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Microbiologic Findings in Acute Facial Palsy in Children

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Objective: Microbiologic causes of facial palsy in children were investigated.
Study Design: Prospective clinical study.
Setting: Tertiary referral center.
Patients: Forty-six children aged 0 to 16 years with peripheral facial palsy.
Interventions: Paired serum samples and cerebrospinal fluid were tested to find indications of microbes associated with facial palsy. The microbes tested were herpes simplex virus 1 and 2, varicella-zoster virus, human herpesvirus-6, *Mycoplasma pneumoniae, Borrelia burgdorferi,* influenza A and B virus, picorna, cytomegalovirus, parainfluenza virus, respiratory syncytial virus, coxsackie B5 virus, adenovirus, and enterovirus, *Chlamydia psittaci,* and *Toxoplasma gondii*. Besides the routine tests in clinical practice, serum and cerebrospinal fluid samples were tested with a highly sensitive microarray assay for DNA of herpes simplex virus 1 and 2; human herpes virus 6A, 6B, and 7; Epstein-Barr virus, cytomegalovirus, and varicella zoster virus.
Results: Incidence for facial palsy was 8.6/100,000/children/year. Cause was highly plausible in 67% and probable in an additional 11% of cases. *Borrelia burgdorferi* caused facial palsy in 14 patients (30%), varicella zoster virus in 5 (11%) (one with concomitant adenovirus), influenza A in 3 (6%), herpes simplex virus 1 in 2 (4%) (one with concomitant enterovirus), otitis media in 2 (4%), and human herpesvirus 6 in 2 (4%). *Mycoplasma pneumoniae*, neurofibromatosis, and neonatal age facial palsy affected 1 child (2%) each.
Conclusion: Microbiologic etiology association of pediatric facial palsy could frequently be confirmed. Borreliosis was the single most common cause; hence, cerebrospinal fluid sampling is recommended for all pediatric cases in endemic areas. Varicella zoster virus accounted for 11% of the cases, being the second most common factor. **Key Words:** Bell's palsy—*Borrelia*—Exanthema subitum—Facial nerve—Facial paralysis—Herpes virus—Pediatric facial palsy.
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There are many known causes for facial palsy (FP), for example, infectious, systemic, congenital, metabolic, toxic, iatrogenic disease, trauma, or neoplasms. Still, Bell's palsy, idiopathic FP without known cause, accounts for most of the cases of adult acute onset peripheral FP (1). A hypothesis has been tendered, that this might not be true with pediatric patients. Although etiologic studies, especially prospective studies, of pediatric FP patients are scarce, a few reports have indicated that a variety of etiologic agents should be considered when investigating FP in children (2–4).

Our study hospital is located in a region endemic for *Borrelia burgdoferi*. Cerebrospinal fluid (CSF) samples are routinely taken from all FP patients up to 16 years of age with no obvious cause for FP. If there is pleocytosis found in CSF, antibiotic treatment toward borreliosis is started without waiting for the anti-borrelia antibody or polymerase chain reaction (PCR) results of the CSF sampling. Later, with full results, the diagnosis of borreliosis is either confirmed or discarded. Rare FP patients with CSF findings suggestive of viral meningitis receive antiviral treatment.

In the diagnosis of borreliosis, CSF sampling is considered as the method of confirmation. In otherwise healthy FP patients, risk for severe complications from CSF sampling (e.g., subdural, epidural, or subarachnoid hemorrhage,

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leakage of CSF and the formation of epidural collections) is very small. The more common headache and backache are seen also in pediatric populations, although studies are scarce, and exact incidences obscure (5).

In some endemic areas, *Borrelia* infections have been suggested to cause 30% to 65% of pediatric FP cases (6–8), whereas in Japan, varicella zoster virus (VZV) accounted for more than 30% of the cases (3). Our provocative question for this study was, whether we can eliminate the diagnosis of Bell's palsy from pediatric FPs with extensive microbiologic studies.

MATERIALS AND METHODS

Children (0–16 yr) with acute peripheral FP attending Children's Hospital or the Department of Otorhinolaryngology, Helsinki University Central Hospital (HUCH), between May 2007 and August 2009 were asked to participate. The study group consisted of 46 consecutive patients, except that 4 patients could not be included because 1 family chose to abstain and 3 families were not offered the possibility to participate. The study plan included recruitment of control patients from the same period; children who did not have FP but whose condition required a CSF sample. Because only 5 control patients were enrolled, they could not be considered a true control group for the 46 FP patients.

The study group of 46 patients included 23 girls and 23 boys. FP was right sided in 27 patients, left sided in 17 patients, and bilateral in 2 patients. The mean age of patients was 9.90 years (SD, 5.17), and the median was 11.27 years (range, 0.04–16.81 yr).

At the baseline visit, besides the clinical evaluation, blood and CSF samples were taken. A second blood sample was drawn at a checkup visit 2 to 4 weeks later. Complete blood count, C-reactive protein, and CSF testing for cells, protein, and glucose were performed routinely. CSF and paired sera were additionally searched for immunoglobulin (Ig) G and IgM antibodies of herpes simplex virus 1 and 2 (HSV 1 and 2), VZV, human herpesvirus 6 (HHV-6), *Mycoplasma pneumoniae* (*M. pneumoniae)*, and *B. burgdoferi.* Moreover, IgG antibodies were assessed using enzyme immunoassay (EIA) for influenza A and B virus (Inf A and B), parainfluenza virus, respiratory syncytial virus (RSV), and coxsackie B5 virus, adenovirus, and enterovirus. The CSF samples were also tested using PCR (DNA extraction by easyMAG instrument; bioMérieux, Inc., Durham, NC, USA) for HSV, VZV, HHV-6, picornavirus (real-time PCR), *M. pneumoniae*, and *B. burgdorferi*. Bacterial cultures were taken from CSF and virus cultures whenever there was enough CSF sample left. Paired sera were additionally tested for antibody titer changes by complement fixation test (CF) for HSV, VZV, Inf A and B, RSV, adenovirus, parainfluenza virus, enterovirus, and cytomegalovirus (CMV), and *M. pneumoniae, Chlamydia psittaci,* and *Toxoplasma gondii.*

Besides the primary samples (above), additional blood and CSF was reserved for a novel microarray. Whenever possible, new DNA extraction was performed from the serum and CSF samples using an easyMAG instrument (bioMérieux), followed by analysis of 8 herpes viruses, HSV 1 and 2; HHV 6A, 6B, and 7; Epstein-Barr virus (EBV); CMV; and VZV, using a commercially available microarray assay (Prove-it Herpes, Mobidiag, Finland) modified from Jääskeläinen et al. (9). Blood cells from the majority of patients were saved and frozen after serum extraction. In case of a positive HHV (1–7) finding from serum or CSF in any of the previous tests, DNA was extracted from blood cells, and the samples were further tested by Prove-it herpes. The recent evaluation of the microarray assay has shown a sensitive performance and a good concordance with the results of current PCR-based herpes virus diagnostics reported by 5 European clinical laboratories (10).

Testing for *Borrelia* Antibodies

Screening of IgM and IgG antibodies in the serum or CSF was routinely performed in an enzyme-linked immunosorbent assay (ELISA). For screening of IgM antibodies, an in-house whole-cell sonicate of *Borrelia afzelii* was used as antigen. For IgG antibody screening, the whole-cell sonicate was combined with recombinant VlsE-protein originating from a *B. burgdorferi* sensu stricto strain. In cases of positive screening of serum antibodies, confirmatory testing with recombinant VlsE antigen (IgG) or VlsE combined with OspC antigen (IgM) was used.

In some serum samples, to confirm the specificity of positive antibody screening results, the samples were further analyzed with either a commercial Line Blot (has replaced in-house Western blots) or a commercial ELISA containing a combination of recombinant borrelial proteins.

In cases of positive CSF antibody screening, assessment of intrathecal production of anti-borrelia antibodies (11) with flagella antigen was performed.

Classification of Neuroborreliosis

Based on the presence or absence of anti-borrelia antibodies and lymphocytic pleocytosis (>5 leukocytes $\times$ 10^6/l) in CSF, patients were divided into 3 groups: confirmed neuroborreliosis (NB), possible NB, and non-NB as described earlier (11). In brief, patients with confirmed NB had pleocytosis and IgG and/or IgM anti-borrelia antibodies in CSF. Possible NB patients had pleocytosis in CSF, and most of them had IgG and/or IgM anti-borrelia antibodies in serum but none in CSF. Patients classified as non-NB had no anti-borrelia antibodies or pleocytosis in CSF.

The study protocol was in accordance with Helsinki Declaration and was approved by the HUCH Ethics Committee. All parents, and when age appropriate, also the patients, gave their written informed consent. The funding source had only a financial role in the study.

RESULTS

The mean age of patients without borreliosis was 10.28 years (SD, 5.46 yr), and their median age was 12.14 years (range, 0.04–16.81 yr). The mean age for borreliosis patients was 9.02 years (SD, 4.48 yr), and the median age was 8.55 (range, 0.82–14.88 yr). The age difference was not statistically significant.

When determining the incidence of FP, patients treated at any of the HUCH district hospitals during the study period were included. Based on a computerized search within the health-care district with 294,900 children (at study time), 59 children diagnosed with FP were found. The mean frequency of all FPs during the first third of the year was 1.4 patients/month, second third 2.8 patients/month, and last third 1.8 patients/month. The FP per month excluding borreliosis patients during the first third of the year was 1.4 patients/month, the summer months 1.4 patients/month, and the last third 1.5 patients/month. The annual incidence was 8.6/100,000 children.

CSF samples were taken from 44 of the 46 study patients. Prove-it Herpes test was performed on 41 CSF samples.

Bacterial cultures (44) and virus cultures (24) carried out from CSF samples were all negative. Paired serum samples were received from 45 patients. Prove-it Herpes test was performed on 42 primary and 37 secondary serum samples and on blood cells from 11 patients.

The time delay from the first FP symptoms to the physician visit in our tertiary clinic ranged from 0 days (examined by a physician the same day) to 13 days (median, 2.0 d). The time interval from first FP symptoms to serum and CSF samples ranged from 0 to 13 days (median, 2.0 d).

As for the cause, confirmed NB was found in 10 and possible NB in 4 patients (Table 1). Thus, in 14 (30.4%) of 46 patients, borreliosis was considered the cause of FP. All patients with confirmed NB had CSF antibodies to *Borrelia*; 9 had both IgG and IgM antibodies, and one had IgM antibodies (Table 1). Intrathecal *Borrelia* antibody production was detected in 7 of the 10 confirmed NB patients. In 3 confirmed NB patients, the intrathecal production index could not be calculated because the serum samples were not taken the same day as the CSF samples (2 patients) or there was inadequate CSF sample left (1 patient). Besides borreliosis, many of the NB patients had findings indicating recent infections with other microbes (HHV-6, adenovirus, VZV, EBV, Inf B, enterovirus, HHV-7, or HSV-1). Six of the NB patients were girls, and 8 were boys.

In 17 of the remaining 32 patients, the cause for FP could be suggested by clinical assessment and microbiologic findings (Table 2). FP was associated with VZV in 5 cases (10.9%), with one patient having concomitant adenovirus infection. Three patients (6.5%) had findings of acute Inf A infection preceding the FP. HSV-1 was detected in 2 patients (4.3%), one having constantly high levels of serum HSV-1 IgG antibodies suggestive of repeated reactivations. This patient also had signs of recent enterovirus infection concomitantly. HHV-6 as a suspected causative agent affected 2 patients (4.3%). The patient with exanthema subitum also had findings of HHV-7, another etiologic factor (besides HHV-6) for exanthema subitum. Many of the patients had concomitant microbiologic findings that were not considered probable etiologic factors, although possible. In a few patients, antibodies to *Borrelia* were slightly elevated, but they were deemed nonspecific antibody reactions or cross-reactions of other microbes. None of the non-borreliosis patients had pleocytosis in CSF. Signs of HHV-6 or HHV-7 infection or reactivation were seen in 8 (57%) of the 14 patients with borreliosis and in 10 (31%) of the 32 non-borreliosis patients.

Ten patients, who all recovered within a month, had no positive findings in serum or CSF samples. Five of the ten patients had signs of respiratory infection within two weeks preceding FP.

TABLE 1. *Facial palsy with neuroborreliosis: findings and patient characteristics*

Diagnosis	Patient no./ age (yr)	Symptoms/tick bites	Elevated serum *Borrelia* ab:s	CSF leukocytes ($\times 10^6$/liter)/ mononuclear %	Elevated CSF *Borrelia* ab:s/ intrathecal ab index	CSF *Borrelia PCR*/*CSF proteins*
NB	23/5.1	Headache, neck pain, balance disturbances, tiredness. Tick bite one month earlier	IgM and IgG, twice	610/98	IgM and IgG/positive	Negative/elevated
NB	24/10.5	Rash (erythema migrans?) 3 wk earlier, lower back pain few days earlier	IgM and IgG, twice	552/99	IgM and IgG/positive	Negative/elevated
NB	25/13.7	Mild ear and neck pain. Two weeks earlier, rash (erythema migrans?), sore throat, mild fever. One week later, facial palsy also on contralateral side	IgM and IgG, twice	224/91	IgM and IgG/positive	Negative/normal
NB	26/8.4	Several tick bites recently, mild malaise	IgM and IgG, twice	57/96	IgM and IgG/positive	Negative/normal
NB	27/8.7	Two weeks earlier, headache for 5 d. Fever in the evenings for 1 wk. Three days later, facial palsy also on contralateral side.	IgM and IgG, twice	125/58	IgM and IgG/positive	Negative/elevated
NB	28/14.3	For 1 wk, malaise, tiredness, muscle ache, fever. Herpes simplex infection on lower lip one month ago	IgM in second sample	236/99	IgM/positive	Negative/elevated
NB	29/14.0	Earache, mild headache. Two weeks earlier, fever, headache	IgM and IgG, twice	201/95	IgM and IgG/positive	Negative/elevated
NB	30/0.8	Torticollis	IgM and IgG, once	91/100	IgM and IgG/NA	Positive/normal
NB	31/12.7	Mild ache around ear, stuffy nose	IgM and IgG, twice	47/92	IgM and IgG/NA	Negative/normal
NB	32/6.9	Ear infection 1 wk earlier. Several tick bites recently	IgM and IgG, twice	230/99	IgM and IgG/NA	Negative/elevated
Possible NB	33/3.0	Fever, stomach ache for 2 d. Aches in extremities for 2 wk. A tick behind ear while recovering from facial palsy	IgG, second sample	145/100	IgM/NA	Negative/normal
Possible NB	34/5.9	Several tick bites recently and over the years	IgM and IgG, twice	62/100	NA	Negative/normal
Possible NB	35/7.2	Headache for 1 wk	IgM and IgG, twice	27/97	Negative	Negative/normal
Possible NB	36/14.9	No associated symptoms	IgM, twice	281/100	Negative	Negative/normal

Ab indicates antibody; CSF, cerebrospinal fluid; NA, not available; NB, neuroborreliosis; PCR, polymerase chain reaction.

TABLE 2. *Facial palsy (non-borreliosis): findings and patient characteristics*

Patient no./ age (yr)	Clinical signs	Suggested facial palsy cause
1/15.2	Tongue blisters	HSV-1 (paired sera IgG rise)
2/0.7	Otitis media 1 wk before/serous secretion in middle ear	Otitis media/culture negative
3/3.0	Ear symptoms 2 wk/purulent+glue-like secretion	Otitis media/culture negative
4/2.1	Respiratory infection and high fever for 4 d, varicella 4 wk earlier, hepatitis A vaccination four days earlier	VZV (positive IgG avidity test); adenovirus (paired sera ab rise)
5/0.6	Varicella blisters 3 d earlier	VZV (paired sera IgG and IgM seroconversion, ab titer rise)
6/15.6	No symptoms	VZV (paired sera IgM first borderline, second strongly positive, ab titer rise)
7/16.2	No symptoms	VZV (paired sera IgM low positive)
8/15.1	Ache around mandible and ear on affected side	*M. pneumoniae* (serum IgM high positive ×2, IgG rise)
9/1.5	Exanthema subitum: high fever 3 d, then rash all over body, facial palsy on fourth day	HHV-6 (paired sera IgG rise, IgM positive, CSF PCR positive), HHV-6B (serum and CSF by Prove it PCR); HHV-7 (serum by Prove it PCR)
10/15.4	Respiratory infection 2 wk earlier	HSV-1 (serum IgG constant high levels); Enterovirus (serum IgG steady high levels)
11/12.2	Mild respiratory infection symptoms	Inf A (serum ab titer high, CSF IgG ab with normal serum/CSF ratio)
12/9.0	Respiratory infection 2 wk earlier	Inf A (serum ab titers high ×2, CSF IgG ab with normal serum/CSF ratio)
13/13.8	Respiratory infection 10 d earlier	Inf A (serum ab titers high ×2)
14/12.0	Respiratory infection for 2 wk	HHV-6 (paired sera IgM seroconversion)
15/6.4	Lumps on forehead and back	Neurofibromatosis type 2/vestibular schwannomas
16/7.5	Runny nose, varicella 5 wk earlier	VZV (paired sera IgG constant levels, IgM borderline positive ×2)
17/0.04	Clear asymmetry of the face at two weeks of age. Possibly blinked more slowly on the affected side one day after birth	Congenital?

Ab indicates antibody; CSF, cerebrospinal fluid; HHV, human herpesvirus; HSV, herpes simplex virus; Inf, influenza virus; M. pneumonia, mycoplasma pneumonia; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

With the borreliosis patients included, cause for FP was highly plausible in 31 (67%) of the 46 patients (Tables 1 and 2). Moreover, in 5 more patients, an association with a microbiologic finding was observed (Inf A, Inf B, HHV-6, HHV-7, EBV, enterovirus, or adenovirus). Altogether, 36 (78%) of the 46 patients had a clinical condition or microbiologic findings either explaining or at least associated with the FP.

DISCUSSION

FP has been reported to occur in 50% to 70% of children with NB (6,12,13) and can be the only objective finding of the disease. In endemic areas, Lyme borreliosis has become the most commonly identified cause of peripheral FP in children, accounting for 0% to 65% of the cases (3,7,14,15). In our study, 30% of the FP patients had confirmed or possible NB. This result concurs with the findings of previous prospective studies from the same geographical area in which 32% to 34% of the pediatric FP cases were caused by borreliosis (8,16).

Is FP an isolated cranial neuropathy in borreliosis, as sometimes suggested, or a sign of inflammatory central nervous system disease with meningitis? All of our study patients with the NB diagnosis had pleocytosis in CSF, many of them also elevated CSF proteins. In a prospective multicenter study of childhood NB, 96.8% of the children whose FP was caused by *Borrelia* infection showed CSF pleocytosis, compared with 11.7% in the non-borreliosis FP group (6). The authors concluded that Lyme borreliosis as the cause of FP is highly improbable if there is no inflammatory CSF syndrome (6). They also suggested that mononuclear dominance (>90%) is strongly supportive of bacterial but not viral cause. Leukocytic pleocytosis in CSF has also been documented in most (65%–100%) NB patients with FP (7,8,12,16,17).

Definite diagnosis of NB can be made if bacterial cultures from CSF grow *Borrelia* or if there is intrathecal production of *Borrelia* antibodies. However, in practice, *Borrelia* cultures are extremely tedious and require special media, thus not being feasible for routine laboratory diagnostics. Antibody levels from the same day in serum, as in CSF, are needed for the calculation of the intrathecal production index. In our study, intrathecal production was found in 50% of FP patients with confirmed or possible borreliosis. Similar findings (43%–47%) have been reported elsewhere (7,8,13). Of our 14 borreliosis patients, *Borrelia* PCR from CSF was positive in only 1 patient. Such poor results on *Borrelia* PCR have also been reported by others (8,11,16). The reason for low sensitivity of *Borrelia* DNA testing is currently unknown.

All study patients with possible or confirmed NB were treated with intravenous ceftriaxone (children younger than 8 yr) or oral doxycycline (children aged 8 years and older).

VZV was associated with FP in about 11% of cases. In earlier Finnish prospective studies, VZV accounted for 12% to 16% (8,16) of cases, all clinically diagnosed, whereas in our study with paired serum tests, 2 of the

cases were zoster sine herpete cases without blisters. The clinical VZV infections were concomitant or had preceded FP by 4 to 5 weeks, raising concern of whether they could still be etiologic factors. A similar time frame of blisters occurring 4 weeks before FP has been reported by others (16), supporting the assumption that VZV infection in the near past is capable of introducing FP. The proportion of VZV as the causative agent for FP has varied in published studies from 2.8% (14) to 37% (3), majority in the latter study being zoster sine herpete cases. Finding VZV infection among FP patients is important because VZV can cause false-positive IgM antibody results for borreliosis (6). In Finland, VZV vaccination is not included in the national vaccination program, but the vaccine is commercially available. It would be interesting to ascertain, whether vaccinated populations had less FP altogether.

A recent Inf A infection was associated with FP in 6% of our study patients. In previous research, Inf A has been seldom tested in FP patients, adults, or children. In a Finnish study from our area, children with suspected central nervous system infections were extensively tested for etiologic factors; among these children were 19 FP patients (16). None of the FP patients had Inf A findings. In the present study, the patients had respiratory infection preceding FP, but the symptoms had not been severe and were not accompanied by neurologic signs before FP onset. Possibly our findings were coincidental, but knowing that influenza viruses are capable of inducing many neurologic symptoms, the association with FP was not surprising.

In adults, HSV-1 has long been considered a possible etiologic factor for FP. Recent large prospective Bell's palsy treatment studies have, however, shown no effect with herpes virus medications (18). In children, HSV-1 seems to be associated with some cases of FP but is not a predominant factor. In our study, 4% of the children had an HSV-1 association; earlier consistent findings have been 2.9% to 5.7% (2,14,19).

We had 2 cases (4%) of otitis media–induced FPs. This concurs with previous studies (1,8,14), although higher frequencies of 30% have also been reported. (2) It would be interesting to know the bacterial cause of the infections, but in both our cases, cultures from the middle ear were negative.

Congenital FP is very rare in Finland. One 2-week-old neonate in this study might have had a mild palsy already at birth, but this could not be confirmed. In other studies, incidences of 7.1% to 11.4% (2,19) have been described. In a Danish 25-year prospective study, almost half of the pediatric FP cases were neonatal (1). In Finland, forceps deliveries are and have been very rare, which could be one factor accounting for the low numbers of FP in neonates at birth (forceps were not used in the 1 case in this study either).

One of our study children had FP associated with exanthema subitum, which is caused by HHV-6 and/or HHV-7. We have previously published a report on the association between exanthema subitum and FP (20). Thus, we submit that the primary infection of HHV-6 or HHV-7 may cause FP, albeit infrequently. Additionally, we found infection or reactivation of HHV-6 or -7 in 57% of the borreliosis FP patients and 31% of the non-borreliosis FP patients. There is little published data on the association of HHV-6 or -7 and FP. Earlier, we have found HHV 6 or 7 DNA in the CSF of a few FP patients, however, with no clear-cut causality (21). HHV-6 reactivation can occur during other infections (22). The high frequency of HHV 6 and 7 findings in this study gives supporting evidence for the associated activation during other infectious illnesses. In borreliosis FP patients, HHV 6 or 7 DNA was often detected in CSF, probably indicating blood-brain barrier damage rather than intrathecal virus replication.

The proportion of Bell's palsy was 22% to 33% in our study, the number depending on whether we consider all associated findings as true etiologic factors. A comparable proportion of 30% was suggested in another prospective study (14), retrospective studies having a wide range from 9% (2) to 50% (19) and beyond.

Limitations of our study were the relatively low number of patients and the medium-term study period of 28 months; a longer study time would have increased the patient number and allowed the diversity of infectious diseases to emerge over the years. Another drawback could be the Prove-it Herpes test, which being very sensitive may detect traces of DNA of herpes viruses that have no clinical significance.

CONCLUSION

Etiologic factors for pediatric FP have been found, and many associated factors might also prove to be etiologic factors with further research. In our study, more than 60% of the FP cases had a highly probable infectious cause, *B. burgdoferi* being the most frequent, followed by VZV. With developing laboratory methodologies and established diagnostic criteria, in the future, it may be possible to discard the diagnosis of Bell's palsy, at least from pediatric FP.

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