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

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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 (63%). In patients with aseptic meningitis, mean leukocyte 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 enterovirus[8] 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),[3,14] and varicella zoster virus (VZV),[2,15] 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 enzyme immunoassays on automated systems were used to identify *B. burgdorferi sensu lato* antibodies (IgG and IgM) as described by the manufacturers ("Vidas Lyme Screen 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

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performed for IgG and/or IgM antibodies (=2-tier testing method) against specific antigens produced by recombinant techniques ("recomBlot BorreliaNB" IgG and IgM, Mikrogen, Martinsried, Germany).[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, Germany) 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 Focusing Kit, Progen, Heidelberg, Germany) performed. Antibody index (cerebrospinal fluid/serum) was calculated for *B. burgdorferi* IgG and IgM according to the formula by Reiber and Lange.[18] An antibody index ≥ 1.5 was considered as proof of intrathecal synthesis 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/mm^3, 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 diagnostic certainty) or no bacterial culture of CSF obtained (level 2 of diagnostic certainty).[19]

A diagnosis of neuroborreliosis required evidence of intrathecal synthesis of *B. burgdorferi* antibodies in CSF (confirmed) or *B. burgdorferi* antibodies in serum and/or CSF, both confirmed by immunoblot (probable).

HSV or VZV infection or reactivation in CNS was defined by the presence of HSV or VZV IgG and/or IgM in serum and a positive CSF PCR for HSV or VZV, respectively.[20] Enterovirus infection was defined by a positive PCR in CSF[21] and tick-borne encephalitis was defined by positive TBEV IgM and IgG antibodies in serum.[22]

Statistical Analysis

Relevant data were analyzed using SAS version 7.1 (Statistical Solutions, Cary, NC). To assess differences between groups we used analysis of variance (ANOVA) with Bonferroni (Dunn) correction to compensate for multiple testing. Statistical significance 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 30 for PFNP with aseptic meningitis. Patient characteristics and etiologic findings by clinical diagnoses are demonstrated in Table 1. In general, patients with aseptic meningitis 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 or unknown diagnoses (mean: 2.0 days, IQR: 1–3 days, $P < 0.01$).

The comparative seasonal distribution of patients with neuroborreliosis, 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, enterovirus 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 meningitis 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

Characteristics	Clinical Diagnosis		
	Aseptic Meningitis (N = 123)	PFNP (N = 28)	Aseptic Meningitis + PFNP (N = 30)
Mean age (yr; IQR)	7.8 (5.3–9.5)	10.4 (7.7–13.0)	8.6 (5.9–11.3)
Male gender (N; %)	86 (70)	16 (57)	16 (53)
Etiologic Agents	N/N Tested (%)	N/N Tested (%)	N/N Tested (%)
B. burgdorferi	9/102 (9)	3/27 (11)	22/30 (73)
Enterovirus	17/27 (63)	0/1 (0)	0/3 (0)
HSV	0/21 (0.0)	0/9 (0)	0/12 (0)
VZV	2/18 (11)	1/8 (13)	0/10 (0)
TBEV	2/73 (3)	0/18 (0)	0/25 (0)
Any of the above	30/123 (24)	4/28 (14)	22/30 (73)

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.[1,4] 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.[17,23]

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%).[24] 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*.[25] 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.[6] In our study population the major peak was in summer.

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

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

*†‡§$P < 0.01$, all other comparisons $P > 0.05$.

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.[24] 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.[26] A model has been suggested by Reiber and Peter[27] 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.[28] 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.[8]

PCR of viral DNA is the current gold standard for central nervous system infections with enterovirus, HSV and VZV.[21,29] 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.[30]

In contrast to other studies we found no evidence of HSV infections in tested CSF specimens.[3,14] 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.[2,15] 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.[31]

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.[9]

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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