ORIGINAL ARTICLE

Infectious causes of peripheral facial nerve palsy in children—a retrospective cohort study with long-term follow-up

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Abstract

The aim of this study was to analyze the clinical and laboratory characteristics of children with peripheral facial nerve palsy (pFP) with a focus on identifying infectious etiology and long-term outcome. We conducted an ICD-10-based retrospective chart review on children hospitalized with pFP between January 1, 2006, and December 31, 2016. Furthermore, a telephone-based follow-up survey was performed. A total of 158 patients were identified, with a median age of 10.9 years (interquartile range 6.4–13.7). An infectious disease was associated with pFP in 82 patients (51.9%); 73 cases were classified as idiopathic pFP (46.2%). Three cases occurred postoperatively or due to a peripheral tumor. Among the infectious diseases, we identified 33 cases of neuroborreliosis and 12 viral infections of the central nervous system (CNS), caused by the varicella-zoster virus, human herpesvirus 6, herpes simplex virus, enterovirus, and Epstein-Barr virus. Other infections were mainly respiratory tract infections (RTIs; 37 cases). Children with an associated CNS infection had more often headache and nuchal rigidity, a higher cerebrospinal fluid cell count, and a longer length of hospital stay. Long-term follow-up revealed an associated lower risk of relapse in CNS infection–associated pFP. Among all groups, permanent sequelae were associated with female sex, a shorter length of hospitalization, and a lower white blood cell count at presentation. pFP is frequently caused by an CNS infection or is associated with concurrent RTIs, with a potential impact on the short- and long-term clinical course.

Keywords Facial nerve palsy · Bell's palsy · Neuroborreliosis · Neurotropic viruses · Children

Introduction

Peripheral facial nerve palsy (pFP) is the most common cranial nerve lesion in children and adults [1]. Its causes are manifold, including infectious diseases such as neuroborreliosis [2], inflammation in the proximity of the facial nerve, such as mastoiditis [3], tumors [4], trauma [5], or systemic inflammatory conditions such as the Melkersson-Rosenthal syndrome [6]. Still, in most

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cases, no underlying cause can be identified, yielding the diagnosis (idiopathic) Bell's palsy.

Clinically, the underlying etiology of pFP is difficult to diagnose. In contrast to international guidelines in which a diagnostic lumbar puncture is not deemed indispensable [7–9], the newest German guideline for pFP [10] advocates performing lumbar puncture and cerebrospinal fluid (CSF) analysis in adults, but even more so in children, since neuroborreliosis (NB) is more common among children as a cause of pFP than in adults [11]. Thus, CSF analysis has direct therapeutic implications [12, 13]. Although regional differences exist, borreliosis is the most frequent tick-borne disease within Germany, with reported incidences over the last years between 26 and 41 per 100,000 [14]. Apart from NB, other infections that have been linked to pFP are mainly viral central nervous system (CNS) infections, such as the Varicella-zoster virus (VZV) [15, 16]. Other neurotropic viruses that have been linked to pFP are Herpes simplex virus (HSV) [17–19], Epstein-Barr virus (EBV) [20–23], Cytomegalovirus (CMV) [24, 25], and human herpesvirus 6 (HHV6) [26]. These etiologies entail therapeutic consequences, e.g., the initiation of

antiviral therapy or the cessation of empirical antibiotics. Most of the aforementioned viruses have been implicated in case reports. Overall, there is a scarcity of systematic studies in children focusing on infections as differential diagnoses. Thus, little is known about the frequency and relevance of other pathogens potentially involved in pediatric pFP. The aim of the study was to analyze clinical and laboratory characteristics in children with infectious and non-infectious etiology of pFP, and to evaluate the long-term outcome.

Materials and methods

Study design

This retrospective cohort study was carried out at the University Children's Hospital, Mannheim, Germany. An approval from the ethics committee was obtained prior to study initiation (2017-541N-MA). All patients presenting to the hospital with pFP between January 1, 2006, and December 31, 2016, were included in this analysis. Charts were identified by searching the hospital database for the ICD-10 primary diagnosis code G51.-. In order to avoid selection bias, an additional search for G51.- as a secondary diagnosis was conducted. Patients with duplicate entries were only included once. Also, patients with central facial palsy were excluded, as were patients presenting for other reasons than the facial palsy (with a longstanding history of pFP).

Files were reviewed for present and past medical history, clinical findings, laboratory microbiological, and radiological findings, treatment, and the physician's final diagnosis.

Etiological classification and infectious disease diagnostics

Patients were classified as idiopathic or non-idiopathic according to the physician's diagnosis and all available data.

For the diagnosis of NB, three subgroups of certainty were used according to guidelines and as previously reported [12, 27, 28]: possible NB, probable NB, and definitive NB.

Possible NB was defined as compatible clinical findings and Borrelia-specific IgG and/or IgM in serum; probable NB was defined as the criteria for possible NB, plus CSF pleocytosis; definitive NB was defined as probable NB, plus the intrathecal synthesis of Borrelia-specific IgG and/or IgM or a positive culture or PCR.

The following diagnostic tests were applied for infectious analysis: blood and CSF IgM and IgG serology for NB (Enzygnost Borreliosis VlsE IgG/IgM ELISA, Dade Behring, Marburg, Germany; Liaison Borrelia IgG/Borrelia IgM Quant CLIA, Diasorin, Saluggia, Italy) with confirmatory western blot (recommBlot Borrelia NB IgG/IgM, and recomLine Borrelia IgG/IgM (lineblot), both Mikrogen,

Neuried, Germany); blood or CSF serology for other viral pathogens; CSF culture; and a multiplex PCR (LIPA-CNS, Innogenetics, Ghent, Belgium) from CSF, including the following: HSV types 1 and 2, VZV, EBV, CMV, HHV6, Enterovirus, JC virus.

Trends in treatment

We compared two time periods, i.e., 2006–2011 and 2012–2016, for changes in treatment strategy. This division was chosen because the German guideline on the treatment of idiopathic facial nerve palsy was published in 2012, with the newest update published in 2017.

Follow-up survey

For the follow-up, a standardized questionnaire was designed, including questions about the course of the disease, further therapies, relapses, residuals, other symptoms, impact on the quality of life, and education. Patients were first contacted and asked for their participation in the study. After receiving the written informed consent, a telephone interview was conducted.

Statistical analysis

Statistical analyses were performed with SAS (Statistical Analysis System, Release 9.4, NC, USA). We compared idiopathic pFP with CNS infection-associated pFP and with pFP associated with concomitant RTI (including acute otitis media and mastoiditis) by using the one-way analysis of variance and Kruskal-Wallis test for comparing more than two groups. For comparisons between two groups, we applied the Mann-Whitney U test and t test for continuous variables and chi^2 and Fisher's exact test for categorical data. Furthermore, we performed a logistic regression to assess potential risk factors associated with the presence of long-term sequelae.

Results

Demographics in children with pFP

We identified 187 patients, of whom 29 were excluded (Fig. 1).

Of 158 patients included, 80 were male (50.6%). The median age at presentation was 10.9 (interquartile range 6.4–13.7). CSF analysis was performed in 137/158 (86.7%). Reasons for deferral were missing consent and unsuccessful lumbar puncture (LP). The most frequent classification was idiopathic pFP in 73 patients (46.2%). In 45 children (30%), an infection of the central nervous system (CNS) was diagnosed. Among those, 33 had NB (20.9%) and 12 had a viral
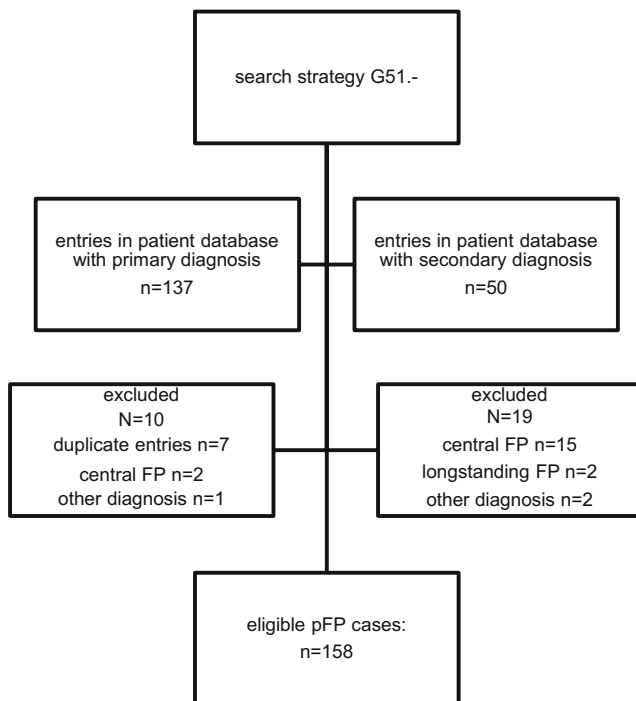
Fig. 1 Flow diagram

CNS infection (7.6%). Furthermore, 12 patients had acute otitis media (AOM) or mastoiditis (7.6%), and an additional 25 patients had another concomitant RTI (15.8%). In three patients (1.9%), pFP occurred due to a peripheral tumor or postoperatively.

Seasonality in subgroups of children with pFP

Most cases were diagnosed between September and November (56/158; 35.4%). While children with RTI had their peak from October through February (16/25; 64%), NB patients mainly presented in June through October (27/33; 81.8%). In contrast, the presentation peak of viral CNS infections was February/March (5/12; 41.7%), while children with AOM/mastoiditis were evenly distributed (Fig. 2).

Infectious CNS diseases etiology in pediatric pFP

Of the 33 patients with NB, 15 were classified as definitive NB; 11 as probable NB; and 7 as possible NB. The median CSF cell count was highest in definitive NB with 168/μL (IQR 82.5–278.5) vs. 65/μL (37.5–83) and 2/μL (2–3) in probable and possible NB, respectively. Although CSF cell count and Borrelia-specific findings differed between the NB subgroups, the median duration of treatment was 14 days for all NB patients, taking outpatient parenteral antibiotic therapy into account.

A viral CNS infection was detected in 12 patients, in the vast majority of herpes viruses. In 3 patients, VZV was identified, while 2 patients were positive for HHV6, and one

patient for Enterovirus (all PCR positive in the CSF). Serological diagnosis was made in two patients with acute HSV and three with acute EBV infection. In one patient, aseptic meningitis was diagnosed without pathogen detection. Antiviral therapy was initiated in 5 patients (3 with VZV, 1 with HSV, 1 without pathogen detection); the median duration of therapy was 7 days (IQR 4–14).

Clinical and laboratory characteristics of patients with pFP

There were no differences between idiopathic FP and CNS infection-associated pFP concerning sex, age at presentation, family history, vaccination status, body temperature, and neurological findings such as vertigo or nystagmus (Table 1). However, a positive tick bite history was more common among CNS infection-associated pFP compared with the other groups, as well as headache and nuchal rigor. The ratio of patients with CNS infection without signs of headache and nuchal rigidity was 21/45 (46.7%) and 39/45 (86.7%), respectively, while in 20/45 (44.4%), neither headache nor nuchal rigidity was reported. A rash was significantly more frequent among CNS infection-associated pFP than in idiopathic pFP, while an altered taste sensation was more frequent in RTI-associated pFP than in CNS infection-associated pFP.

There was no difference in CRP and leukocyte levels, while CSF cell counts differed significantly between all groups, with the highest values in patients with CNS infection-associated pFP. Similarly, patients with CNS infection-associated pFP had significantly higher CSF protein than the other groups. Lastly, length of stay (LOS) was significantly higher in this specific patient group, too.

Trends in treatment in pFP

We found an increased use of corticosteroids (CS), a decreased use of antibiotics, and a slightly decreased use of antivirals among all groups in the period 2012–2016 compared with 2006–2011 (Fig. 3a). This was most markedly seen in idiopathic pFP (Fig. 3b). In children with NB, no change of antibiotic utilization was observed (Fig. 3c).

Long-term follow-up

Data on follow-up were obtainable from 84/158 (53.2%) patients, with a median follow-up interval of 7.7 years (IQR 6.1–9.2). Recurrence of disease was significantly more often in idiopathic pFP compared with those with associated CNS infections, while there was no significant difference between temporary or persistent sequelae (Table 2). We observed more paresthesia and fatigue in CNS infection-associated pFP; furthermore, children with CNS infection-associated pFP reported to have limitations in daily activity more often than

Fig. 2 Seasonal distribution of pFP cases. NB, neuroborreliosis; AOM, acute otitis media; Mast., mastoiditis; RTI, respiratory tract infection
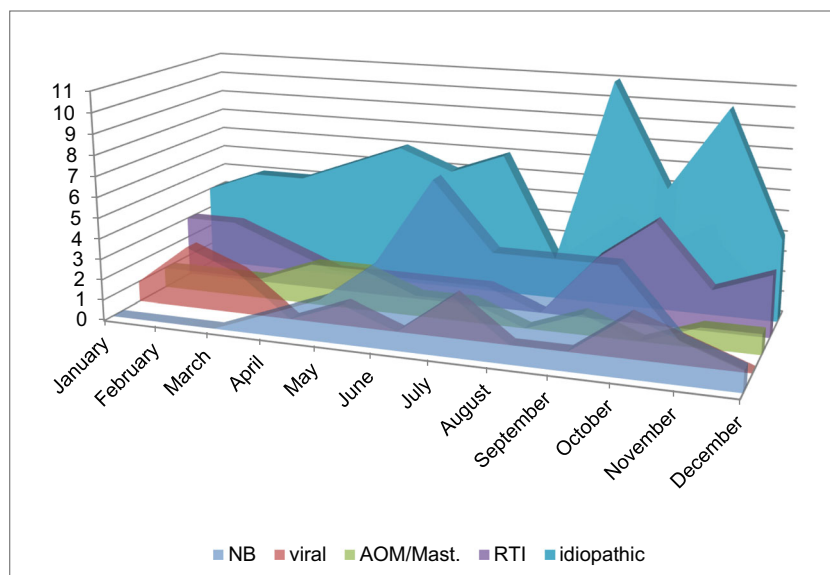
children with idiopathic pFP. Both differences were not statistically significant. Data on education was missing for some cases, while those still attending elementary school were not taken into account.

Logistic regression yielded the following three parameters as potentially influencing factors for permanent sequelae among all groups (*c*-index 0.756): female sex as a risk factor (odds ratio 3.60; 95% confidence interval 1.14–11.36; $p = 0.029$), long length of hospitalization (OR 0.85; 95%CI 0.70–1.02; $p = 0.084$), and a higher white blood cell count at presentation (OR 0.77; 95%CI 0.58–1.04; $p = 0.087$) as potential protective factors.

Discussion

We have shown in our cohort that a substantial amount of pediatric pFP cases is either caused by a CNS infection or associated with a RTI. Moreover, our data support that CNS pathogens other than *Borrelia burgdorferi* play a role in pFP. In our cohort, pFP caused by CNS infections differs in clinical presentation from the other groups with a higher rate of headache and nuchal rigor. Still, relying on clinical parameters might lead to underdiagnosis of infectious causes, since only 6/45 with CNS infection-associated pFP presented with nuchal rigor. The higher rate of positive tick bite history might have constituted a recall bias.

CSF analysis yielded significantly higher cell count and protein levels in CNS infection-associated pFP. Moreover, pFP associated with CNS infections lead to less recurrence than idiopathic cases. The comparison of idiopathic cases with RTI-associated pFP yielded a comparable presentation and long-term outcome, raising the question whether the latter

should be regarded as idiopathic cases with concomitant, but not causally relevant RTI.

The strengths of our study are the cohort size, the thorough diagnostic work-up, and the long follow-up with a median interval of > 7 years. On the other hand, some patients were lost to follow-up or unwilling to participate. Therefore, conclusions on the outcome were hampered by a smaller sample size. Aside from that, a follow-up clinical examination of each patient would have been beneficial in order to obtain a more objective outcome parameter such as the House Brackmann Facial Nerve Grading Scale, as performed previously [29, 30]. Moreover, due to the retrospective design, only a selection of infectious diseases diagnostics initiated by the physician in charge may have led to an underestimation of other causes of pFP. In addition, the causative role of some viruses that were detected via serology remains questionable, since positive serology may not only indicate active disease but can also reflect possible simultaneous virus reactivation (especially HSV).

Our data confirm the prominent role of NB in children with pFP, comparable with other studies [12, 29, 31], and simultaneously highlight the difficulty in diagnosing probable or possible cases, given the fact that in some patients, LP cannot be performed due to various reasons (2/7 in our cases of possible NB). All cases of NB in our cohort, irrespective of diagnostic certainty, were treated with an adequate antibiotic for a median duration of 14 days. Still, patients with CNS infection-associated pFP and hence NB had the highest rate of limitation in daily activity, albeit without statistical significance, which further underscores the importance of a thorough diagnostic work-up and the initiation of an adequate therapy. Interestingly, no substantial effect of NB on the long-term social and educational outcome was found in a recent Danish cohort study with more than 2000 cases [32],

Table 1 Comparison of clinical and laboratory characteristics of patients with idiopathic and infectious pFP. For continuous variables, medians and IQR are given. *p* refers to differences between idiopathic and infectious pFP and between idiopathic and RTI-associated pFP; *ns* not significant

Features	Idiopathic pFP	CNS infection-associated pFP	*p* value (vs. idiopathic pFP)	RTI-associated pFP	*p* values (vs. idiopathic/ CNS infection-associated pFP)
N (%)	73 (46.2%)	45 (30%)		37 (23.4%)	
Male	40/73	22/45	ns	17/37	ns/ns
Age, years	11.7 (8.6–14.3)	10.0 (6.4–12.9)	ns	9.9 (5.7–13.7)	ns/ns
Duration of illness, days	2 (1–3)	1 (1–3)	ns	1 (0.3–2)	ns/ns
pFP right side	36/73	27/45	ns	20/37	ns/ns
Family history positive for pFP	7/73	2/45	ns	1/37	ns/ns
Vaccine status complete	46/73	30/45	ns	26/37	ns/ns
Tick bite history positive	9/73	16/45	0.0111	2/37	ns/0.0028
Fever ($\geq$ 38.0 °C)	12/73	11/45	ns	8/37	ns/ns
Headache	21/73	24/45	0.0089	10/37	ns/0.0161
Nuchal rigor	0/73	6/45	0.0025	0/37	ns/0.0299
Vertigo	5/73	2/45	ns	0/37	ns/ns
Nystagmus	1/73	1/45	ns	0/37	ns/ns
Altered taste sensation	5/73	0/45	ns	4/37	ns/0.0378
Rash	2/73	8/45	0.0065	4/37	ns/ns
Body temperature, °C	37.5	37.5	ns	37.4	ns/ns
CRP, mg/L	2.8 (2.8–2.8)	2.8 (2.4–2.8)	ns	2.8 (2.8–3.4)	ns/ns
White blood count, 10^9/L	8.1 (6.8–9.6)	7.7 (6.9–9.0)	ns	8.6 (6.7–10.1)	ns/ns
LP performed	60/73	43/45	ns	33/37	ns/ns
CSF cell count, /µL	1 (1–2)	42 (4.3–214.5)	< 0.0001	2 (1–4)	< 0.0001/< 0.0001
CSF glucose, mg/dL	58 (53–61)	55.1 (51–59)	ns	59 (51–60.3)	ns/ns
CSF protein, mg/L	273.3 (232.2–319.5)	327.6 (258.2–611.5)	0.0026	252 (216.6–314.0)	ns/0.0016
Length of stay, days	4 (3–5)	7 (5–14)	< 0.0001	4 (3–5)	ns/< 0.0001

confirming previous findings from Sweden [33]. In a previous German study [31], no statistically significant differences in time to recovery and residual symptoms were found between children with idiopathic FP and children with NB. In the same analysis, infectious etiologies other than NB included infections with adenovirus, *Mycoplasma pneumoniae*, and mumps virus. However, the methodology was insufficiently reported, thus limiting generalizability.

The role of HSV and VZV has been repeatedly reported previously [15, 19], which is further underlined by our findings. Additionally, our data support the role of HHV6 [26] and EBV [20, 34] in the context of pFP. In a study by Genizi and colleagues [35], HHV6 was found in the saliva of 71% of children with pFP, while other herpes viruses were less prevalent. Even after the resolution, HHV6 was detectable in most cases. Interestingly, no viral CSF analyses were reported.

As a rather novel finding, we observed an association between enteroviral infection and pFP. Given the high frequency of enterovirus among CNS infections in children [36], this singular case of a pFP may simply represent a chance finding. Prospective surveillance studies are warranted to confirm this potential association.

Our data on the treatment trends show a decrease in the use of antibiotics in idiopathic pFP, correlating with the updated German national guideline on the management of pFP. Treatment with CS, which is the evidence-based therapy in adults with idiopathic pFP [37], lacks conclusive data to be advocated likewise in children. This is reflected in the increased yet still low rate of CS use within the second time frame of our analysis. Due to the small number of patients who received CS and were available for follow-up, no firm conclusion could be made about CS therapy and its effect on the outcome. There is only limited data, mainly from retrospective studies, for the benefit of CS in children with pFP [38, 39]. Data from randomized controlled trials are scarce or, as in the case of the BellPIC study, yet to be reported [40]. The use of CS in NB has been implicated with worse outcomes in a recent study [41], which further underscores the importance of a thorough diagnostic work-up for clarifying the etiology.

We identified lower white blood cell count and shorter duration of hospitalization as possible risk factors for sequelae, as well as female sex. The latter finding is remarkable seeing that in a previous study, male sex had been identified as a risk factor for having pFP among patients with Lyme disease [42], while in another study, female

Fig. 3 Trends in treatment for the two time periods 2006–2011 and 2012–2016, concerning the use of corticosteroids (CS), antibiotics (AB), and antivirals (AV). All pFP (**a**), idiopathic pFP (**b**), neuroborreliosis (**c**)
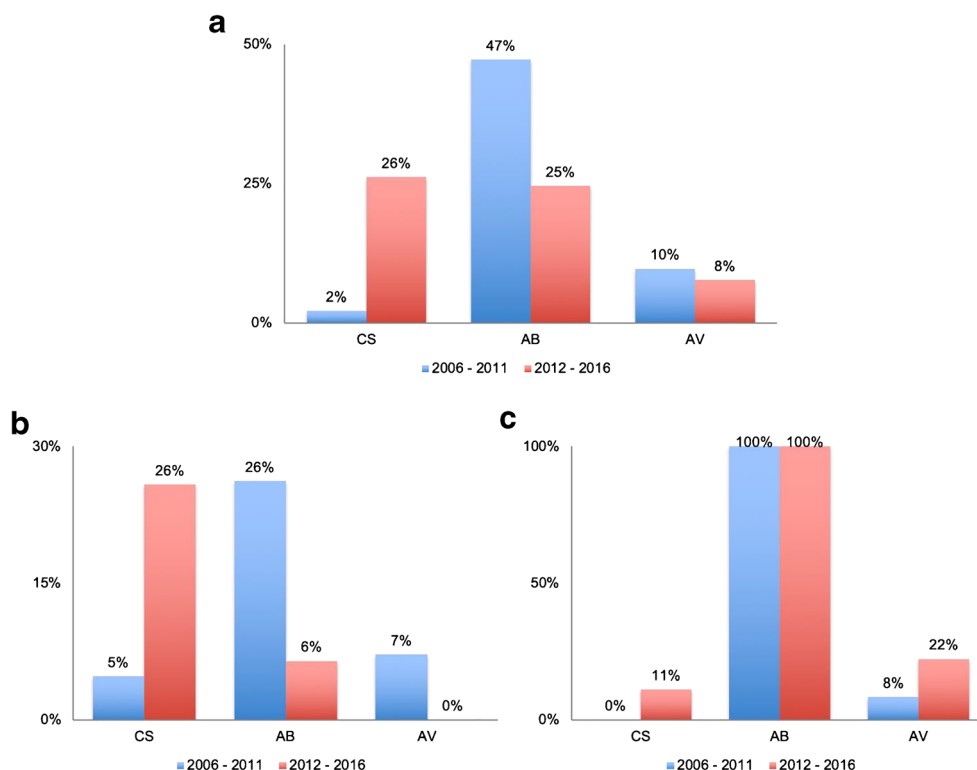
sex was associated with a higher risk of recurrence among patients with pFP [43]. The rate of recurrence in idiopathic pFP of 10/37 (27%) is seemingly higher than in other studies, in which rates between 0.8 and 19% have been reported [6, 38, 44, 45]. This discrepancy could be partly explained by a more thorough follow-up in our study. Moreover, other etiologies than idiopathic pFP could have

biased the recurrence rates in other studies due to the heterogeneity of cohorts and less strict group stratifications, which is somehow reflected in the broad distribution of recurrence rates over several studies. Standardized outcome measures that have recently been proposed may help harmonize future studies and render them more comparable with each other [46].

Table 2 Data on follow-up (F/U)

	Idiopathic pFP	CNS infection-associated pFP	p	RTI-associated pFP	p
F/U available	37/73	24/45	ns	13/37	ns/ns
F/U interval in years, median (IQR)	7.5 (6.2–8.6)	8.3 (7.1–9.8)	ns	5.5 (3.0–10.0)	ns/ns
Recurrence	10/37	0/24	0.004	2/13	ns/ns
Permanent sequelae	10/37	5/24	ns	6/13	ns/ns
Temporary symptoms					
Paresthesia	8/37	10/24	ns	1/13	ns/ns
Fatigue	3/37	7/24	ns	2/13	ns/ns
Headache	10/37	10/24	ns	7/13	ns/ns
Vertigo	6/37	6/24	ns	2/13	ns/ns
Concentration difficulty	8/37	2/24	ns	1/13	ns/ns
Sleep disorder	2/37	2/24	ns	0/13	ns/ns
Speech disturbance	2/37	0/24	ns	0/13	ns/ns
Hearing impairment	0/37	1/24	ns	0/13	ns/ns
Limitation in daily activity	3/37	6/24	ns	2/13	ns/ns
High school attendance/degree	11/18	17/21	ns	6/10	ns/ns

The generalizability of our results has to be handled with caution; the proportion of NB may be higher in some parts of the world [47] and lower in other parts, although undamped climate change may affect both incidence and seasonality of borreliosis [48]. Still, there is a lack of extensive data on children with pFP concerning potential infectious etiologies, and further studies, especially from other geographic backgrounds, are warranted.

Novel diagnostic techniques, such as next-generation sequencing (NGS), have helped to detect new organisms [49–52] or long-known but atypically presenting pathogens [53] in CNS infections. It remains to be seen how NGS can be exploited to fully elucidate hitherto underestimated etiologies of pFP. In conclusion, our data support the importance of infectious disease etiology in pediatric pFP patients, with potential impact on the long-term outcome. Novel diagnostics may help to unveil other causes of pFP that may falsely be labelled idiopathic.

Compliance with ethical standards

This study was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University (2017-541N-MA). Informed consent was obtained from patients prior to the follow-up interview.

Conflict of interest   The authors declare that they have no conflict of interest.

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