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**Original Article**

# Growth and development in children with periodic fever, aphthous stomatitis, pharyngitis, lymphadenitis syndrome: a case-control study

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## ABSTRACT

**Background.** Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome is the most common cause of recurrent fever in childhood. Although normal growth and development are included in the diagnostic criteria, this assumption has not been systematically evaluated in controlled studies. This study aimed to compare growth patterns and developmental screening outcomes between children with PFAPA and healthy controls.

**Methods.** A total of 138 children were enrolled, including 69 patients diagnosed with PFAPA according to the modified Marshall criteria and 69 age- and sex-matched healthy controls. The PFAPA group consisted of 26 females (37.7%) and 43 males (62.3%), while the control group included 26 females (37.7%) and 43 males (62.3%). The mean age was 52.1 ± 13.86 months in the PFAPA group and 50.28 ± 13.70 months in the control group. Growth was assessed using anthropometric parameters, including height, weight, body mass index (BMI), weight-for-height, and mid-upper arm circumference. The primary outcome was overall growth pattern, assessed by anthropometric measures, with particular attention to BMI. Developmental screening was performed using the Denver II Developmental Screening Test.

**Results.** Mean anthropometric measures, including height, weight, and BMI, were comparable between patients with PFAPA and controls. However, overweight/obesity was more prevalent in the PFAPA group than in controls (18.8% vs. 5.8%; odds ratio [OR] 3.77, 95% confidence interval [CI] 1.16–12.24, p=0.020). Patients with PFAPA who were overweight/obese had received a higher number of corticosteroid treatments (p=0.046). Developmental screening outcomes did not differ significantly between groups.

**Conclusion.** In this case-control study, children with PFAPA demonstrated overall growth patterns and developmental screening results similar to those of healthy peers, although a higher prevalence of overweight/obesity was observed. These findings support, but do not definitively establish, the assumption of preserved growth and development in PFAPA and underscore the need for further longitudinal studies.

**Key words:** PFAPA syndrome, growth, development, corticosteroids, obesity.

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Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is one of the most common autoinflammatory syndromes of childhood. It is characterized by regularly recurring febrile episodes accompanied by aphthous stomatitis, pharyngitis, and cervical lymphadenitis, with complete resolution of symptoms between attacks. PFAPA typically presents before the age of five years and is generally regarded as a benign, self-limited condition.[1]

Normal growth and development are included among the original diagnostic criteria for PFAPA syndrome and are frequently emphasized in the literature.[2,3] However, this assumption is largely based on clinical observation rather than systematic, objective evaluation. Children with PFAPA experience recurrent episodes of systemic inflammation during early childhood, which is a critical period for somatic growth and neurodevelopment. Chronic inflammatory conditions have been associated with disruption of the growth hormone–insulin-like growth factor-1 (GH–IGF-1) axis, increased metabolic demands, and growth-plate perturbations, which may plausibly influence growth trajectories.[4,5]

In addition, PFAPA attacks are commonly treated with intermittent systemic corticosteroids to rapidly terminate febrile episodes. Although these treatments usually involve short courses, repeated exposure over time may contribute to increased appetite and changes in body composition, raising concern about potential overweight/obesity in susceptible children.[6,7]

Despite these biologically plausible mechanisms, controlled studies systematically evaluating growth and developmental outcomes in children with PFAPA remain limited. Most available reports lack appropriate control groups, standardized anthropometric measurements, or formal developmental screening. Therefore, the primary aim of this study was to compare growth patterns and developmental screening outcomes in children aged 2-6 years diagnosed with PFAPA syndrome with those of age- and sex-matched healthy controls using standardized anthropometric measurements and a validated developmental screening tool. We hypothesized that overall growth and developmental outcomes in children with PFAPA would be similar to those of healthy peers, while the prevalence of overweight and obesity might be higher in the PFAPA group due to intermittent corticosteroid exposure.

## Materials and Methods

A total of 138 children aged 2-6 years were included in this case–control study, comprising 69 patients diagnosed with PFAPA syndrome and 69 age- and sex-matched healthy controls. Patients with PFAPA were recruited from the pediatric rheumatology and general pediatrics outpatient clinics of our institution. Healthy controls were recruited from the general pediatrics outpatient clinic during the same study period. PFAPA diagnosis was established according to the modified Marshall criteria. Controls were matched to patients with PFAPA by age and sex. The same exclusion criteria were applied to both groups. Children with known chronic systemic diseases, congenital anomalies, or a prior diagnosis of or follow-up for growth or developmental delay were excluded from the study. Anthropometric measurements including height, body weight, body mass index (BMI), weight-for-height (WFH), and mid-upper arm circumference, were obtained using standardized techniques. Height, weight, and BMI z-scores and percentiles were calculated according to the World Health Organization (WHO) Child Growth Standards. Nutritional status was additionally evaluated using the Gómez and Waterlow classifications to assess acute and chronic malnutrition. Overweight was defined as a BMI-for-age percentile between the 85th and 95th percentiles, and obesity was defined as a BMI-for-age percentile at or above the 95th percentile, in accordance with WHO growth standards. Developmental assessment was performed using the Denver II Developmental Screening Test (DDST II) by

a trained child development specialist. The DDST II evaluates gross motor, fine motor, language, and personal–social domains. In accordance with standard clinical practice, DDST II results were interpreted using the overall test classification (normal, questionable, or abnormal), and domain-specific results were not reported separately. Demographic and socioeconomic data collected included age, sex, number of household members, parental education level, and family income. For patients with PFAPA, clinical characteristics such as age at disease onset, frequency and duration of febrile episodes, longest interval between episodes, and total number of attacks were recorded. PFAPA attacks were treated with intermittent systemic corticosteroids according to standard clinical practice. Data regarding the number of corticosteroid administrations were obtained from medical records. Detailed information on cumulative corticosteroid dose (mg/kg), dose per episode, or time since the last dose at the time of assessment was not consistently available and therefore could not be included in the analysis. Ethical approval was obtained from the institutional ethics committee (Approval date: 11/01/2023; decision number: 2022/12-17), and written informed consent was obtained from the parents or legal guardians of all participants. The study was conducted in accordance with the Declaration of Helsinki.

To detect a moderate effect size (Cohen's d = 0.50) with 90% statistical power and a type I error rate of 5%, a minimum of 64 participants per group (128 total) was required. Our final sample exceeded this minimum with 69 participants in each group. This calculation was based on the primary hypothesis that overall growth parameters would be comparable between children with PFAPA and healthy controls.

### *Statistical analysis*

Data were analyzed using IBM SPSS Statistics for Windows, Version 30.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as means ± standard deviations (SD) if normally distributed, or as medians (Q1–Q3; i.e., 25th–75th percentiles) if not normally distributed. For comparisons between two independent groups, Student's t-test was used for normally distributed variables, and the Mann-Whitney U test was used for non-normally distributed variables. The chi-square test and Fisher's exact test were employed for the comparison of categorical data. A p-value of $<0.05$ was considered statistically significant.

To assess correlations between variables, Spearman's rank correlation coefficient was used. The strength of correlations was interpreted as follows: $r \geq 0.91$: very strong, $0.71 \leq r < 0.91$: strong, $0.51 \leq r < 0.71$: moderate, $0.31 \leq r < 0.51$: weak, $r < 0.31$: negligible or no correlation.

## Results

A total of 138 children, including 69 patients with PFAPA and 69 healthy controls, were included in the study. The descriptive characteristics of the children were compared between the two groups. Of the 69 patients with PFAPA, 43 (62.3%) were male and 26 (37.7%) were female. When the income status of the children's families was examined, families reporting that their income was equal to their expenses were statistically significantly more prevalent in the PFAPA group ($p = 0.002$). There was a statistically significant difference in the number of family members between the two groups ($p = 0.032$) (Table I). The mean age at onset of PFAPA symptoms was 25.29 ± 13.76 months, the mean age at diagnosis was 38.46 ± 13.78 months, and the mean interval between attacks was 27.2 ± 8.02 days (Table II).

The growth parameters of patients with PFAPA including weight, height, BMI, WFH, and mid-upper arm circumference, were similar to those of the control group when examined as categorical variables. In the PFAPA group, the weight was below the third percentile in 1 (1.4%) case. When compared with the control

**Table I.** Descriptive characteristics of PFAPA and control groups (n = 138).

| | | PFAPA (n=69) n (%) | Control (n=69) n (%) | p-value |
|---|---|---|---|---|
| Sex | Girl | 26 (37.7) | 26 (37.7) | 1.000* |
| | Boy | 43 (62.3) | 43 (62.3) | |
| Income status | Income <Expenses | 2 (2.9) | 16 (23.2) | 0.002* |
| | Income = Expenses | 65 (94.2) | 52 (75.4) | |
| | Income > Expenses | 2 (2.9) | 1 (1.4) | |
| | Illiterate | 1 (1.4) | 1 (1.4) | |
| Mother educational status | Primary school | 7 (10.1) | 13 (18.8) | |
| | Secondary school | 15 (21.7) | 10 (14.5) | 0.191* |
| | High school | 22 (31.9) | 30 (43.5) | |
| | University | 24 (34.8) | 15 (21.7) | |
| | Illiterate | 0 (0) | 1 (1.4) | |
| Father educational status | Primary school | 7 (10.1) | 11 (15.9) | |
| | Secondary school | 14 (20.3) | 13 (18.8) | 0.664* |
| | High school | 31 (44.9) | 26 (37.7) | |
| | University | 17 (24.6) | 18 (26.1) | |
| Age (months) | | 52.1 ± 13.86 | 50.28 ± 13.70 | 0.141** |
| Number of family members | | 3.8 ± 0.95 | 4.14 ± 0.96 | 0.032** |

*Chi-square test; **Independent samples t- test

**Table II.** Clinical characteristics of patients with PFAPA (n=69).

| Variable | Value mean ± SD or median (Q1-Q3) |
|---|---|
| Age of onset (months) | 24 (13-36) |
| Age at diagnosis (months) | 36.0 (28.5-49.0) |
| Periodicity (days) | 30 (21-30) |
| Frequency of attacks (per year) | 12 (12-15) |
| Duration of attacks (days) | 4 (3-5) |
| Total number of attacks | 20.0 (13.0-32.5) |
| Maximum interval between attacks (days) | 30 (30-40) |
| Highest temperature (°C) | 40.01 ± 0.68 |
| Number of steroids taken | 8 (2-12) |

SD: Standard deviation.

group, there were no statistically significant differences between groups in weight standard deviation score (SDS) value or weight percentile value.

In the PFAPA group, short stature was detected in 2 (2.9%) cases. When compared with the control group, no statistically significant difference was detected between the groups in terms of the SD of height SDS or height percentile values.

Malnutrition was detected in 5 (7.2%) cases among patients with PFAPA, as determined by BMI, but no statistically significant difference was found between the PFAPA and control groups.

The groups did not show any statistically significant difference in terms of WFH SDS. In the PFAPA group, WFH was below the third percentile in 6 (8.7%) cases, and WFH SDS was below -2 SDS in a total of 10 (14.5%) cases. When compared with the control group, no statistically significant difference was found between the groups in terms of WFH SDS or percentile values (Table III).

When cases with overweight or obesity, defined as BMI above the 85th percentile were compared with the control group, 13 (18.8%) cases in the PFAPA group and 4 (5.8%) cases in the control group were identified. This difference was statistically significant (p = 0.02; odds ratio [OR] 3.77, 95% confidence interval [CI] 1.16–12.24) (Table IV).

No statistically significant difference was detected between the two groups in terms of DDST II results (Table V). Additionally, the neuromotor development parameters of the cases were evaluated according to the number of steroid administrations received (Table VI). The mean number of steroids administrations among patients with abnormal DDST II was 8.78 ± 5.35, and the mean number of steroids taken by patients with normal and suspicious DDST II was 7.86 ± 6.25. No statistically significant difference was found between the groups. The number of corticosteroid administrations

**Table III.** Comparison of continuous growth parameters of the cases between the two groups.

| | PFAPA (n=69) | Control (n=69) | p-value |
|---|---|---|---|
| | mean ±SD or median (Q1-Q3) | mean ± SD or median (Q1-Q3) | |
| Weight (kg) | 16.9 (15.0-20.0) | 16.8 (14.9 -19.5) | 0.523* |
| Weight SDS | 0.01 (-0.80-0.80) | 0.01 (-0.60-0.57) | 0.998* |
| Weight percentile | 30.21 (20.55-77.61) | 50.40 (27.20-71.55) | 0.997* |
| Height (cm) | 105.91 ± 9.26 | 104.95 ± 9.12 | 0.577** |
| Height SDS | 0.17 (-0.52–0.74) | 0.17 (-0.45-0.77) | 0.788* |
| Height percentile | 57.93 (30.51-77.62) | 56.7 (32.4-78.5) | 0.905* |
| BMI (kg/m$^2$) | 15.67 ± 1.83 | 15.48 ± 1.44 | 0.249** |
| BMI SDS | -0.05 (-0.86-0.69) | -0.10 (-0.77-0.49) | 0.667* |
| BMI percentile | 46.4 (18.0-75.5) | 44.4 (21.6-66.0) | 0.603* |
| WFH (%) | 101.26 ± 12.02 | 100.25 ± 9.08 | 0.289** |
| WFH SDS | 0.04 (-0.84-0.82) | -0.05 (-0.47-0.56) | 0.958* |
| WFH percentile | 51.6 (24.2-79.51) | 48.0 (31.7-73.4) | 0.919* |
| AAW (%) | 101.43 ± 15.56 | 101.56 ± 14.37 | 0.480** |
| AAH (%) | 100.41 ± 4.49 | 100.33 ± 3.71 | 0.452** |
| Mid-upper arm circumference (cm) | 19.14 ± 1.11 | 17.88 ± 1.55 | 0.155** |

AAH: age adjusted height; AAW: age adjusted weight; BMI: Body Mass Index; *Mann-Whitney U test; **Independent samples t-test; SD: Standard deviation; WFH: weight-for-height.

**Table IV.** Distribution of BMI categories in PFAPA and control groups.

| BMI category | PFAPA (n=69) n (%) | Control (n=69) n (%) | p-value |
|---|---|---|---|
| Malnutrition | 5 (7.2) | 4 (5.8) | 0.117 |
| Normal weight | 51 (74) | 61 (88.4) | |
| Overweight | 8 (11.6) | 2 (2.9) | |
| Obesity | 5 (7.2) | 2 (2.9) | |

**Table V.** Denver II Development Test outcomes.

| Result | PFAPA (n=69) n (%) | Control (n=69) n (%) | p-value |
|---|---|---|---|
| Normal | 51 (73.9) | 57 (82.6) | 0.189 |
| Suspicious | 9 (13.0) | 3 (4.3) | |
| Abnormal | 9 (13.0) | 9 (13.0) | |

**Table VI.** Steroid Usage by Development outcome (PFAPA group only).

| Developmental Status | Median (Q1-Q3) | p-value |
|---|---|---|
| Normal/suspicious (n=60) | 7.5 (2-12.5) | 0.411* |
| Abnormal (n=9) | 10 (3.5-13.5) | |

*Mann-Whitney U test.

was significantly higher in children who were overweight or obese compared to those who were not (10.5 [2–18] vs. 6 [2–32], p = 0.046). A weak positive correlation was found between BMI and the number of steroids administrations (r = 0.34, p=0.046)

## Discussion

According to current literature, PFAPA syndrome is generally considered to have minimal effects on growth and development in the pediatric population, and there is insufficient evidence to suggest a significant impact on long-term physical or neurodevelopmental outcomes. Although disease attacks may transiently affect appetite and general health status, these effects are episodic. The observation that children return to their baseline health status between attacks supports the expectation that overall growth remains preserved. Accordingly, normal growth and development have long been included among the diagnostic criteria for PFAPA syndrome.[1,2] However, despite this assumption, objective data derived from case–control studies addressing growth and development in PFAPA remain limited.[1,8]

In the present study, 69 children diagnosed with PFAPA were evaluated and compared with age- and sex-matched healthy controls. Although isolated cases of low weight, short stature, or malnutrition were observed among patients with PFAPA, no statistically significant differences were identified between the groups in most growth parameters, including weight, height, BMI, and WFH. However, the prevalence of overweight/obesity was significantly higher in the PFAPA group. These findings suggest that PFAPA does not involve a pathophysiological mechanism leading to sustained impairment of linear growth. PFAPA is characterized by intermittent inflammatory episodes presenting with fever, pharyngitis, aphthous stomatitis, and cervical lymphadenitis, driven by an autoinflammatory process rather than continuous systemic inflammation.[9]

In contrast to chronic inflammatory or autoinflammatory conditions associated with persistent disease activity, PFAPA follows a self-limiting course and does not exhibit an ongoing inflammatory burden between episodes. Moreover, spontaneous resolution with increasing age is commonly observed, further reducing the likelihood of long-term growth compromise.[8] Chronic inflammatory diseases are known to impair growth through mechanisms such as increased metabolic demand, reduced nutritional intake, and alterations in the GH–IGF axis. Indeed, Cimaz et al. reported reduced IGF-1 levels and growth failure in children with chronic inflammatory diseases characterized by sustained inflammation.[10] Such mechanisms, however, appear less applicable to PFAPA given its episodic and non-continuous inflammatory nature.

An important finding of this study was the higher prevalence of overweight and obesity among patients with PFAPA compared with controls, as well as the observed association between increased cumulative corticosteroid exposure and BMI. In PFAPA syndrome, systemic corticosteroids are typically administered intermittently and for short durations to abort febrile episodes.[11] This treatment approach is generally considered safe with respect to linear growth; however, repeated exposure over time may influence appetite regulation and body composition.[11,12] In the present cohort, overall growth parameters were preserved, supporting previous observations that PFAPA does not impair linear growth. Nevertheless, the increased frequency of overweight and obesity among patients with PFAPA underscores the importance of careful growth and metabolic monitoring, particularly in children receiving repeated corticosteroid treatments. Clinicians should balance the benefits of rapid symptom control with the potential metabolic effects of recurrent steroid exposure.

Regarding neurodevelopment, no significant differences were observed between patients with PFAPA and controls based on the DDST II. Although abnormal screening results were identified in a minority of patients with PFAPA, these findings were not associated with corticosteroid exposure. As the Denver II is a screening tool rather than a comprehensive neuropsychological assessment, these results suggest that, at the level of screening, neurodevelopmental outcomes in children with PFAPA are comparable to those of healthy peers.

This study has several limitations that should be acknowledged. First, although the overall sample size was adequate, the exploratory nature of the study and the relatively small number of overweight and obese cases limited the feasibility of multivariable analyses adjusting for potential confounders such as socioeconomic status and household characteristics. Additionally, the cross-sectional design limits the ability to establish causal relationships between variables. Therefore, residual confounding cannot be excluded, particularly with respect to obesity-related outcomes. Second, a clearly defined primary endpoint was not prespecified, and multiple anthropometric and developmental outcomes were assessed, introducing the possibility of multiple testing and chance findings. Third, developmental outcomes were evaluated using the DDST II, which is a screening instrument rather than a comprehensive neuropsychological assessment, and subtle or domain-specific differences may not have been fully captured. Fourth, the number of overweight and obese cases was relatively small, limiting statistical power and precision. Additionally, corticosteroid exposure was assessed using the number of administrations rather than cumulative dose or timing, which represents a coarse measure and limits causal interpretation.

### *Conclusion*

In this case–control study, children with PFAPA syndrome demonstrated overall growth patterns and developmental screening outcomes comparable to those of healthy peers, despite the presence of isolated cases of growth or developmental delay. No association was observed between corticosteroid use and linear growth or developmental screening results. However, a higher prevalence of overweight and obesity was noted among patients with PFAPA, and these children had greater corticosteroid exposure. Although this observation should be interpreted with caution, it highlights the importance of monitoring growth and metabolic outcomes in children receiving repeated corticosteroid treatment for PFAPA. Further prospective studies with larger sample sizes and more detailed assessment of steroid exposure are needed to better clarify these relationships.

## Ethical approval

The study was approved by Ethics Committee of Izmir Tepecik Training and Research Hospital, Ministry of Health (date: January 11, 2023, number: 2022/12-17).

## Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: AK, YD, ÇB, BKD, MİA, HÖH; data collection: YD; analysis and interpretation of results: AK, ÇB, BKD; draft manuscript preparation: AK, ÇB, MİA, BKD. All authors reviewed the results and approved the final version of the manuscript.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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