Diagnosing PFAPA during the COVID-19 era: clarity during quarantine

Periodic fever accompanied by aphthous stomatitis, pharyngitis and/or cervical adenitis (PFAPA) was first described in 1987 by Marshall *et al*. Fever periodicity is a hallmark of the diagnosis, and there is a noted absence of upper respiratory tract (URTI) symptoms and sick contacts. Diagnosing PFAPA can be challenging for clinicians. The most common treatment is corticosteroids, given at the first sign of fever. A single dose of prednisone will abort the febrile episode; this is unique to PFAPA and essentially diagnostic.[1 2] Tonsillectomy has also been reported to be curative.[2]

On 22 March 2020, New York State issued an executive 'stay-at-home' order due to the COVID-19 pandemic. This facilitated the diagnosis of PFAPA in our patient population. Travel and exposure to sick contacts, especially in day care, were markedly decreased, but a group of patients were still having periodic fevers. Furthermore, household members were not getting sick during these episodes.

A retrospective case–control study was performed at NYU Langone Hospital-Long Island using International Classification of Diseases 10th Revision (ICD-10) diagnosis codes (A68.9 (relapsing/recurrent fever]), M04.1 (periodic fever) and M04.8 (PFAPA)) to search for patients. Patients from 23 March 2020 to 1 November 2020 were selected as the 'quarantine' cohort, and patients from 1 January 2019 to 21 March 2020 served as controls. The primary outcome was time to diagnosis of PFAPA, defined as time from first visit to prescription of abortive corticosteroids.

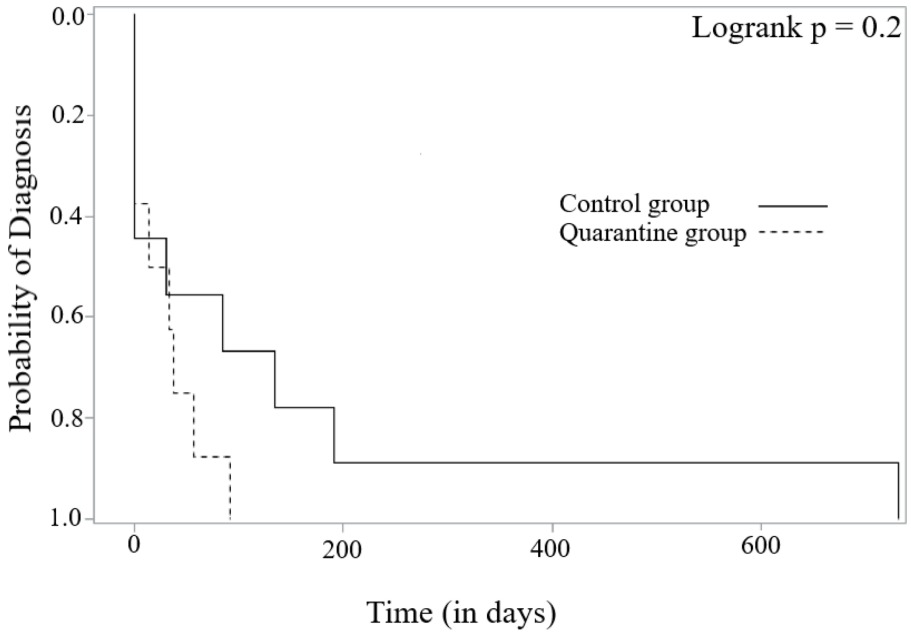
Eight and nine patients were identified for the 'quarantine' and 'control' cohorts, respectively. There was a statistically significant difference in exposure to sick contacts and/or day care ($p<0.0004$) and travel in the year prior ($p<0.02$) between groups (table 1). Within the 'quarantine' cohort, time to diagnosis of PFAPA was shorter than the 'control' group (24 days vs 31 days, $p<0.2$, figure 1). Adjusting for number of fever recurrences prior to initial visit, the 'quarantine' cohort was 2.7 times more likely to be diagnosed with PFAPA at a particular point in time compared with 'controls' (HR=2.74, 95% CI (0.87 to 8.62), $p<0.08$). 'Controls' had an increased risk of diagnostic delay (HR=0.37; 95% CI (0.12 to 1.15)) and a larger IQR than the 'quarantine' cohort (0–57 vs 0–191, respectively).

A minimum of 5–6 months of documented periodic fevers is required to diagnose PFAPA.[3 4] Some patients in our clinic had more than 6 months of documented fevers on presentation—these patients received steroids right away, while others were monitored. A similar study by Ng *et al* reported an increase in PFAPA cases during the pandemic, citing a lack of respiratory virus diversity. The authors report an increase in referrals to their clinic; our practice's

Table 1 Demographics and clinical manifestations of the quarantine and control cohorts of patients with PFAPA

Variable	Quarantine group (n=8)	Control group (n=9)	P value*
Age in years, median (IQR)	2.82 (1.74–4.62)	3.11 (3.06–3.64)	0.88
Male sex, *n* (%)	3 (37.5%)	2 (22.2%)	0.62
Family history of recurrence of: fevers, aphthous ulcers and/or tonsillitis in first-degree relative, *n* (%)	4 (50%)	6 (66.6%)	0.64
Presence of aphthous ulcers, *n* (%)	1 (12.5%)	1 (11.1%)	1.00
Presence of pharyngitis, *n* (%)	3 (37.5%)	2 (22.2%)	0.62
Presence of exudative pharyngitis, *n* (%)	3 (37.5%)	4 (44.4%)	1.00
Presence of lymphadenopathy, *n* (%)	5 (62.5%)	5 (55.6%)	1.00
History of sick contacts and/or child care centre attendance, *n* (%)	**0 (0%)***	**8 (88.9%)***	**0.0004***
History of travel in past year, *n* (%)	**1 (12.5%)***	**5 (55.6%)***	**0.02***
Additional siblings at home, *n* (%)	6 (75.0%)	6 (66.7%)	1.00
Household (family) members getting sick when subject is febrile? *n* (%)	0 (0%)	2 (22.2%)	0.32

*As determined by Mann-Whitney test for continuous variables and Fisher's exact test for categorical variables, with statistical significance at p<0.05.
PFAPA, periodic fever accompanied by aphthous stomatitis, pharyngitis and/or cervical adenitis.



	Quarantine Group	Control Group	P value
Median time to diagnosis, in days (IQR)	24 days (0-57)	31 days (0-191)	0.2

Figure 1 Time to diagnosis of periodic fever accompanied by aphthous stomatitis, pharyngitis and/or cervical adenitis,[1] defined as time from first visit with paediatric infectious diseases to prescription of steroids (used to abort febrile episodes).

numbers were consistent before and after pandemic.[5]

We take into account the limitations that come with any retrospective chart review, including incompleteness of coding systems, historian reporting and subsequent result bias. Our small sample size may have led to an overestimation of the quarantine's impact on diagnosis of PFAPA.

In the differential of recurrent fevers, viral infections (particularly URTIs) are always a consideration, particularly for those who attend day care. Without the outside impact of infectious exposures during the COVID-19 quarantine, the clinical picture of PFAPA was easier to ascertain. Physicians should consider PFAPA in a child with recurrent, periodic fevers lacking infectious exposures.

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