Etiology of Aseptic Meningitis, Peripheral Facial Nerve Palsy, and a Combination of Both in Children

Nicolas Waespe, MD,* Ingrid Steffen, MD,† and Ulrich Heininger, MD*

Background: A variety of microorganisms have been shown to cause peripheral facial nerve palsy (PFNP) and/or aseptic meningitis in children. Clinical findings and history may help to predict the specific etiology of these entities.

Method: Children ≥12 months old hospitalized at the University Children’s Hospital Basel, Switzerland, from 2000 to 2005 with clinical signs of PFNP and/or aseptic meningitis were studied retrospectively. History, clinical, and laboratory findings were evaluated using analysis of variance with Bonferroni (Dunn) correction.

Results: Of 181 patients, 123 (68%) had aseptic meningitis, 28 (15%) had PFNP, and 30 (17%) had a combination of both. PFNP with aseptic meningitis was associated with Borrelia burgdorferi (Bb) infection in the majority of patients (73%) compared with 11% and 9% of patients with PFNP or aseptic meningitis, respectively. The majority of patients with aseptic meningitis without PFNP had enterovirus infection (61%). In patients with aseptic meningitis, mean leucocyte counts in cerebrospinal fluid (CSF) were higher with enterovirus (565/μL) compared with Bb infection (191/μL; P < 0.01) or unknown causes (258/μL; P < 0.01). Further, CSF mean mononuclear cell proportion was higher in patients with Bb (89%) than in those with enterovirus infection (51%; P < 0.01) or unknown causes (60%; P < 0.01). Mean time interval between onset of disease and admission to hospital showed significant differences between Bb (7.6 days) and enterovirus infection (2.8 days; P < 0.01) or unknown causes (2.0 days; P < 0.01).

Conclusions: Time interval between onset of disease and hospital admission and CSF characteristics can contribute to distinguishing the etiology of aseptic meningitis with or without PFNP. As expected the most common etiology for aseptic meningitis with PFNP was Bb infection whereas enterovirus infection was the predominant cause for aseptic meningitis alone.

Key Words: aseptic meningitis, peripheral facial nerve palsy, borreliosis, herpes simplex virus, varicella-zoster-virus, tick borne encephalitis

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Several pathogens have been identified as causative agents of peripheral facial nerve palsy (PFNP).1–3 Lyme borreliosis (caused by Borrelia burgdorferi sensu lato), the most common illness transmitted by ticks in Western Europe, has been held responsible in 2% to 50% of patients with PFNP depending on the study region and design, case definitions and diagnostic approach to Lyme borreliosis.4,5 Aseptic meningitis is also a neurologic manifestation of Lyme borreliosis and, together with PFNP, is the predominant clinical feature of neuroborreliosis in children.6,7

The most common etiologies of aseptic meningitis in children in Europe are enterovirus8 and tick-borne encephalitis virus (TBEV) infections, especially in summer and early fall.9 Only a few studies have compared features of aseptic meningitis caused by B. burgdorferi with those of other causes (eg, enterovirus infection) in children. These retrospective studies identified duration of headache, presence of cranial neuritis (mainly PFNP), and the proportion of mononuclear cells in cerebrospinal fluid as predictors for Lyme meningitis.10–13 A number of other viral infections, mainly herpes simplex virus (HSV),2,14 and varicella zoster virus (VZV),2,13 have been discussed as possible causes of PFNP but it still remains controversial what role they play in the pathogenesis of the disease.

The goal of this study was to analyze retrospectively the etiology and possible predictive factors for a specific etiology of aseptic meningitis, PFNP, or both in children with specific regards to B. burgdorferi, HSV, VZV, and TBEV infections.

MATERIALS AND METHODS

Study Design

Children ≥12 months of age, hospitalized with clinical signs of aseptic meningitis and/or PFNP at the University Children’s Hospital Basel, Switzerland between 2000 and 2005 were identified by searching laboratory records of cerebrospinal fluid (CSF) analyses and ICD-10 codes. Search terms were “nonpyogenic meningitis,” “viral meningitis,” “enterovirus meningitis,” “other bacterial meningitis,” “meningitis unspecified,” “facial nerve palsy,” “Lyme disease,” “central European tick-borne encephalitis,” and “tick-borne viral encephalitis unspecified.” Patient charts and laboratory records were cross-checked to verify diagnoses and to collect demographic, clinical, serological and laboratory data in a standardized data file. Laboratory analyses of the initial evaluation as documented in patients charts as well as findings of retrospective laboratory tests were considered in evaluation of possible etiologies. Patients with missing CSF sample results were excluded.

Approval was granted by the ethics committee of the University of Basel.

Laboratory Assays

Specific analyses on CSF and serum samples were performed either immediately during hospitalization of patients or retrospectively on samples stored at −20°C.

Laboratory Assays Performed During Hospitalization

Commercial recombinant immune immunoaassays on automated systems were used to identify B. burgdorferi sensu lato antibodies (IgG and IgM) as described by the manufacturers (“Vidas Lyme Screening II,” BioMérieux, Marcy l’Etoile, France, from 2000 to 2001, and “recomWell Borrelia,” Mikrogen, Martinsried, Germany, from 2002 onwards). In case of positive B. burgdorferi IgG and/or IgM results, a confirmatory immunoblot test was
performed for IgG and/or IgM antibodies (=2-tier testing method) against specific antigens produced by recombinant techniques (“re-
comBlot BorreliaNB” IgG and IgM, Mikrogen, Martinsried, Ger-
many).16,17 Varicella zoster virus (VZV) IgM and IgG antibodies were measured by an enzyme immunoassay (“Enzygnost Anti-VZV,”
Dade Behring, Eschborn, Germany); similar tests were used for HSV
IgG (“Enzygnost Anti-HSV/IgG,” Dade Behring, Eschborn, Ger-
many) and HSV IgM antibodies (“HSV IgM,” HUMAN, Wiesbaden,
Germany). The results obtained with photometric measurement were
interpreted as described by the manufacturer.

From 2000 to 2001, an enzyme immunoassay was used to
detect antibodies against TBEV (“Immunozym FSME/TBE” IgM and
IgG, Progen, Heidelberg, Germany) in serum (IgM and IgG) and CSF
(IgG only) specimens. It was replaced for serum specimens by a
different immunoassay from 2002 onwards (“Enzygnost Anti-TBE/-
FSME” IgM and IgG, Dade Behring, Eschborn, Germany), while the
assay for the examination of CSF remained the same.

Some CSF specimens were also examined by PCR for the
presence of enterovirus, VZV, and HSV based on the treating
physician’s decision.

Retrospective Laboratory Assays
If specific B. burgdorferi antibodies were present in CSF
specimens and sufficient material was left, serum and CSF samples
were further tested for concentrations of albumin, total IgG, IgA,
and IgM by nephelometry (“IMMAGE,” Beckman Coulter Inc.,
Fullerton, CA) and IgG isoelectric focusing (IgG-Isoelectric Fo-
cusing Kit, Progen, Heidelberg, Germany) performed. Antibody
close index (cerebrospinal fluid/serum) was calculated for
B. burgdorferi
IgG and IgM according to the formula by Reiber and Lange.18 An
index index > 1.5 was considered as proof of intrathecal syn-
thesis of antibodies.

PCR testing was performed for VZV and/or HSV if IgG
and/or IgM was positive in serum and/or CSF if sufficient material
was left.

Case Definitions
PFNP was a clinical diagnosis. A diagnosis of aseptic meningitis was retrospectively verified by use of the Brighton
Collaboration case definition which requires clinical evidence of
acute meningitis (fever, headache, vomiting, nuchal rigidity, or
other signs of meningeal irritation), a CSF leukocyte count of more
than 5 leukocytes/mm3, absence of any microorganism on Gram
stain of CSF, and negative bacterial culture of CSF in the absence
of antibiotic treatment before obtaining the CSF sample (level 1 of
corrective to compensate for multiple testing. Statistical signifi-
cance was determined as P values < 0.05.

Statistical Analysis
Relevant data were analyzed using SAS version 7.1 (Statis-
tical Solutions, Cary, NC). To assess differences between groups
we used analysis of variance (ANOVA) with Bonferroni (Dunn)
correction to compensate for multiple testing. Statistical signifi-
cance was determined as P values < 0.05.

RESULTS

General Characteristics
A total of 181 patients (118 males; 65.2%) were included
with an age range from 20 months to 16 years. Of these, 123
fulfilled criteria for aseptic meningitis, 28 for PFNP without
meningitis, and 50 for PFNP with aseptic meningitis. Patient
characteristics and etiologic findings by clinical diagnoses are
demonstrated in Table 1. In general, patients with aseptic menin-
gitis were younger than those with PFNP (P < 0.01). Time interval
between first onset of symptoms (any of the following: headache,
fever, nausea/vomiting, meningism, PFNP) and hospital admission
was significantly longer in patients with neuroborreliosis (mean:
7.6 days, inter quartile range: 3–9 days) compared with patients
with enterovirus infection (mean: 2.8 days, IQR: 1–5 days, P < 0.01)
or other unknown diagnoses (mean: 2.0 days, IQR: 1–3 days, P < 0.01).

The comparative seasonal distribution of patients with neu-
roborreliosis, enteroviral meningitis, or unknown causes of aseptic
meningitis (with or without PFNP) is demonstrated in Figure,
Supplemental Digital Content 1, http://links.lww.com/INF/A308.
Peaks for all entities occurred during the warm season (April to
October).

Etiologic Findings
Amounts of CSF and serum specimens were not always
sufficient to perform all laboratory tests in all patients (Table 1);
priority of tests to be performed was at the discretion of the
treating physicians at the time of hospitalization.

The majority of patients with combined PFNP and aseptic
meningitis (73%) could be attributed to confirmed or probable
neuroborreliosis, compared with significantly lower proportions of
patients with PFNP alone (11%), or in patients with aseptic
meningitis alone (9%). Intrathecal synthesis of specific IgG and/or
IgM antibodies against B. burgdorferi could be analyzed in a
subset of patients and was demonstrated in 3 of 4 patients with
aseptic meningitis, 5 of 7 with combined PFNP and aseptic
meningitis, but not in one patient with PFNP alone.

In patients with aseptic meningitis without PFNP, enterovi-
rus infection was the most frequent diagnosis (63%). Two patients
had tick-borne encephalitis. Two of 18 (11%) patients with aseptic
meningitis and one of 8 (12%) patients with PFNP without menin-
gitis had VZV infection demonstrated by a positive PCR. The 2
patients with aseptic meningitis were positive for VZV IgG in

TABLE 1. General Characteristics and Etiologies in Patients With Aseptic Meningitis, Peripheral Facial Nerve Palsy (PFNP), or Both

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Aseptic Meningitis (N = 123)</th>
<th>PFNP (N = 28)</th>
<th>Aseptic Meningitis + PFNP (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr; IQR)</td>
<td>7.8 (5.3–9.5)</td>
<td>10.4 (7.7–13.0)</td>
<td>8.6 (5.9–11.3)</td>
</tr>
<tr>
<td>Male gender (N; %)</td>
<td>86 (70)</td>
<td>16 (57)</td>
<td>16 (53)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>N/N Tested (%)</td>
<td>N/N Tested (%)</td>
<td>N/N Tested (%)</td>
</tr>
<tr>
<td>B. burgdorferi</td>
<td>9/102 (9)</td>
<td>3/27 (11)</td>
<td>12/20 (70)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>17/27 (63)</td>
<td>0/1 (0)</td>
<td>17/28 (57)</td>
</tr>
<tr>
<td>HSV</td>
<td>0/21 (0.0)</td>
<td>0/9 (0.0)</td>
<td>0/21 (0.0)</td>
</tr>
<tr>
<td>VZV</td>
<td>2/18 (11)</td>
<td>1/8 (13)</td>
<td>3/26 (23)</td>
</tr>
<tr>
<td>TBEV</td>
<td>2/73 (3)</td>
<td>0/18 (0)</td>
<td>2/91 (3)</td>
</tr>
<tr>
<td>Any of the above</td>
<td>30/123 (24)</td>
<td>4/28 (14)</td>
<td>34/131 (26)</td>
</tr>
</tbody>
</table>

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serum and CSF specimens, whereas the patient with PFNP without meningitis was VZV IgG positive only in serum. None of 42 tested patients had evidence of HSV infection.

No deaths or other serious complications occurred during hospitalization and all patients were discharged after recovery or significant clinical improvement.

**CSF Findings**

CSF findings in patients with aseptic meningitis are shown in Table 2. Enterovirus infection caused significantly higher mean CSF leukocyte counts compared with *B. burgdorferi* infection (P < 0.01) or unknown etiology (P < 0.01). Further, mean proportion of mononuclear cells in CSF was higher in patients with meningitis (with or without concomitant PFNP) due to *B. burgdorferi* infection compared with those with enterovirus meningitis (P < 0.01) or unknown etiology (P < 0.01). Mean mononuclear cell counts were similar in patients who tested negative for *B. burgdorferi* and in those who tested negative for enterovirus (62%, IQR: 26%–95% and 69%, IQR: 55%–95%, respectively).

There were 22 patients with aseptic meningitis and sufficient amounts of serum and CSF specimens left for examination of IgG oligoclonal bands by isoelectric focusing. Only 2 of these showed IgG oligoclonal bands. Similarly, IgG oligoclonal bands were found only in one of 11 tested patients with combined PFNP and aseptic meningitis.

**DISCUSSION**

In this study, an etiology was found in most patients with combined aseptic meningitis and PFNP and this exclusively was *B. burgdorferi* infection which is in accordance with previous reports. In contrast, in only a minority of patients with PFNP without aseptic meningitis and in patients with aseptic meningitis without PFNP was a specific etiology found. However, not all microbiologic tests were applied in all of these patients. As a strength of this study, the 2-tier testing method (confirmation of positive ELISA results by immunoblot) as recommended by the Centers for Disease Control and an international consensus was used for diagnosis of neuroborreliosis.

It has to be noted that in a healthy adult population in Western Europe the prevalence of *B. burgdorferi sensu lato* antibodies in serum ranges from 1% to 8%, whereas in exposed persons in endemic areas the seropositivity can be much higher (up to 30%). The diagnosis of neuroborreliosis therefore relies on clinical examination, history (including exposure to tick-bites), other factors determining the pretest probability, and serologic evidence of antibodies against *B. burgdorferi sensu lato*. A seasonal distribution of cases with peaks in the spring and autumn months has been noted which corresponds to the highest activity of ticks during the year. In our study population the major peak was in summer.

A significant problem remains with the diagnosis of neuroborreliosis as *B. burgdorferi* specific antibodies can persist for a prolonged period of time in serum specimens and both specific IgG and IgM antibodies can also be found after exposure to *B. burgdorferi* without clinical manifestations. Uncertainty remains about the diagnosis of neuroborreliosis. There is evidence that evaluation of intrathecal synthesis of specific antibodies combined with basic CSF values (ie, elevated leukocyte count, predominant IgM antibody response, blood/brain-barrier dysfunction) increases diagnostic sensitivity. A model has been suggested by Reiber and Peter to determine intrathecal synthesis of antibodies with *B. burgdorferi*. However, patients may be missed with this restrictive case definition. Further, there is also evidence of persistent intrathecal synthesis of antibodies against *B. burgdorferi* for several months after recovery of the acute illness. Also, investigation for oligoclonal bands, which we performed in those patients with *B. burgdorferi* antibodies present in CSF specimens where sufficient material was left, was not helpful in this regard. Therefore, laboratory findings have to be correlated with the clinical presentation and remain only one aspect in the process of establishing the diagnosis.

The majority of tested patients with aseptic meningitis alone were due to enterovirus infection. This is in accordance with previous studies on the etiology of aseptic meningitis. PCR of viral DNA is the current gold standard for central nervous system infections with enterovirus, HSV and VZV. Another diagnostic tool is serologic evidence of specific antibody production in CSF which, however, is delayed by several days in comparison with demonstration of viral DNA.

In contrast to other studies we found no evidence of HSV infections in tested CSF specimens. This may be a result of decreased diagnostic sensitivity in stored specimens. VZV in CSF was detected by PCR in only 2 patients with aseptic meningitis and in one patient with PFNP. This, too, is in contrast to other studies which suggested VZV to be the etiologic agent in about one-third of pediatric patients with PFNP. A possible bias is the fact that we required serologic evidence of VZV or HSV, respectively (ie, presence of IgM or IgG antibodies in serum and/or CSF) to prompt PCR testing. Newer data suggest that primary infection with HSV or VZV in children could also lead to PFNP and IgM or IgG antibodies need not to be present on initial presentation.

Problems with diagnosis can also arise from cross-reactive antibodies in different serologic assays. Specifically, false-positive test results have been described for *B. burgdorferi* infection in patients with VZV meningoencephalitis and Epstein-Barr virus infection.

There were only 2 cases of tick-borne encephalitis in our study cohort. This can be explained by the fact that tick-borne encephalitis is not endemic in our area although it occurs in nearby regions in Switzerland and Southern Germany.

Our study has limitations. As with any retrospective analysis, the spectrum of laboratory analyses was variable depending on clinical presentation of the patient, amount of specimens obtained, and individual judgments by the treating physicians. Further, although we attempted to complete missing analyses in stored serum and CSF specimens, the data set remained incomplete.

In conclusion, the majority of patients with combined aseptic meningitis and PFNP had Lyme borreliosis whereas the etiology could be determined only in a small fraction of these single entities. Ideally, prospective regional studies should be performed to determine the etiologies of aseptic meningitis and PFNP in children as there remains uncertainty about the etiological role of viral infections such as HSV and VZV.

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**TABLE 2. CSF Findings in 153 Patients With Aseptic Meningitis With or Without Concomitant PFNP**

<table>
<thead>
<tr>
<th>Etiologic Agents</th>
<th>Leukocyte Count Mean per µL (IQR)</th>
<th>Mononuclear Cells Mean % (IQR)</th>
<th>Total Protein Mean g/L (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>B. burgdorferi</em> (N = 31)</td>
<td>191* (75–273)</td>
<td>89* (90–99)</td>
<td>0.54 (0.39–0.74)</td>
</tr>
<tr>
<td>Enterovirus (N = 17)</td>
<td>565* (125–614)</td>
<td>51* (27–80)</td>
<td>0.40 (0.24–0.53)</td>
</tr>
<tr>
<td>Others/unknown (N = 105)</td>
<td>258* (42–336)</td>
<td>59* (30–93)</td>
<td>0.47 (0.28–0.49)</td>
</tr>
</tbody>
</table>

*P < 0.01, all other comparisons P > 0.05.
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REFERENCES


