical characteristics of neuroborreliosis in children in an endemic area of Northern Europe.

Material and Methods

Study area and patients

The population of the South-Rogaland district, Norway, includes approximately 62,000 children up to 14 years of age. Stavanger University Hospital receives all hospital admissions for acute childhood disease in this area, and all children with suspected meningitis and neuroborreliosis are referred to this hospital. All the general practitioners and oto-rhino-laryngologists in the region received during the autumn 1995 a written recommendation that all children below 14 years of age with acute FNP should be referred without delay to the Paediatric department at Stavanger University Hospital. Only children living in South-Rogaland were included in the study, and consequently the study was population based. Annual community-based demographic data for the population were obtained from the Official Bureau of Statistics.

Testing procedures

From January 1996 to December 2006, we investigated all children admitted for possible neuroborreliosis by a standard protocol including history, clinical examination, blood tests and a lumbar puncture. This included all children with suspected meningitis and other symptoms indicating possible neuroborreliosis, and all children admitted with FNP regardless of other symptoms or not. Data regarding clinical symptoms, age, month of admission, number of days from onset of symptoms to admission, and results from blood tests and lumbar puncture were registered.
During the whole study period, serum and cerebrospinal fluid (CSF) were analysed for IgM or IgG antibodies against BB using enzyme-linked immunosorbent assay (ELISA) (Enzygnost Lyme borreliosis test, Dade Behring, Marburg, Germany). In addition, from January 1999 we used the Lyme neuroborreliosis Dako test for detection of intrathecal antibody production (Dako, Glostrup, Denmark). The antibody index is a semiquantitative measure of intrathecal antibody production. Optical density (OD) is a measure of antibody production, and the index formula is $OD_{CSF}/OD_{serum} \times (OD_{CSF} - OD_{serum})$. The test was considered positive when the index was $> 0.3$. CSF white blood cells (WBC) (Fuchs Rosenthal chamber) and protein (turbidimetric technic (Roche, Basel, Switzerland)) were measured.

**Diagnostic criteria**

Children were diagnosed as having neuroborreliosis if, in addition to neurological symptoms, either IgM or IgG antibodies for BB were identified in serum and/or CSF. This diagnostic approach was suggested by several authors in Europe at the time of study start and did not include immunoblotting [14]. If serology was negative, but medical history revealed a possible erythema migrans during the past 8 weeks prior to submission, a child was considered to have possible neuroborreliosis.

Meningitis was diagnosed when the lumbar puncture demonstrated pleocytosis ($\geq 5$ WBC x $10^6/l$). FNP was defined as an acute palsy involving the facial muscles in both upper and lower part of the face, either unilateral or bilateral.

All children except two were treated with intravenous ceftriaxone 50 mg/kg once daily for two weeks. Two children were treated with oral amoxicillin. The children were seen for a clinical evaluation at the end the treatment period.
Differences between groups were analysed by the non-parametric Mann-Whitney U test using the SPSS 15.0 statistical package (SPSS Inc, Chicago, IL, USA).

**Results**

A total of 143 children were given the diagnosis of neuroborreliosis during the study period. The results of antibody testing and the presence of meningitis and erythema migrans in these are presented in table 1. In two children with isolated FNP and a positive IgM for BB in serum the investigational procedure was not followed and a lumbar puncture not performed. Three children without meningitis but with other neurological symptoms had antibodies against BB in serum. The remaining 138 children had both meningitis and antibodies to BB in either serum or CSF in addition to the neurological symptoms (table 1).

In addition, three children had meningitis without antibodies but with a recent history of EM. They were considered to have possible neuroborreliosis, but were not included in the further analysis.

The average annual incidence of children with neuroborreliosis was 21/100,000 children for the whole study group. However, the number of children diagnosed each year increased significantly during the study period [15]. Further, the incidence varied significantly by age, with the highest incidence of 52/100,000 in the ages six to seven years (figure 1). The median age of all children was 6 years, but children with FNP were younger (6 years; 3-9, median, quartiles) than children without FNP (7; 4-10 years) (p=0.001) (figure 1). The majority of children were diagnosed during the months from June to November, whereas no children were diagnosed from January to March (figure 2).

There was a median number of seven days from debut of neurological symptoms to admission (range 0-90).
Symptoms and meningitis

The clinical symptoms at admission and numbers of children with different symptoms are presented in table 2. Based on the clinical symptoms a division into three major groups of children could be suggested: children with isolated cranial neuropathy without other symptoms (Group A; n=36), those with both cranial neuropathy and other neurological symptoms (Group B; n=67), and those with neurological symptoms without cranial neuropathy (Group C; n=40). Two thirds (69%) of the children had peripheral 7th nerve palsy (FNP) during the course of the infection [9], and no cases of bilateral FNP were registered. Few children presented with other cranial neuropathies. Ten children noted radicular pain; all of these had pain in the head and neck region, and nine of the 10 children had FNP (table 2). The age of the children with radicular pain (5.5; 4-7) did not differ from the rest of the children (p=0.4). A total of 107 children (75%) demonstrated symptoms of mild meningitis with either headache or meningismus, or more general symptoms such as fatigue and anorexia (table 2). Few children presented with fever, but this symptom was not systematically registered.

In group A, three of the children did not have meningitis whereas a lumbar puncture was not taken in two children. The rest of the children in group A and all children in group B and C had lymphocytic meningitis. The median levels of WBC and protein in CSF of children with meningitis were 155 cells/mm³ (range 8-950) and 510 g/l (112-1950), respectively. The three children with a negative lumbar puncture were all diagnosed within 48 hours after debut of symptoms.

A more detailed presentation of laboratory analysis and results from the CSF examination is given elsewhere (Tveitnes et al, unpublished data).

By the end of the treatment period, four children had minor sequelae of FNP, whereas all other children had recovered completely.
Discussion

Our study is one of the largest clinical studies of childhood neuroborreliosis in Europe and gives valuable information about the clinical characteristics of this disease in European children. One major finding was that all but very few children had lymphocytic meningitis, including children presenting clinically with isolated cranial neuropathy. Two thirds of the children had FNP as one of the symptoms, the majority of these also presenting with other symptoms of meningitis. Painful radiculitis was demonstrated in only a few children.

Epidemiology

The incidence of neuroborreliosis reported by us is probably one of the highest in Europe for this age group. However, few studies have evaluated the local incidence in a strict population based way as in our study. In a Norwegian national survey the incidence of disseminated Lyme borreliosis was 8/100,000 children aged 5-9 years [16]. In a study from an endemic area in southern Sweden from 1995 the incidence of borreliosis in children was about 60/100,000, with 28% of these having neuroborreliosis [17]. This gives a comparable incidence to our area, whereas the incidence seems to be lower in children in a recent German survey [18].

We found the highest incidence of neuroborreliosis in the age of four to seven years (figure 1), and in a Norwegian national survey of both children and adults the highest incidence of neuroborreliosis was in the age group 5-9 years [16]. A high proportion of children with neuroborreliosis have FNP, and the chance of having neuroborreliosis when presenting with FN seems to be much higher in children than in adults [9,19]. A Swedish study demonstrated that the most common site for tick bites in children was the head and neck region (49%), and much more common than in adults (2%) [17]. When playing, children may
expose their head and neck to grass and bushes in another way than adults, and a tick bite in this region may have a higher tendency to result in FNP. Therefore, activity habits in children may be the reason for both the high incidence of neuroborreliosis and the high proportion of children with neuroborreliosis presenting with FNP.

The monthly distribution demonstrated in this study is in keeping with similar studies from other countries in northern Europe [17,18], with most cases diagnosed during the period from June to October.

Clinical symptoms and meningitis

In this endemic area FNP was the most common symptom of neuroborreliosis, occurring in more than two thirds of the children. However, 64% of children with FNP also had other symptoms of meningitis. In total, as much as 75% had clinical symptoms of meningitis throughout the course.

BB sensu stricto is the only genospecies known to cause disease in humans in USA, and neuroborreliosis in USA usually presents as lymphocytic meningitis. Studies have demonstrated that Bannwarth’s syndrome is the most common presentation of neuroborreliosis in Europe [2]. This is a painful radiculitis with or without paresis, and it has been suggested that Bannwarth’s syndrome is a hallmark of infection with B. garinii [2].

In our study, the proportion of children presenting with symptoms of mild meningitis was high, whereas painful radiculitis was reported in only few children (table 2). This may be explained by differences in the manifestations of neuroborreliosis between children and adults [5]. Bites in the head and neck region may be less susceptible to result in painful radiculitis, and all children with this symptom in our study noted pain in the head and neck region. It is further possible that there may be different genospecies of BB in different areas of Europe. Little is known about the presence of different genospecies of BB in our region, but one study
has demonstrated that B. afzelii is the most common genospecies in southern Norway [20]. In another Scandinavian study from southern Sweden, 94% of EM skin isolates were B. afzelii [21]. It is therefore possible that the clinical pattern demonstrated in the present study represent the typical symptoms in children with neuroborreliosis caused by B. afzelii. However, different genetic properties within the three pathogenic genospecies may differ between regions and explain the difference in clinical presentation of neuroborreliosis [6].

Except for two children in whom a lumbar puncture was not done, all but three of the children with neuroborreliosis had meningitis. Furthermore, these three children were diagnosed very early after initial symptoms, and it is possible that meningitis could have developed in these children as well if diagnosis had been delayed. The majority of the children presenting with only clinical symptoms of cranial neuropathy demonstrated laboratory signs of meningitis, which is different from other studies [11,12]. However, except for those with FNP, our study included children with cranial neuropathy or other symptoms severe enough to warrant hospitalisation. For those being hospitalised we had a high awareness of possible neuroborreliosis and of performing a lumbar puncture throughout the study period, but it is possible that children with neuroborreliosis with minor symptoms and without cranial neuropathy were not hospitalised and therefore not diagnosed. The true incidence of meningitis in neuroborreliosis is thus difficult to estimate.

In only 27% of the children a history of EM was recalled. Even if there may be some recall bias, this is consistent with other studies from Europe. Whereas EM commonly precedes neuroborreliosis in USA, 58% of neuroborreliosis cases had no preceding EM in a large German study [2].

*Diagnosis of neuroborreliosis*
The conclusions in our study depend on a correct diagnosis of neuroborreliosis. We diagnosed neuroborreliosis according to European recommendations at the time of study start, the diagnosis depending on clinical symptoms and demonstration of antibodies against BB in either serum or CSF [14,22]. The diagnosis is based on a combination of history, examination, analysis of CSF and antibodies in serum and CSF [1-3,14,23]. However, at present there is no available method that with 100% accuracy can diagnose neuroborreliosis, with the possibility for both under- and over-diagnosis. Serologic tests for BB have low sensitivity during early stages of disease, whereas neuroborreliosis occurs three to 12 weeks after the primary infection [1]. At this stage, serologic tests will have higher sensitivity, with many patients having IgG antibodies in serum [1]. Ideally, in children with suspected borreliosis and negative serology, the test should have been repeated after three to four weeks. This was not done in our study, and consequently, more children with neurological symptoms could possible have been diagnosed as neuroborreliosis in our department. The three children with possible neuroborreliosis had symptoms compatible with the diagnosis (two with FNP), lymphocytic meningitis and a recent history of EM. They were all investigated within four days after debut of symptoms, and this may be the reason why antibodies were negative.

Serologic tests may have limited specificity as well. Recommendations for the diagnosis of Lyme borreliosis from the Center for Disease Control suggest a two-step approach: first a serologic test with high sensitivity, and when positive, the diagnosis should be confirmed by immunoblotting with high specificity [1,8,24]. Immunoblotting was not included in European guidelines at the time of study start and was not performed in our study [22]. Further, the value of immunoblotting in neuroborreliosis may be of less value in Europe than in USA, and authors have claimed that immunoblotting does not influence decision making during Lyme disease [2,14,25]. It has also been demonstrated that a positive titer in CSF and/or a positive index strongly suggest Lyme borreliosis as the reason for FNP.
[3,23,24], and this was present in 79 of the children diagnosed as borreliosis. However, a negative antibody index does not rule out neuroborreliosis [26].

Other infectious agents causing meningitis may also induce false positive IgM antibodies to BB. This is true for Epstein Barr virus, but this is an uncommon cause of meningitis in childhood [1]. A total of 18 children with meningitis had only IgM in serum as the serological indication for a BB infection, but in three of these EM had been observed during the proceeding weeks. Therefore, only 15 children were diagnosed by clinical symptoms, meningitis and IgM in serum alone.

Other guidelines have suggested the occurrence of at least two of the following for the diagnosis of neuroborreliosis: 1) recent erythema migrans, 2) CSF pleocytosis, 3) antibodies to BB in serum or CSF, 4) intrathecal BB antibody production [22]. If these criteria had been employed in our study, all the 138 children with meningitis (including the 18 children with only IgM for BB in serum) would have been diagnosed as having neuroborreliosis. Further, the three children with possible neuroborreliosis would also have been diagnosed as neuroborreliosis. Based on these criteria it can be argued that the diagnosis is less optimal in the five children where lumbar puncture was negative or not performed. However, the favourable clinical course after antibiotic treatment and the fact that all children diagnosed as neuroborreliosis were admitted during the expected season for Ixodes ticks in our area (figure 2), gives further support that the diagnosis of neuroborreliosis in all children in our study was correct.

**Conclusion**

We have shown that in an endemic area for borreliosis of northern Europe, the typical clinical presentation of a child with neuroborreliosis is facial nerve palsy with or without
symptoms of mild meningitis. In the vast majority of children laboratory signs of meningitis are present.

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References:


15. Øymar K, Tveitnes D. Increase in childhood neuroborreliosis. Tidsskr Nor Legeforen;128:2060-1.


Legend to Figure 1
Age of 143 children diagnosed with neuroborreliosis at Stavanger University Hospital during a period of 11 years from 1996 – 2006. Children with and without facial nerve palsy (FNP) as one of the symptoms are presented separately.

Legend to Figure 2
Month of presentation in 143 children diagnosed with neuroborreliosis at Stavanger University Hospital during a period of 11 years from 1996 – 2006.
Table 1  The occurrence of IgM and/or IgG antibodies against Borrelia (Yes serology) in serum and CSF, CSF-serum antibody index (Yes when OD_{CSF}/OD_{serum} \times (OD_{CSF} - OD_{serum}) \geq 0.3), results of investigation of cerebrospinal fluid (CSF) and the occurrence of erythema migrans in 143 children diagnosed with neuroborreliosis at Stavanger University Hospital during 1996-2006.

<table>
<thead>
<tr>
<th>Numbers</th>
<th>Positive serum serology</th>
<th>Positive CSF serology</th>
<th>Antibody index Positive/negative/not taken</th>
<th>CSF-pleocytosis \geq 5 cells/mm$^3$</th>
<th>Erythema migrans Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>Yes</td>
<td>Yes</td>
<td>74/3/13</td>
<td>Yes</td>
<td>27/63</td>
</tr>
<tr>
<td>38</td>
<td>Yes</td>
<td>No</td>
<td>0/38/0</td>
<td>Yes</td>
<td>11/27</td>
</tr>
<tr>
<td>8</td>
<td>No</td>
<td>Yes</td>
<td>8/0/0</td>
<td>Yes</td>
<td>1/7</td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>Not taken</td>
<td>0/0/1</td>
<td>Yes</td>
<td>0/1</td>
</tr>
<tr>
<td>1</td>
<td>Not taken</td>
<td>Yes</td>
<td>0/0/1</td>
<td>Yes</td>
<td>0/1</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>0/3/0</td>
<td>No</td>
<td>0/3</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Not taken</td>
<td>0/0/2</td>
<td>Not taken</td>
<td>0/2</td>
</tr>
<tr>
<td>143</td>
<td>134/8/1</td>
<td>99/41/3</td>
<td>82/44/17</td>
<td>138/3/2</td>
<td>39/104</td>
</tr>
</tbody>
</table>

Yes/No/not taken
Table 2 Clinical symptoms in 143 children with neuroborrellosis. Group A is children with cranial neuropathy without other neurological symptoms, group B is children with cranial neuropathy and other neurological symptoms, and Group C is children with neurological symptoms without cranial neuropathy.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of children</th>
<th>Facial nerve palsy</th>
<th>Other cranial neuropathy</th>
<th>Radicular pain</th>
<th>Headache</th>
<th>Meningismus</th>
<th>Fatigue</th>
<th>Anorexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>143</td>
<td>99</td>
<td>3</td>
<td>10</td>
<td>35</td>
<td>51</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>A</td>
<td>36</td>
<td>36</td>
<td>0</td>
<td>8 *</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>67</td>
<td>63</td>
<td>3 **</td>
<td>2*</td>
<td>25</td>
<td>25</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>C</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>26***</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

* all head or neck, ** 2: diplopia/nystagmus, 1: paresis of nervus abducens, *** 2: vertigo, 1: ataxia, 1 torticollis
Figure 2

Number of children

January  
February  
March  
April  
May  
June  
July  
August  
September  
October  
November  
December