Risk factors for periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome: A case–control study

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What is known:

- The pathogenesis and genetics of Periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome remain unsolved.
- PFAPA syndrome has been shown to cluster in families.

What is new:

- Maternal smoking and lack of breastfeeding are more common in patients with PFAPA syndrome than in the controls.
- Environmental risk factors may be important in the pathogenesis of the syndrome.

Abstract

The etiology and pathogenesis of periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome are unclear. We performed a case–control study to evaluate potential environmental or lifestyle factors associated with PFAPA morbidity. We enrolled 119 patients with PFAPA syndrome who had undergone tonsillectomy in Oulu University Hospital between 1987 and 2007. We recruited 230 controls, matched for sex, birth date and place from the database of the Population Register Center of Finland. All the patients and controls completed a questionnaire regarding exposure to environmental triggers during early childhood. Maternal smoking was more common among PFAPA syndrome patients than controls (23% vs. 14%; $P = 0.005$). PFAPA patients had lower breastfeeding rates than controls (94% vs. 99%; $P = 0.006$). No other environmental factors were associated with PFAPA syndrome, except having an aquarium at home ($P = 0.007$). The patient group also used natural or herbal medicines more often than the controls ($P = 0.01$).

Conclusion: Maternal smoking and lack of breastfeeding, known risk factors for common childhood infections, were more common in patients with PFAPA syndrome than in matched controls. Environmental factors may be important in the pathogenesis of PFAPA syndrome and should be evaluated in future studies.

Abbreviations

A	adenoidectomy
aOR	adjusted odds ratio
CI	Confidence interval
IL	Interleucin
NA	not applicable
OR	odds ratio
PFAPA	periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome
TE	Tonsillectomy
TEA	Adenotonsillectomy

Introduction

Periodic fever, aphthous, stomatitis, pharyngitis, adenitis (PFAPA) syndrome, which was first described by Marshall et al. in 1987, is the most common periodically occurring fever in children (1, 2). In PFAPA syndrome, febrile episodes lasting from 3 to 6 days reoccur at regular intervals in 3 to 8 week cycles (3). The symptoms most often manifest before the age of 5 years. Children with PFAPA syndrome are asymptomatic between febrile episodes (3).

The etiology and pathogenesis of PFAPA syndrome remain unknown. Recent studies support the hypothesis that PFAPA syndrome involves inflammasome-driven proinflammatory interleukin (IL)-1β production during febrile episodes (4, 5). Inflammasomes may be activated by microbes or other environmental stimuli (6, 7). Recent studies showed clear family clustering of PFAPA syndrome (8-11). However, whole exome sequencing failed to find a unique gene as the trigger of PFAPA syndrome (12). Familial clustering suggests that environmental factors may be involved in the pathogenesis of the syndrome. We performed a case–control study to evaluate potential environmental or lifestyle factors associated with PFAPA morbidity and the pathogenesis of PFAPA syndrome.

Materials and methods

PFAPA patients

Our study population comprised all PFAPA patients who were diagnosed with PFAPA syndrome and underwent a tonsillectomy (TE) or adenotonsillectomy (TEA) in Oulu University Hospital, Oulu, Finland between 1987 and 2007. Data were retrieved from the hospital's records, as previously described (13). In our hospital, TE has been the main treatment choice for PFAPA syndrome since the 1990s. As there is no specific diagnosis code for PFAPA syndrome, we reviewed the records of all patients who underwent a TE or TEA before the age of 12 years because of regularly reoccurring fevers. We defined a PFAPA patient as one who had had at least five

regularly occurring febrile episodes and remained fully asymptomatic between the febrile episodes. Other periodic fevers than PFAPA syndrome are extremely rare in Finland (14).

Control subjects

Controls were selected randomly from the database of the Population Register Center of Finland. The controls were matched with PFAPA syndrome patients by sex, birth date (± 1 year), and place of residence at the time of birth. To try to have at least two controls per PFAPA patient, 915 candidates were selected from the Population Register Center. The controls were approached by a mailed questionnaire.

Questionnaires

The questionnaire contained 25 questions regarding different risk factors during childhood. The socioeconomic status of the family was estimated by stratifying the occupational status of the parents into eight classes. The questionnaire included detailed questions about the type of housing and surrounding environment, duration of breastfeeding, day care attendance, sucking habits, vaccinations, hygiene practices, possible exposure to environmental chemicals and passive smoking, and exposure to pets and farm animals. Most of the questions in the survey focused on the subjects' histories in three age periods: < 2 years, 2–7 years, and > 7 years.

Statistical analysis

All analyses were performed using IBM SPSS statistics, version 18.0. For continuous variables, means with standard deviations in each group were calculated, in addition to the differences in means between groups and their confidence intervals (CI). Statistical differences between the groups were tested with the Student's *t* test and Mann–Whitney *U* test according to the distribution of the data.

A univariate logistic regression analysis was used to estimate the odds ratios (OR) of various risk factors. As the data on the controls were collected 3 years after the data on the PFAPA patients, logistic regression was used to adjust the age at the time when the questionnaire was filled. The socioeconomic status of the family as defined by occupation of mother or father was also adjusted. .Adjusted odds ratios (aOR), with their 95% CIs and *P*-values are presented.

Finally, we performed a multivariate logistic regression, including all variables with statistically significant differences in the univariate analyses, adjusted for age at the time of data collection and the social class of the family, as defined by the occupation of the mother or father.

Results

The search revealed 825 patients, and the medical records of these patients were reviewed (Fig. 1). In total, 132 patients fulfilled the inclusion criteria and were invited for an outpatient visit. Thirteen patients were not reached or did not respond. Thus, the study population comprised 119 PFAPA patients. In 74/119 (62 %) patients, there was a definite observation of at least one of the following symptoms during fever flares: aphthous stomatitis, pharyngitis or adenitis. There was one pair of siblings in the patient series. The mean age of the 119 patients in the study population at the onset of PFAPA symptoms was 2.7 years (SD 2.4) and 4.4 years (SD 2.6) at the time of TE or TEAs. The mean interval between febrile episodes (from the first day of a febrile episode to the first day of the next episode) was 27.6 days (SD 9.2), and the mean duration of a fever was 4.1 days (SD 1.3).

After three postings, 205 controls returned completed questionnaires. Three of these controls were excluded due to reports of PFAPA syndrome-like symptoms in their history. Twenty-eight additional controls were interviewed by telephone. Thus, the final study included data from 230 control subjects (Fig. 1). The data on the controls were collected 3 years after the data on the patients with PFAPA syndrome.

The study group consisted of 119 PFAPA syndrome patients, whose mean age was 13.3 years (SD 5.4) at the time of the interview and a control group consisting of 230 subjects, whose mean age was 15.7 years (SD 5.4) at the time of the data collection. In the PFAPA group, 60% (N = 71) of subjects were males, whereas 61% (N = 140) of subjects in the control group were males. There were no between-group differences in the social class of the family, as determined by the occupation of mother. The residential environment was similar in both groups. More PFAPA patients than controls had lived in apartments when they were aged < 7 years (Table 1).

PFAPA patients had lower breastfeeding rates than controls (94% vs. 99%; aOR: 0.1, CI: 0.02 to 0.5, P = 0.006), and the mean duration of breastfeeding was shorter in PFAPA patients compared to controls (7.0 months vs. 8.0 months, P = 0.08). More mothers of PFAPA patients smoked than mothers of controls (23% vs. 14%; aOR: 2.5, CI: 1.3 to 4.6, P = 0.005). Fathers' smoking habits did not differ significantly between the groups (Table 1).

At age < 2 years, the PFAPA patients had attended day care centers less often compared to the controls (23% vs. 31%; aOR: 0.6, CI: 0.3 to 1.0, P = 0.048). There was no difference in day care attendance at the age of 2–7 years. There were also no between-group differences in subjects having siblings or in the mean number of siblings (Table 1).

There were no between-group differences in exposures to fluoride toothpastes, pesticides, insecticides, or sunscreens (data not shown). The PFAPA patients reported significantly more frequent use of herbal medicines or naturopathic products than controls (Table 1).

Higher numbers of PFAPA patients than controls had an aquarium at home (26% vs. 14%; aOR: 2.3, CI: 1.3 to 4.1, P = 0.007). There were no between-group differences in histories of contact with domestic animals, including household pets (Table 2).

The adjusted multivariate model of variables that showed significant differences in the univariate analysis revealed that lack of breastfeeding, maternal smoking, having an aquarium at home, and

using herbal medicines or naturopathic products were independent factors affecting the risk of PFAPA syndrome (Table 3). The results were not influenced further by adjusting the modelling along the occupation of the father.

Discussion

In this case control study maternal smoking and lack of breastfeeding, known risk factors for common childhood infections, were more common in patients with PFAPA syndrome than in matched controls, even when controlling for the socioeconomic status of the family. Exposure to passive smoke induces inflammation processes in mucous membranes (15). Breastfeeding enhances protection against infectious diseases and supports the maturation of the immune system (16-18). In our study, the proportion of smokers among the mothers of the controls (14%) reflects the universal smoking habits of women in Finland (19). In this study, 23% of mothers of PFAPA patients smoked. Lack of breastfeeding was also more common in the PFAPA group as compared to the controls, and the duration of breastfeeding was shorter in the patient group.

The first reports of PFAPA syndrome were sporadic cases (1, 3). However, more familial cases were reported as the syndrome became better known and recognized (8-11). The syndrome seems to be multifactorial rather than monogenic (12). Familial occurrence, abnormal microbiome findings, and elevated IL-1b production support the idea of a multifactorial background (20). Environmental factors may also play a major role in the induction of inflammatory responses and symptoms of PFAPA.

Previous studies reported an association between PFAPA symptoms and proinflammatory cytokine IL-1β production (4, 5). Cheung et al. reported that a CARD8 polymorphism (CARD8-FS) in inflammasome-related genes was more common in PFAPA patients with a more severe phenotype (21). A TE, with removal of the microbial layer on the tonsils, in addition to lymphatic tissue, is a highly effective treatment for PFAPA syndrome (22). Dysregulation of cytokine production may also be triggered by microbes or their metabolic products (23, 24). In our previous study, PFAPA patients' tonsils yielded Candida and Cyanobacteria more often than the tonsils of controls, and Cloacibacterium was isolated only from PFAPA patients' tonsils (6, 7). The results suggest that

microbial activity, together with exposure to various triggers, such as maternal smoking, with known immunomodulatory effects may lead to the development of PFAPA syndrome. Both Cyanobacteria and Cloacibacteria are water microbes (25, 26). In the present study, more PFAPA patients than controls had an aquarium at home. The water in an aquarium might provide a source of respiratory microbial flora.

The main strengths of our study were a large sample size and healthy controls as a comparison group. Nevertheless, epidemiological data are vulnerable to many sources of bias. Response rate in the control group was only 25% which may lead to selection bias. The main limitation in the present study was possibility of recall bias. The same survey was used in both groups, the controls completed the questionnaire 3 years after the PFAPA group. This was accounted for by adjusting the analyses for the age upon completion of the questionnaire. In addition, the PFAPA cases completed the survey during an outpatient visit, where they had an opportunity to ask about any questions they found unclear. In contrast, most of the controls completed a mailed questionnaire in their homes. One limitation of this study is that all PFAPA patients in this cohort had underwent TE and the results may thus be applied only to the most serious cases.

All cases in this patient cohort did not have either aphthous stomatitis, pharyngitis or adenitis during the fever flares. These signs have traditionally been required to the diagnosis of PFAPA (3). However, we have previously shown that the cases with fever as an only symptom are otherwise similar and respond to TE as well as the classic cases (13). Recently a large international survey showed that most of the clinicians taking care of these patients do not demand the oropharyngeal symptoms for the diagnosis of PFAPA (27).

In conclusion, in this case–control study, maternal smoking, the absence or short duration of breastfeeding, contact with an aquarium at home, and use of herbal and naturopathic products were more common in children with PFAPA syndrome than healthy controls. These associations

emphasize the possibility that environmental risk factors may act as triggers for inflammatory processes, probably by altering the microbiota of the respiratory tract. Environmental factors may be important in the pathogenesis of PFAPA syndrome and should be evaluated in future studies.

Authors contributions. KS collected the data on the controls, participated in the analyses of the data and wrote the first draft of the manuscript. UL collected the data on the cases and revised the manuscript. PK participated in the study design and revised the manuscript. TT participated in the analyses of the data and revised the manuscript. MU participated in the study design and revised the manuscript. MR participated in the study design, performed data analyses, supervised drafting and revising the manuscript. All authors interpreted the data, contributed to the intellectual content, reviewed the manuscript and approved the final version of the manuscript as submitted.

Compliance with Ethical Statements

Conflict of interest. The authors do not have conflicts of interest.

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Informed consent and ethical approval. This study was approved by the ethical committee of Northern Osthrobothnia hospital district. Informed consent was obtained from the subjects, guardians, or both, depending on the age of the subjects.

References

1. Marshall GS, Edwards KM, Butler J, Lawton AR. Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. J Pediatr. 1987 Jan;110(1):43-6.

2. Forsvoll J, Kristoffersen EK, Oymar 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. 2013 Feb;102(2):187-92.

3. Thomas KT, Feder HM,Jr, Lawton AR, Edwards KM. Periodic fever syndrome in children. J Pediatr. 1999 Jul;135(1):15-21.

4. Kolly L, Busso N, von Scheven-Gete A, Bagnoud N, Moix I, Holzinger D, et al. Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome is linked to dysregulated monocyte IL-1beta production. J Allergy Clin Immunol. 2013 Jun;131(6):1635-43.

5. Stojanov S, Hoffmann F, Kery A, Renner ED, Hartl D, Lohse P, et al. Cytokine profile in PFAPA syndrome suggests continuous inflammation and reduced anti-inflammatory response. Eur Cytokine Netw. 2006 Jun;17(2):90-7.

6. Lantto U, Koivunen P, Tapiainen T, Glumoff V, Hirvikoski P, Uhari M, et al. Microbes of the tonsils in PFAPA (periodic fever, aphtous stomatitis, pharyngitis and adenitis) syndrome - a possible trigger of febrile episodes. APMIS. 2015 Jun;123(6):523-9.

7. Tejesvi MV, Uhari M, Tapiainen T, Pirttila AM, Suokas M, Lantto U, et al. Tonsillar microbiota in children with PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis) syndrome. Eur J Clin Microbiol Infect Dis. 2016 Jun;35(6):963-70.

8. Adachi M, Watanabe A, Nishiyama A, Oyazato Y, Kamioka I, Murase M, et al. Familial cases of periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. J Pediatr. 2011 Jan;158(1):155-9.

9. Hofer M, Pillet P, Cochard MM, Berg S, Krol P, Kone-Paut I, et al. International periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome cohort: Description of distinct phenotypes in 301 patients. Rheumatology (Oxford). 2014 Jun;53(6):1125-9.

10. Wurster VM, Carlucci JG, Feder HM,Jr, Edwards KM. Long-term follow-up of children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. J Pediatr. 2011 Dec;159(6):958-64.

11. Manthiram K, Nesbitt E, Morgan T, Edwards KM. Family history in periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome. Pediatrics. 2016 Sep;138(3):10.1542/peds.2015-4572.

12. Di Gioia SA, Bedoni N, von Scheven-Gete A, Vanoni F, Superti-Furga A, Hofer M, et al. Analysis of the genetic basis of periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome. Sci Rep. 2015 May 19;5:10200.

13. 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 Dec;179:172,177.e1.

14. Korppi M, Korhonen J, Lindstrom K, Mononen T. Genetic fever--internet consultation, mutation in the envelope. Duodecim. 2003;119(16):1567-71.

15. Amatngalim GD, Broekman W, Daniel NM, van der Vlugt LE, van Schadewijk A, Taube C, et al. Cigarette smoke modulates repair and innate immunity following injury to airway epithelial cells. PLoS One. 2016 Nov 9;11(11):e0166255.

16. Iyengar SR, Walker WA. Immune factors in breast milk and the development of atopic disease. J Pediatr Gastroenterol Nutr. 2012 Dec;55(6):641-7.

17. Hosea Blewett HJ, Cicalo MC, Holland CD, Field CJ. The immunological components of human milk. Adv Food Nutr Res. 2008;54:45-80.

18. Duijts L, Ramadhani MK, Moll HA. Breastfeeding protects against infectious diseases during infancy in industrialized countries. A systematic review. Matern Child Nutr. 2009 Jul;5(3):199-210.

19. Reitan T, Callinan S. Changes in smoking rates among pregnant women and the general female population in australia, finland, norway, and sweden. Nicotine Tob Res. 2017 Mar 1;19(3):282-9.

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 Sep;29(5):493-9.

21. Cheung MS, Theodoropoulou K, Lugrin J, Martinon F, Busso N, Hofer M. Periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis syndrome is associated with a CARD8 variant unable to bind the NLRP3 inflammasome. J Immunol. 2017 Mar 1;198(5):2063-9.

22. Renko M, Salo E, Putto-Laurila A, Saxen H, Mattila PS, Luotonen J, et al. A randomized, controlled trial of tonsillectomy in periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome. J Pediatr. 2007 Sep;151(3):289-92.

23. Joly S, Ma N, Sadler JJ, Soll DR, Cassel SL, Sutterwala FS. Cutting edge: Candida albicans hyphae formation triggers activation of the Nlrp3 inflammasome. J Immunol. 2009 Sep 15;183(6):3578-81.

24. Witzenrath M, Pache F, Lorenz D, Koppe U, Gutbier B, Tabeling C, et al. The NLRP3 inflammasome is differentially activated by pneumolysin variants and contributes to host defense in pneumococcal pneumonia. J Immunol. 2011 Jul 1;187(1):434-40.

25. Jurelevicius D, Alvarez VM, Marques JM, de Sousa Lima LR, Dias Fde A, Seldin L. Bacterial community response to petroleum hydrocarbon amendments in freshwater, marine, and hypersaline water-containing microcosms. Appl Environ Microbiol. 2013 Oct;79(19):5927-35.

26. Revetta RP, Gomez-Alvarez V, Gerke TL, Curioso C, Santo Domingo JW, Ashbolt NJ. Establishment and early succession of bacterial communities in monochloramine-treated drinking water biofilms. FEMS Microbiol Ecol. 2013 Dec;86(3):404-14.

27. Manthiram K, Li SC, Hausmann JS, Amarilyo G, Barron K, Kim H et al. Physicians' perspectives on the diagnosis and management of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome. Rheumatol Int. 2017 Jun;37(6):883-889.

Figure legends

Figure 1. Flow chart of the recruitment of the patients with PFAPA syndrome and controls.

Table 1. Social risk factors and hygiene practices during childhood in 119 PFAPA cases and 230 controls. Univariate regression model, adjusted for age at time of data collection and the social class of the family, as determined by the occupation of the mother.

Environmental factors	**Cases**	**Controls**	**aOR**	**95% CI**	***P***
Born by a cesarean section, *N* (%)	15 (13.0%)	33 (14.5%)	0.974	0.493-1.923	0.939
Having siblings, *N* (%)	102 (90.3%)	200 (87.7%)	0.962	0.445-2.078	0.921
Breastfed, *N* (%)	103 (93.6%)	228 (99.1%)	0.093	0.017-0.505	0.006
Adherence to vaccination program, *N* (%)	116 (100%)	228 (99.6%)	NA		
Use of reusable diapers, *N* (%)	19 (16.8%)	37 (17.1%)	1.181	0.621-2.248	0.611
Place of residence, *N* (%) (aged < 7 years) Rural (prior) Urban	 62 (53.4%) 54 (46.6%)	 128 (56.4%) 99 (43.6%)	1.159	0.716-1.876	0.549
House type (aged < 7 years)					
Farm house	4 (3.4%)	13 (5.7%)	Ref.		
Apartment	14 (12.1%)	12 (5.2%)	0.212	0.049-0.918	0.038
Terraced house	21 (18.1%)	41 (17.9%)	0.538	0.147-1.976	0.351
Detached house	77 (66.4%)	163 (71.2%)	0.754	0.233-2.546	0.649
Mother smokes, *N* (%)	27 (22.9%)	30 (13.6%)	2.454	1.305-4.613	0.005
Father smokes, *N* (%)	34 (29.8%)	52 (23.3%)	1.538	0.902-2.624	0.114

Nail chewing, N (%)	44 (37.9%)	87 (37.8%)	1.053	0.648-1.713	0.834
Pica symptoms, *N* (%)	17 (14.8%)	21 (9.2%)	1.366	0.663-2.813	0.379
Use of a pacifier, *N* (%)	98 (86.0%)	176 (77.2%)	1.758	0.928-3.332	0.083
Thumb sucking, *N* (%)	4 (3.5%)	20 (9.0%)	0.569	0.182-1.784	0.334
Use of herbal and naturopathic products, N (%)	17 (14.8%)	14 (6.1%)	2.811	1.266-6.241	0.011
Daycare center (aged < 2 years), *N* (%)	26 (22.6%)	70 (30.8%)	0.563	0.319-0.994	0.048
Daycare center (aged 2–7 years), *N* (%)	71 (61.2%)	143 (63.0%)	0.816	0.495-1.344	0.424
Family daycare (aged < 2 years), *N* (%)	16 (13.8%)	58 (25.6%)	0.533	0.284-1.002	0.051
Family daycare (aged 2–7 years), *N* (%)	30 (25.9%)	41 (18.1%)	1.746	0.988-3.086	0.055
Foreign travel, *N* (%)	83 (71.6%)	158 (68.7%)	1.545	0.895-2.667	0.118

aOR: OR adjusted for the age at data collection and social class of the family

CI: confidence interval

Table 2. Exposure domestic animals, including household pets in 119 PFAPA cases and 230 controls. Univariate regression model, adjusted for age at the time of data collection and the social class of the family, as determined by the occupation of the mother.

Products	**Cases**	**Controls**	**aOR**	**95% CI**	***P***
Cat, *N* (%)	44 (37.6%)	87 (37.8%)	0.946	0.580-1.545	0.825
Dog, N (%)	69 (59.0%)	125 (54.3%)	1.472	0.902-2.401	0.122
Rodent, *N* (%)	34 (29.3%)	51 (22.2%)	1.715	0.993-2.962	0.053
Aquarium, *N* (%)	30 (25.9%)	33 (14.3%)	2.262	1.247-4.104	0.007
Terrarium, *N* (%)	11 (9.5%)	12 (5.2%)	2.385	0.906-6.279	0.079
Cows, *N* (%)	4 (3.5%)	14 (6.1%)	0.562	0.168-1.879	0.350
Sheep, *N* (%)	7 (6.1%)	7 (3.0%)	1.700	0.529-5.459	0.373
Horses, *N* (%)	11 (9.4%)	11 (4.8%)	1.578	0.630-3.954	0.330

aOR: OR adjusted for the age at data collection and social class of the family

CI: confidence interval

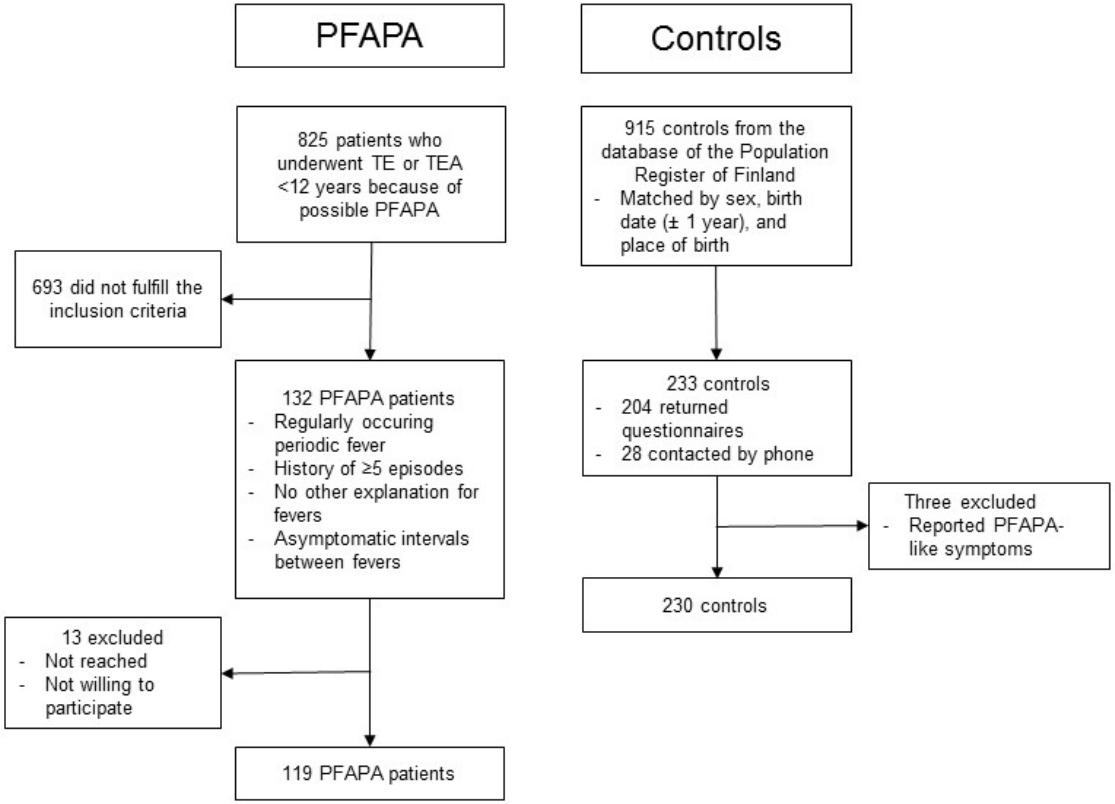
Table 3. Results of a multifactorial logistic regression model, adjusted for age at the time of data collection and the social class of the family, as determined by the occupation of the mother.

Factor	**aOR**	**95% CI**	***P***
Breastfeeding (yes/no)	0.095	0.017-0.538	0.008
Daycare center (aged < 2 years)	0.681	0.365-1.268	0.226
Mother smokes	2.489	1.202-5.155	0.014
Type of housing (aged < 7 years)			
Farm house	Ref.		
Apartment	0.358	0.069-1.848	0.220
Terraced house	0.597	0.143-2.490	0.479
Detached house	0.953	0.248-3.662	0.944
Aquarium at home	2.385	1.218-4.672	0.011
Use of herbal and naturopathic products	3.816	1.499-9.716	0.005

aOR: OR adjusted for the age at data collection and social class of the family

CI: confidence interval

Figure 1.


PFAPA
Controls
825 patients who underwent TE or TEA <12 years because of possible PFAPA
915 controls from the database of the Population Register of Finland
- Matched by sex, birth date (± 1 year), and place of birth
693 did not fulfill the inclusion criteria
132 PFAPA patients
- Regularly occuring periodic fever
- History of ≥5 episodes
- No other explanation for fevers
- Asymptomatic intervals between fevers
233 controls
- 204 returned questionnaires
- 28 contacted by phone
Three excluded
- Reported PFAPA-like symptoms
230 controls
13 excluded
- Not reached
- Not willing to participate
119 PFAPA patients