Comorbidity of PFAPA (periodic fever, aphthous stomatitis, pharyngitis and adenitis) patients: a case control study

U. Lantto[1,2], S. Kettunen[1], T. Tapiainen[1,3], P. Koivunen[1,2], M. Uhari[1,3], M. Renko[1,4,5]

[1]PEDEGO Research Unit, Medical Research Centre, University of Oulu; [2]Department of Otorhinolaryngology, Head and Neck Surgery, Oulu University Hospital; [3]Department of Children and Adolescents, Oulu University Hospital; [4]Tampere Centre for Child Health Research, University of Tampere; [5]Department of Children and Adolescents, Tampere University Hospital, Finland.

Ulla Lantto, MD
Sallamaaria Kettunen, BM
Terhi Tapiainen, MD, PhD
Petri Koivunen, MD, PhD
Matti Uhari, MD, PhD
Renko Marjo, MD

Please address correspondence to:
Dr Ulla Lantto,
Department of Otorhinolaryngology - Head and Neck Surgery,
Oulu University Hospital,
P.O. Box 21,
FIN-90029 Oulu, Finland.
E-mail: ulla.lantto@ppshp.fi, ulla.lantto@student.oulu.fi

Received on September 5, 2017; accepted in revised form on February 6, 2018.

Clin Exp Rheumatol 2018; 36 (Suppl. 115): S129-S134.

Key words: periodic fever, PFAPA, autoinflammatory syndrome, comorbidity, infection.

Competing interests: none declared.

ABSTRACT

Objective. *To compare the long-term morbidity of patients with periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome treated by tonsillectomy (TE) in childhood to that of matched controls.*

Methods. *We identified 132 PFAPA patients from the medical records treated by TE in 1987-2007 in Oulu University Hospital, Finland. Altogether 119 patients participated the follow-up study and 94 were clinically examined on average 9.0 years after TE. The controls consisted of 230 randomly selected age-, sex-, and birth place-matched individuals from the Population Register Center of Finland. The patients and controls completed a detailed questionnaire about their current health and the data were compared.*

Results. *Self-estimated general health was good and growth was normal among PFAPA patients and controls at long-term follow-up. There were no between-group differences in the occurrence of autoimmune or other chronic diseases. Thirty percent of the PFAPA patients and 13% of the controls reported infections as causes of hospital visits during their lifetime ($p<0.001$). Usage of antibiotics during lifetime was reported by 99% of the PFAPA patients and by 88% of the controls ($p= 0.009$). Twelve percent of PFAPA patients and 0.4% of the controls reported oral thrush in their history ($p=0.003$).*

Conclusion. *The health of the PFAPA patients was as good as that of healthy matched controls. Autoimmune or other chronic diseases were not more prevalent among PFAPA patients treated with TE in childhood than among controls. Respiratory infections and oral thrush were more common among the PFAPA patients than controls.*

Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) is a paediatric fever syndrome first described by Marshall *et al.* (1). The cumulative incidence of the syndrome in children up to five years of age is estimated to be 2.3/10,000 (2) making PFAPA the most common periodic fever syndrome of childhood (3, 4). Although the aetiology of PFAPA is unknown, tonsillectomy (TE) has been shown to be an effective treatment for the syndrome (5-7). The diagnosis of PFAPA is based on the clinical course of the disease. The principal characteristics of PFAPA are unexplained and regular fever episodes, which are interspersed by healthy periods between (4, 8, 9).

PFAPA has been suggested to be an autoinflammatory disease due to an abnormal INFγ-dependent (Th1) inflammatory response (10, 11), possibly triggered by microbial or other stimuli in the tonsils (12-15). Other autoinflammatory periodic fever syndromes, such as familial Mediterranean fever (FMF), tumour necrosis factor receptor-associated periodic syndrome (TRAPS), and hyper immunoglobin D syndrome (HIDS), often have permanent or progressive long-term sequealae (16). PFAPA syndrome may also have a chronic nature, with an average duration of four to five years if untreated (2, 17-19). However, unlike other periodic fever syndromes, PFAPA can be effectively treated by removing the tonsils (5-7, 9, 20).

Data about general health and other diagnoses of PFAPA patients are very limited (17). As the genetic background, aetiology, and exact pathogenesis of PFAPA are unclear, we hypothesised that its occurrence may be associated with other inflammatory disorders,

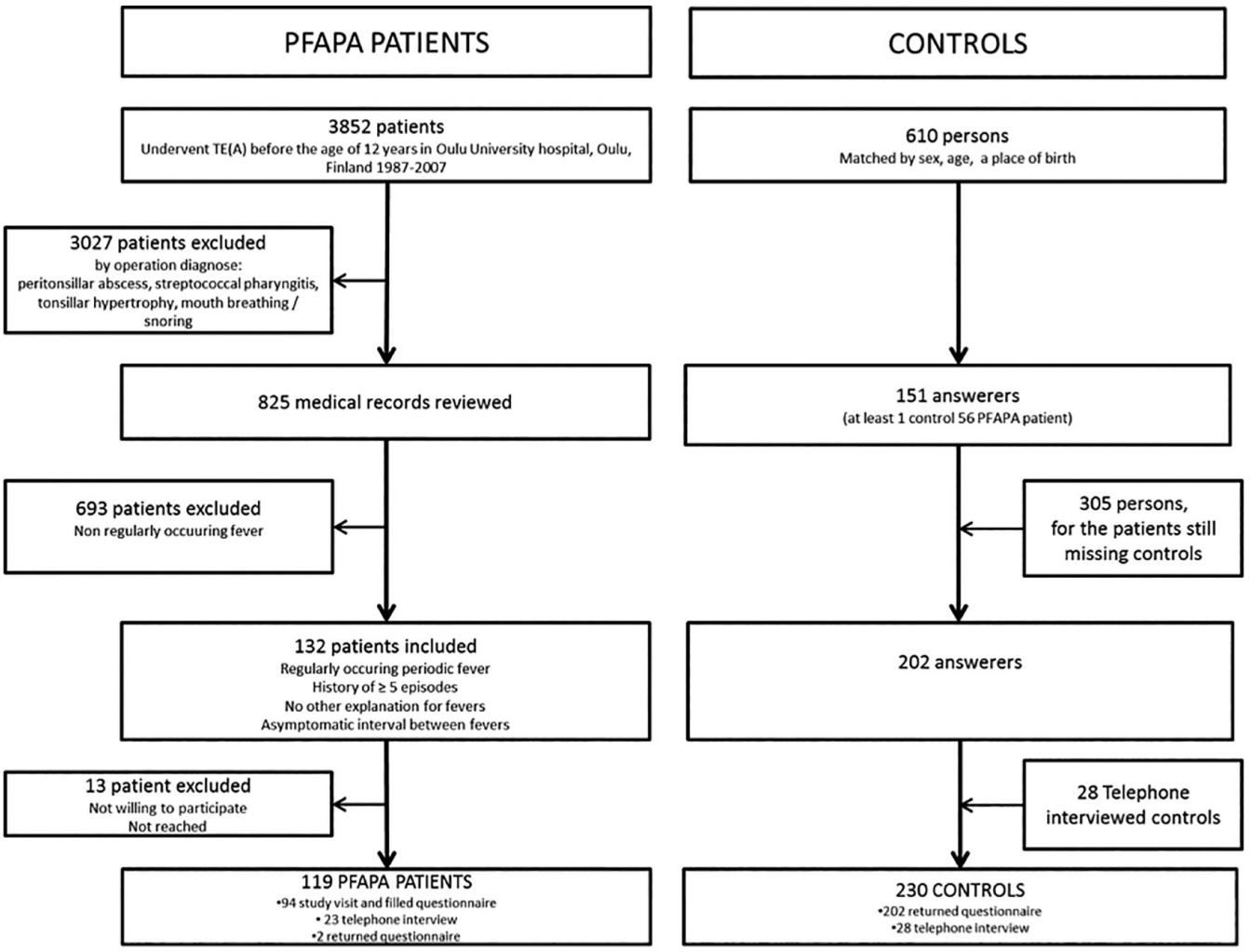

Fig. 1. Flow chart illustrating how the study population and the controls were obtained.

such as autoimmune diseases, allergies, or susceptibility to infections. We have previously published a 9 year follow up of classic and incomplete PFAPA patients after TE (9). To elucidate the long-term health of PFAPA patients before and after TE we collected data of growth and other morbidity from this cohort and compared these to that of matched controls.

Patients and methods

We identified PFAPA patients from all children who had underwent TE or adenotonsillectomy (TEA) under the age of 12 years in Oulu University Hospital, Finland, between years 1987 and 2007. The study design has been previously described in detail (9). This hospital is a tertiary hospital, which serves a population of 405,635 people in the Northern Ostrobothnia Hospital District (Statistics Finland 31.12.2014). It is the only hospital in the area responsible for the diagnosis and treatment of all childhood periodic fever syndromes. The protocol of the study was approved by the Regional Ethics Committee of the Northern Ostrobothnia Hospital District, Oulu, Finland. All the patients and controls and/or their parents gave their written informed consent.

In brief, 132 of 3852 children who had undergone TE/TEA were included in the study (9). The children had experienced at least five fever episodes at regular intervals and had completely asymptomatic intervals between these episodes, with no other explanation for the fevers other than PFAPA (Fig. 1). They were invited for a study visit during years 2009 and 2010. We posted them a detailed questionnaire of the symptoms before and after TE/TEA and long-term postoperative condition and health. Ninety-four of the 132 patients (71.2%) participated the follow-up study visit, which included a thorough clinical examination. Four patients did not wish to take part in the study, eight could not be reached, and one had died in a drowning accident. Follow up information was received from 119/132 (90.2%) PFAPA patients who had underwent TE/TEA between 1990 and 2007. Outcome data concerning PFAPA symptoms among 108 of these 119 patients has been previously published (9). At the time of study visit, approximately nine years after the TE/TEA, 3/119 (3%) patients reported relapse of PFAPA syndrome years after the TE and 2/119 (2%) patients reported low grade fevers not resembling PFAPA syndrome after the TE.

Controls were randomly selected from

the database of the Population Register Center of Finland, which includes data on all Finnish citizens alive in 2014. The controls were matched by sex, age, and place of birth. For each PFAPA patient, the aim was to have two sex-, age- (born within ± 1 year), and birth place-matched (born in the same municipality) controls. A questionnaire was mailed to 915 prospective controls, and we received 202 completed questionnaires. Three of the controls were excluded due to a history of PFAPA-like symptoms. To ensure at least one control for each PFAPA patient, 28 of the original 915 controls who had not responded to the mailed questionnaire were contacted by telephone. The questionnaires were then completed via telephone interviews. Finally, 230 control subjects were enrolled (Fig. 1). In the final study population, 1/119 (0.8%) PFAPA patient had four controls, 16/119 (13%), had three controls, 75/119 (63%) had two controls, and 27/119 (22%) had one control.

A predesigned form was used to collect information on the general health and well-being of the cases and controls. Ninety-four of the 119 (79%) PFAPA patients attended the hospital for a study visit and were interviewed at that time. The remaining PFAPA patients were interviewed by phone (23/119, 19%) or a mailed questionnaire (2/119, 1.7%). All the controls were interviewed by phone (28/230, 12%) or mail (202/230, 88%). In 117/119 (98%) PFAPA patients and 195/226 (86%) controls, the questionnaires were completed with the assistance of parents.

As our primary hypothesis was that PFAPA syndrome might be associated with other diseases and disorders of the immune system, we collected data on physician and hospital visits due to diagnosed or suspected infections, allergies, and autoimmune diseases, in addition to data on the use of antibiotics. We also collected data on other diseases, symptoms, regular medications, and surgical histories. To distinguish symptoms and signs due to PFAPA syndrome, data on hospital visits by the PFAPA patients before and after the TE/TEA were recorded separately. For the analyses, the reported causes of physician or hospital visits were grouped into seven main categories (infections, autoimmune diseases, traumas, migraine, asthma, neurological problems, and any kind of tumour). To estimate the social class of the family, the parents were asked to give their occupations in the questionnaire, and they were then then grouped into seven categories.

With the assistance of their parents, the cases and controls estimated their general health on a Likert scale as 0-10, where 0 was the poorest possible health and 10 denoted excellent health. The heights and weights of the PFAPA patients were measured at the study visit. The controls recorded their heights and weights in the questionnaire form. The new Finnish age- and gender-specific growth standards for children and adolescents aged 0-20 years was used to transform the length measurements into age- and gender-specific *z*-scores. Weight was assessed as the relative percentage difference from the gender-specific median weight-for-height (21). The mean age of the PFAPA patients at the time of the study visit or interview was 13.3 years (SD 5.4, n=119), and the mean age of the controls was 15.7 years (SD 5.4, n=230). The ethnic background of all the patients and controls was white Caucasian, North European. The clinical profiles of the PFAPA patients are reported in Table I.

Table I. Characteristics of the PFAPA patients in the follow-up study (n=119).

	PFAPA patients n=119
Sex, male (%)	79 (66.4%)
Age at onset of fever episodes, years, mean (SD)	2.7 (2.4, n=113)
Age at the time of TE/TEA, years, mean (SD)	4.4 (2.6)
Age at the time of the study visit/interview (SD)	13.4 (5.5)
Follow-up time from the onset of the syndrome to the study visit clinical control/interview, years, mean (SD)	10.4 (4.9, n=113)
Follow-up time after TE/TEA, years, mean (SD)	9.0 (4.7)
Prompt and constant response to TE/TEA (%)	114 (95.8%)
Length of PFAPA cycle, days, mean (SD)	27.6 (9.2, n=113)
Duration of fever phase, days, mean (SD)	4.1 (1.3, n=107)
Highest measured body temperature °C, mean (SD)	39.3 (0.7)
Onset of the syndrome under the age of five years (%)	91 (80.5%, n=113)
Aphthous stomatitis at the time of fever (%)	31 (27.2%, n=114)
Pharyngitis at the time of fever (%)	69 (59.5%, n=116)
Adenitis at the time of fever (%)	62 (52.5%, n=118)
Fever as the only symptom of PFAPA (%)	24 (31.2%, n=109)
Pauses in the syndrome before TE/TEA, (%)	23 (20.5 %, n=112)
PFAPA cases in first-degree relatives, (%)	39 (32.8%)

PFAPA: periodic fever, aphthous stomatitis, pharyngitis, and adenitis; TE: tonsillectomy; TEA: adenotonsillectomy.

Statistical analysis

All the statistical analyses were performed with the IBM SPSS Statistics program, vs. 22.0 (IBM Corp, Armonk, New York). Proportions were compared between the PFAPA patients and controls, and differences and their 95% confidence intervals (CI) were calculated. The standard normal deviate test (SND) was used to analyse the statistical significances of the differences in proportions. For continuous variables, means and standard deviations (SD) or medians, with ranges were calculated. To test the statistical significance of the differences, a *t*-test or Mann–Whitney *U* test was used, depending on the distributions. The occurrence of diseases in the cases and controls was compared using a univariate logistic regression model, adjusted for the participant's age at the time of the data collection and the social class of the family, as determined by the occupation of the father and adjusted Odds Ratios (ORs) with their CIs and adjusted *p* values are reported.

Results

The self-reported general health of the PFAPA patients and controls was good at the time of the follow up (mean

Table II. Numbers and proportions of 119 PFAPA patients and 230 controls with reported current diseases and diagnoses in history, at the mean age of 13.3 years (patients) or 15.7 years (controls). Odds ratios are adjusted for age at data collection and social class of the family.

Cause of physician visit	PFAPA patients N (%), n = 119	Controls N (%), n = 230	Adjusted OR (95% CI)*	*p*-value
Current diseases				
Allergies	21 (17.9%)	66 (28.7%)	0.832 (0.397-1.744)	0.626
- Pollen allergy	7 (6.0%, n = 117)	39 (17.0%)	0.347 (0.147-0.820)	0.016
- Animal allergy	6 (5.1%, n = 117)	19 (8.3%)	0.725 (0269-1.959)	0.527
- Food allergy	8 (6.8%, n = 117)	22 (9.6%)	0.444 (0.173-1.144)	0.093
- Drug allergy	4 (3.4%, n = 117)	10 (4.3%)	0.779 (0.232-2.617)	0.686
Asthma	8 (6.7%)	15 (6.5%)	1.299 (0.480-3.147)	0.667
Autoimmune diseases	3 (2.5%)	9 (3.9%)	1.055 (0.267-4.171)	0.939
Migraine	3 (2.5%)	9 (3.9%)	1.123 (0.274-4.595)	0.872
Medical history				
Use of antibiotics	115 (99.1%, n = 116)	201 (88.2%, n = 228)	14.819 (1.967-111.640)	0.009
Fungal infections	21 (18.1%, n = 116)	16 (7.0%)	3.619 (1.681-7.792)	0.001
- Oral candidiasis	14 (12.0%, n = 117)	1 (0.4%)	23.904 (3.041-187.964)	0.003
- Other fungal infections	7 (6.0%, n = 117)	15 (6.5%)	1.384 (0.509-3.763)	0.525
Physical traumas	13 (10.9%)	14 (6.1%)	2.401 (1.022-5.640)	0.045
Tumors*	4 (3.4%)	6 (2.6%)	1.877 (0.303-5.372)	0.739

CNS: central nervous system; CI: confidence interval; OR: odds ratio; PFAPA: periodic fever, aphthous stomatitis, pharyngitis, and adenitis.
*No malignant tumours were reported.

Table III. Numbers and proportions of 119 PFAPA patients and 230 controls with hospital stays from birth to the mean age of 17 years.

	PFAPA patients (n=119)			Controls (n=230)		
	Before TE/TEA (n=115)	After TE/TEA (n=116)	All patients who reported hospital visits	All controls who reported hospital visits	*p*-value	Proportion difference (95% CI)
Autoimmune disease	0 (0.0%)	2 (1.7%)	2 (1.7%)	7 (3.0%)	0.503	-1.4% (-4.8 to 3.1%)
Allergy/atopy	5 (4.3%)	4 (3.4%)	9 (7.6%)	15 (6.5%)	0.664	1.0% (-4.3 to 7.8%)
Infections	24 (20.9%)	16 (13.8%)	36 (30.3%)	31 (13.5%)	0.0002	16.8% (7.8 to 26.5%)
- Otitis	17 (14.8%)	6 (5.2%)	21 (17.76%)	11 (4.8%)	<0.0001	12.9% (6.2 to 21.1%)
- Pneumonia	0 (0%)	2 (1.7%)	2 (1.8%)	1 (0.4%)	0.154	1.2% (-1.0 to 5.5%)
- Superior respiratory infection	2 (1.7%)	1 (0.9%)	3 (2.5%)	4 (1.7%)	0.465	0.8% (-2.3 to 5.6%)
- Laryngitis	5 (4.3%)	0 (0%)	5 (4.2%)	0 (0.0%)	0.002	4.2% (1.8 to 9.5%)
- Tonsillitis	0 (0%)	1 (0.9%)	1 (0.8%)	2 (0.9%)	>0.9999	-0.03% (-2.4 to 3.8%)
- Gastrointestinal infection	1 (0.9%)	2 (1.7%)	3 (2.5%)	8 (3.5%)	0.550	-1.0% (-4.7 to 4.0%)
- CNS infection*	2 (1.7%)	1 (0.9%)	3 (2.5%)	1 (0.4%)	0.065	2.1% (-0.3 to 6.8%)
Asthma	3 (2.6%)	3 (2.6%)	5 (4.2%)	8 (3.5%)	0.574	0.7% (-3.3 to 6.3%)
Migraine	1 (0.9%)	2 (1.7%)	3 (2.5%)	3 (1.3%)	0.260	1.2% (-1.7 to 6.0%)
Neurological problem	6 (5.2%)	6 (5.2%)	11 (9.2%)	12 (5.2%)	0.122	4.0% (-1.4 to 11.0%)
Physical trauma	2 (1.7%)	5 (4.3%)	7 (5.9%)	14 (6.1%)	>0.999	0.2% (-5.2 to 6.1%)
Tumors*	1 (0.9%)	3 (2.6%)	3 (2.5%)	5 (2.2%)	>0.999	0.3% (-3.0 to 5.2%)
Operative treatments		42 (35.3%)	70 (30.4%)		0.357	
- Tympanostomy		14 (11.8%)	11 (4.8%)		0.016	
- Trauma		6 (5%)	3 (1.3%)		0.037	
- Tumors*		1 (0.8%)	4 (1.7%)		0.503	
- Congenital anomaly		1 (0.8%)	1 (0.4%)		0.634	

CNS: central nervous system; CI: confidence interval; PFAPA: periodic fever, aphthous stomatitis, pharyngitis, and adenitis; TE: tonsillectomy.
*No malignant tumours were reported.

9.1/10 in both groups). In the 94 PFAPA patients who attended the follow-up visit, no acute or chronic diseases not mentioned in their medical histories or reported in the questionnaires were diagnosed. The mean age- and gender-specific *z*-scores of height was -0.2 (SD 1.2, n=112) among PFAPA patients and -0.2 in the controls (SD 1.08, n=222). A relative percentage difference from the gender-specific median weight-for-height of PFAPA patients was +5.0% (SD 15.4, n=112), and in controls +7.5% (SD 18.6, n=216), (*p*=0.278).

Autoimmune diseases were reported by three of 119 (2.5%) PFAPA patients and 9/230 (3.9%) controls, with celiac disease being the most common autoimmune disease (1/119 PFAPA patients and 4/230 controls; *p*=0.555) (Table II). More controls reported allergies (21/119, 18%) than did PFAPA patients (66/230, 29%). However, when adjusted, the difference was not statistically

significant (p=0.626). Pollen allergies were significantly less common in the cases (7/117, 6.0%) than in the controls (39/230, 17%) (p=0.016). Regarding medication usage, 10/118 (9%) PFAPA patients and 30/230 (13%) controls reported regular usage (p=0.17). There were no between-group differences in the reported occurrences of any other chronic diseases (Table II).

Hospital visits due to infections during their lifetime were reported by 36/119 (30%) PFAPA patients and 31/230 (13%) controls (p<0.001). Other reported diseases or conditions, other than infections, leading to hospital visits were as common in the histories of the cases as in the controls (Table III).

Use of antibiotics during lifetime was reported by almost all the PFAPA patients (115/116, 99%) and by 201/228 (88%) controls (p=0.009) (Table II). The mean age at the time of the first antibiotic treatment was 15.4 months (SD 19.1) among the cases and 30.5 months (SD 49.1) among the controls (p<0.001). Twenty-one of 116 (18%) PFAPA patients and 16/230 (7.0%) controls reported a history of fungal infections (p=0.001). With regards to subgroups of fungal infections, 14/117 (12%) PFAPA patients and 1/230 (0.4%) controls reported a history of oral thrush (p=0.003, OR 23.9, 95% CI 3.0- 188.0).

PFAPA cases in the family were reported by 39/118 (33%) of PFAPA patients. There were no significant differences in self-estimated general health, growth, reported diseases, or use of antibiotics between the PFAPA patients with or without a positive family history of PFAPA (data not shown).

Discussion

In this long-term follow up the patients who underwent TE/TEA in childhood because of PFAPA syndrome had excellent self-estimated general current health and it did not differ from that of matched controls. The incidence of autoimmune and other chronic disease diagnoses was similar in the PFAPA patients and controls, except for pollen allergies, which were less common in the PFAPA cases than in the controls.

PFAPA syndrome is considered as an autoinflammatory disorder as well as other periodic fever syndromes like HIDS, TRAPS and MEF, which have mostly permanent and progressive nature and are associated with remarkable co-morbidities by adulthood (16). Unlike in those diseases, our controlled study shows the prognosis of PFAPA syndrome and a long-term outcome after TE to be good. There were no differences in the occurrence of autoimmune diseases, any other chronic diseases, use of regular medications, or reported operative treatments other that tympanostomy tube insertion between the groups.

In the cohort of Wurster *et al*., the only published cohort reporting data about other than infectious diseases in PFAPA patients, 12% had symptoms of allergic rhinitis and 8% food or drug allergy at the age of 20 years (17). In the present study, 18% of PFAPA patients and 29% of the controls had a diagnosed allergy. When the data were adjusted for age at the time of the survey, there were no statistically significant differences in the occurrence of any allergies between the PFAPA patients and controls, although pollen allergies remained significantly more common among the controls.

As shown by the medical histories of the PFAPA patients, in the present study, infections and the use of antibiotics were prevalent in our cohort. Similar findings were reported earlier in other PFAPA cohorts (2, 17). In the only published case–control study comparing the occurrence of infections in PFAPA patients and controls, recurrent otitis media and tympanostomy tube insertion were as common in PFAPA patients as in controls recruited from primary health care (22). It is difficult to study the lifetime history of infections among PFAPA patients, as the differential diagnosis of PFAPA is not easy in very young children. From the primary physician's point of view, the syndrome is rare, and the clinical state of the fever phases resembles that of common viral or bacterial infections. According to the data in the present study, 21% of the PFAPA patients reported a history of infections leading to hospitalisations before the TE/ TEA, and 14% reported a history of infections leading to hospitalisations after the treatment. In contrast, throughout their whole lifetime 14% of the controls reported a history of infections leading to hospitalisations. Thus, it is possible that PFAPA patients are more susceptible to infections than healthy controls, even after treatment.

As shown by the medical histories, oral thrush was significantly more common among the cases than the controls. However, the incidence of other fungal infections was similar among the cases and controls. As the use of antibiotics was more common among the PFAPA patients, this may have promoted the occurrence of oral candidiasis. However the finding is interesting in the light of the theory of triggered inflammasome being behind the syndrome (12, 13, 15). A previous study also reported that *Candida albicans* was able to trigger inflammasomes and cause pyroptosis, leading to inflammation (23). In particular, hyphae formation of *Candida* species is a strong trigger for production of the pro-inflammatory cytokine interleukin-1b (23). In addition, our previous research reported that *C. albicans* was significantly more common in the tonsils of PFAPA patients than in those of controls and suggested that it could be a possible trigger for PFAPA flares (14).

In published PFAPA cohorts, 6-45% of PFAPA patients reported a history of familial PFAPA cases (2, 17, 19, 24). In a long-term follow-up study of a PFAPA cohort, Wurster *et al*. reported that patients with persistent PFAPA were more likely to have a positive family history of the syndrome (44%) than patients with resolved symptoms (4%) (17). In the present study, the outcome of patients with a positive or negative PFAPA family history was equally good.

The present study is the first to compare the growth of PFAPA patients to that of controls. The growth of PFAPA patients treated with TE was similar to that of the matched controls in this study. Normal growth and development has been one of the classical diagnostic criteria for PFAPA (19) and the growth of PFAPA patients has been mentioned

to be normal in several cohorts (17-19, 25). As our study population was ethnically homogeneous, it was possible to use Finnish growth references for children and adolescents. As the growth of every child is regularly followed in child health clinics in Finland, the growth-related data collected by the questionnaires are very reliable.

The strengths of the present study are the long-term follow-up of a large cohort of PFAPA patients and the controlled study design. Although the data are based on medical records and questionnaires, errors in documentation of the information, as well as recall bias, are possible. To avoid recall bias, multiple questions were asked about a history of diagnosed diseases. In addition, the participants were asked about the reasons for hospital stays, which might be more memorable to the patients and their families. Another weakness of the study is that the study population included only PFAPA patients treated by TE/TEA and not PFAPA patients with a milder or shorter disease and spontaneous healing. Selection bias of the controls is possible, as the health of those willing to participate in the study might differ from that of unwilling individuals. Furthermore, the timing of the interviews of the controls might have influenced the results, even when adjusted in the analyses.

Conclusions

In conclusion, in this long-term follow-up study, the current health of PFAPA patients after tonsillectomy TE/TEA was good. The risk of chronic or autoimmune diseases was not increased in PFAPA patients, even among the PFAPA patients who reported a familial history of PFAPA.

References

1. MARSHALL GS, EDWARDS KM, BUTLER J, LAWTON AR: Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. *J Pediatr* 1987; 110: 43-6.
2. FØRSVOLL J, KRISTOFFERSEN EK, ØYMAR K: Incidence, clinical characteristics and outcome in Norwegian children with periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome; A population-based study. *Acta Paediatr Int J Paediatr* 2013; 102: 187-92.
3. TER HAAR N, LACHMANN H, OZEN S *et al.*: Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. *Ann Rheum Dis* 2013; 72: 678-85.
4. HOFER M, PILLET P, COCHARD M *et al.*: International periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome cohort: Description of distinct phenotypes in 301 patients. *Rheumatology* 2014; 53: 1125-9.
5. RENKO M, SALO E, PUTTO-LAURILA A *et al.*: A Randomized, Controlled Trial of Tonsillectomy in Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome. *J Pediatr* 2007; 151: 289-92.
6. GARAVELLO W, PIGNATARO L, GAINI L, TORRETTA S, SOMIGLIANA E, GAINI R: Tonsillectomy in children with periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome. *J Pediatr* 2011; 159: 138-42.
7. BURTON MJ, POLLARD AJ, RAMSDEN JD, CHONG LY, VENEKAMP RP: Tonsillectomy for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA). *Cochrane Database Syst Rev* 2014; 9: CD008669.
8. HAUSMANN JS, BIGGS C, DEDEOGLU F: Looking back at the diagnosis of PFAPA: A retrospecitve analysis of a prospective cohort study. *Pediatr Rheumatol* 2015; 13 (1).
9. LANTTO U, KOIVUNEN P, TAPIAINEN T, RENKO M: Long-Term Outcome of Classic and Incomplete PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis) Syndrome after Tonsillectomy. *J Pediatr* 2016; 179: 172, 177.e1.
10. BROWN KL, WEKELL P, OSLA V *et al.*: Profile of blood cells and inflammatory mediators in periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome. *BMC Pediatr* 2010; 10: 65.
11. STOJANOV S, HOFFMANN F, KÉRY A *et al.*: Cytokine profile in PFAPA syndrome suggests continuous inflammation and reduced anti-inflammatory response. *Eur Cytokine Netw* 2006; 17: 90-7.
12. BROWN KL, WEKELL P, KARLSSON A, BERG S: On the road to discovery in periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome. *Proc Natl Acad Sci USA* 2011; 108: E525.
13. TEJESVI MV, UHARI M, TAPIAINEN T *et al.*: Tonsillar microbiota in children with PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis) syndrome. *Eur J Clin Microbiol Infect Dis* 2016; 35: 963-70.
14. LANTTO U, KOIVUNEN P, TAPIAINEN T *et al.*: Microbes of the tonsils in PFAPA (Periodic Fever, Aphtous stomatitis, Pharyngitis and Adenitis) syndrome - A possible trigger of febrile episodes. *APMIS* 2015; 123: 523-9.
15. PETRA D, PETRA K, MICHAELA K *et al.*: Polyclonal, newly derived T cells with low expression of inhibitory molecule PD-1 in tonsils define the phenotype of lymphocytes in children with Periodic Fever, Aphtous Stomatitis, Pharyngitis and Adenitis (PFAPA) syndrome. *Mol Immunol* 2015; 65: 139-47.
16. CATTALINI M, SOLIANI M, LOPALCO G, RIGANTE D, CANTARINI L: Systemic and organ involvement in monogenic autoinflammatory disorders: a global review filtered through internists' lens. *Intern Emerg Med* 2016; 11: 781-91.
17. WURSTER VM, CARLUCCI JG, FEDER HM, EDWARDS KM: Long-term follow-up of children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. *J Pediatr* 2011; 159: 958-64.
18. PADEH S, BREZNIAK N, ZEMER D *et al.*: Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome: Clinical characteristics and outcome. *J Pediatr* 1999; 135: 98-101.
19. THOMAS KT, FEDER HM, JR, LAWTON AR, EDWARDS KM: Periodic fever syndrome in children. *J Pediatr* 1999; 135: 15-21.
20. MANTHIRAM K, LAPIDUS S, EDWARDS K: Unraveling the pathogenesis of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis through genetic, immunologic, and microbiologic discoveries: An update. *Curr Opin Rheumatol* 2017; 29: 493-9.
21. SAARI A, SANKILAMPI U, HANNILA M, KIVINIEMI V, KESSELI K, DUNKEL L: New Finnish growth references for children and adolescents aged 0 to 20 years: Length/height-for-age, weight-for-length/height, and body mass index-for-age. *Ann Med* 2011; 43: 235-48.
22. MANTHIRAM K, NESBITT E, MORGAN T, EDWARDS KM: Family history in periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome. *Pediatrics* 2016; 138: 3.
23. KRYSAN DJ, SUTTERWALA FS, WELLINGTON M: Catching Fire: Candida albicans, Macrophages, and Pyroptosis. *PLoS Pathog* 2014; 10: e1004139.
24. COCHARD M, CLET J, LE L *et al.*: PFAPA syndrome is not a sporadic disease. *Rheumatology* (UK) 2010; 49: 1984-7.
25. MARSHALL GS, EDWARDS KM, LAWTON AR: PFAPA syndrome. *Pediatr Infect Dis J* 1989; 8: 658-9.