

## COVID-19 Confinement Unmasking PFAPA Syndrome

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### INTRODUCTION

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is characterized by recurrent episodes of fever of unexplained origin, pharyngitis, oral aphthous ulcers, and cervical lymphadenopathy.<sup>1</sup> It was first described in 1987 and was known as the Marshall's syndrome until the abbreviation PFAPA was introduced in 1989.<sup>2</sup> Generally, the onset is before the age of five years and resolves spontaneously before the adult age<sup>3</sup> with febrile episodes lasting for four to five days and recurring every three to six weeks.<sup>4</sup> Patients with PFAPA are usually healthy children with normal developmental milestones and growth. The lack of evidence of infection and the asymptomatic intervals between the flare-ups are characteristics of this syndrome.

The pathophysiology and etiology of PFAPA syndrome remain unknown. However, it appears to be multifactorial with a familial predisposition. The swift response of the febrile attack to a single dose of steroids and the absence of an infectious microorganism suggests an autoinflammatory origin of the disease.<sup>5</sup> Furthermore, emotional stress may play a role in the development of PFAPA exacerbations. For example, during the Coronavirus Disease (COVID-19) pandemic outbreak and the global lockdown, the level of stress, whether familial or personal, acted as a trigger to the induction of flare of PFAPA.<sup>6</sup>

In fact, in the era of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and COVID-19, the medical community has witnessed a dramatic change in how healthcare is delivered and experienced. The impacts of COVID-19 were noticeable at multiple levels of care: initial screening, diagnosis, treatment initiation, and during ongoing care.<sup>7</sup> Moreover, after the implementation of public health measures, the incidence of common viral and bacterial infections has decreased,<sup>8,9</sup> while the incidence of autoimmune and autoinflammatory diseases increased.<sup>10</sup>

We hereby describe a series of five patients presenting to our outpatient pediatric department with PFAPA syndrome between December 2020 and March 2021.

### CASE REPORT

Five children with a mean age of 3.7 years presented to the same clinic between December 2020 and March 2021 with high-grade fever of 39.4°C and above, lasting three to four days with one or more of the

following: pharyngitis, tonsillitis, aphthous ulcers, and cervical adenitis (Figure 1). All of them had similar episodes recurring with an interval of five to six weeks with asymptomatic periods in between. They were previously healthy, with no reported sick contacts, daycare attendance, or similar symptoms in the family. Family history was negative for autoimmune diseases except for one patient whose brother had Familial Mediterranean Fever and another patient whose father has psoriasis. A rapid streptococcal antigen test was performed during the febrile episode in most of the patients and was negative. The five children were given one dose of prednisolone 1 mg/kg and an excellent response was observed the second day (Table 1).



Figure 1. Picture during episodes of tonsillitis in one of the patients with 40 days in between. (a): a distinct white ulcer on the uvula base. (b) erythema of the tonsils with right sided exudate.

### DISCUSSION

PFAPA syndrome is a common autoinflammatory disease during childhood and an essential differential diagnosis in children with recurrent fevers.<sup>3</sup> Its exact incidence remains undetermined as the data concerning the epidemiology was limited. The most conclusive data came from a Nordic study that reported an incidence of 2.3 per 10,000 children up to five years of age.<sup>11</sup> With the ongoing COVID-19 confinement and the lack of outside impact of infectious exposure, PFAPA syndrome seemed easier to ascertain and diagnose in clinical practice.<sup>12</sup>

The diagnosis of PFAPA is based on the Modified Marshall's diagnostic criteria which require the presence of recurring fevers with either aphthous stomatitis, cervical lymphadenitis, or pharyngitis in a normally developing child less than five years of age.<sup>13</sup> Despite the presence of these criteria, PFAPA remains a challenge with the diagnosis based solely on clinical judgment after exclusion of other causes of recurrent fevers. Because of the absence of specific diagnostic tests and the incomplete knowledge and awareness of this disease, the diagnosis commonly is delayed to up to 28 months (2.3 years) after presentation, and the disease is misinterpreted as recurrent infections.<sup>14</sup>

In the present report, the diagnosis of PFAPA syndrome did not come to our attention straightaway leading to a one-year delay in diagnosis on average. The recurrent nature of the symptoms and the clear lack of exposure due to home confinement guided us to make a PFAPA diagnosis. The response to a single corticosteroid dose confirmed our suspicion making a PFAPA diagnosis even more likely. The diagnosis particularly was challenging in the context of constant infectious exposures in the community and at schools, where PFAPA commonly is misinterpreted as streptococcal or viral tonsillitis by primary care

**Table I. Summary of findings of the patients.**

| Patient                                 | 1                   | 2                   | 3                   | 4                   | 5                     |
|---|---------------------|---------------------|---------------------|---------------------|-----------------------|
| Age at first episode (years)            | 2.8                 | 1.8                 | 2.7                 | 2                   | 3.7                   |
| Age at diagnosis (years)                | 3.4                 | 4.4                 | 3.1                 | 2.8                 | 4.8                   |
| Time to diagnosis (years)               | 0.6                 | 2.6                 | 0.4                 | 0.8                 | 1.1                   |
| Total number of episodes                | 4                   | 8                   | 4                   | 9                   | 9                     |
| Time between episodes (days)            | 46                  | 45                  | 42                  | 41                  | 40                    |
| Average temperature (°C)                | 39.5                | 39.1                | 39.4                | 39.8                | 39.5                  |
| Pharyngitis*                            | Yes                 | Yes                 | Yes                 | Yes                 | Yes                   |
| Tonsillitis**                           | Yes                 | Yes                 | Yes                 | Yes                 | Yes                   |
| Aphthous ulcers                         | Yes                 | Yes                 | Yes                 | Yes                 | Yes                   |
| Cervical adenitis                       | No                  | No                  | No                  | No                  | Yes                   |
| Asymptomatic between episodes           | Yes                 | Yes                 | Yes                 | Yes                 | Yes                   |
| Daycare/Nursery/Sick contact            | No                  | No                  | No                  | No                  | No                    |
| Previously healthy                      | Yes                 | Yes                 | Yes                 | Yes                 | Yes                   |
| Family history of autoimmune diseases   | Brother with FMF*** | No                  | No                  | No                  | Father with psoriasis |
| Rapid strep test result <sup>a</sup>    | Negative            | Not done            | Not done            | Negative            | Negative              |
| Prednisolone 1 mg/kg                    | Once                | Once                | Once                | 8 times             | 5 times               |
| Response to single dose of prednisolone | Complete resolution | Complete resolution | Complete resolution | Complete resolution | Complete resolution   |

\* Refers to the inflammation of the pharynx between the tonsils exclusively.

\*\*Refers to inflammatory changes localized at the tonsils.

\*\*\*PMF= Familial Mediterranean Fever

<sup>a</sup> Strep test performed at the time of febrile attack.

physicians. Hence, patients undergo multiple unnecessary medical examinations, emergency department visits, throat swabs, and laboratory tests and often will receive inappropriate antibiotics treatment.

With the start of the COVID-19 pandemic and the implementation of public health measures including home confinement, mask use, frequent handwashing, physical distancing, and closure of schools, playground, and public places, the exposure to pathogens has decreased, thus making the diagnosis of PFAPA in the right clinical context less susceptible to misinterpretation. This could explain this cluster of five patients that presented to our clinic within a short period of time.

Another explanation to this finding could be justified by the Hygiene Hypothesis: a decrease in exposure to microorganisms is correlated with an increased incidence of autoimmune diseases. This hypothesis remains relevant during the COVID-19 pandemic with the stricter hygienic practices and more robust public health measures.<sup>15</sup>

Despite having a benign clinical course with no long term sequelae, PFAPA significantly impacts the life of the patients. In fact, children with PFAPA were found to have lower scores of quality of life, physical and psychosocial functioning, and higher levels of fatigue when compared to children with Familial Mediterranean Fever.<sup>16</sup> Additionally, the extensive medical workup has a significant economic burden on the family and the healthcare system.<sup>13</sup>

Therefore, the aim of our report was to increase awareness and shed the light on the importance of prompt recognition of PFAPA syndrome

by primary care physicians and pediatricians particularly in the era of COVID-19. Keeping PFAPA high on the differentials will lead to a faster diagnosis, earlier treatment with steroids, a decline in overall medical expenses, and the avoidance of unnecessary antibiotics use.

## CONCLUSIONS

Although common, PFAPA probably remains underdiagnosed in children and symptoms often are misinterpreted especially in the setting of sick contacts and exposures to infections at home or at school. This report suggested that confinement and school closure during the COVID-19 pandemic were key to uncover our cluster of PFAPA cases. It also raised questions about a potential association between PFAPA and COVID. Increasing awareness during these times leads to prompt recognition of the disease which is crucial as it would shorten the duration of the illness and improve the quality of life.

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