Letter

Rise in children presenting with periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome during the COVID-19 pandemic

Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome is characterised by episodes of fever lasting a few days that classically exhibit clockwork periodicity. Since the initial description of PFAPA syndrome by Gary Marshall in 1987, it has been recognised that stomatitis, pharyngitis and adenitis are variably present.[1] Its phenotype is consistent with an autoinflammatory condition of unknown genetic aetiology possibly involving an infectious/environmental trigger, given that a family history is present in approximately 27% of cases.[2] The natural history is onset before 6 years old, followed by spontaneous resolution by 15 years. Treatment with colchicine can reduce the frequency of episodes and tonsillectomy is usually curative.[3]

The diagnosis of PFAPA syndrome is clinical but can be challenging because it predominantly affects young children who typically experience frequent febrile viral infections. We hypothesised that reduced transmission of viruses due to COVID-19 public health control measures may result in increased recognition of PFAPA syndrome. We performed a retrospective descriptive analysis of routinely collected clinical data from our tertiary paediatric immunology and rheumatology outpatient clinics at Bristol Royal Hospital for Children, UK between 1 January 2015 and 31 March 2021.

Over the study period, 77/957 (8%) referrals were diagnosed with PFAPA. The number of children diagnosed with PFAPA syndrome increased significantly during the COVID-19 pandemic (incidence rate ratio 2.54; 95% CI 1.56 to 4.02) and their characteristics were similar to children diagnosed in the pre-pandemic era (figure 1 and table 1). In comparison, there was a modest overall increase in referrals to the service (incidence rate ratio 1.71; 95% CI 1.46 to 2.00). During the pandemic, 16/26 (62%) children with PFAPA syndrome had undergone a median of 5 (range 1–15) tests for SARS-CoV-2 infection by PCR, and in 2/16 (13%) at least one test was positive. A SARS-CoV-2 antibody test was performed in 4/26 (15%) children and in 1/4 (25%) was positive.

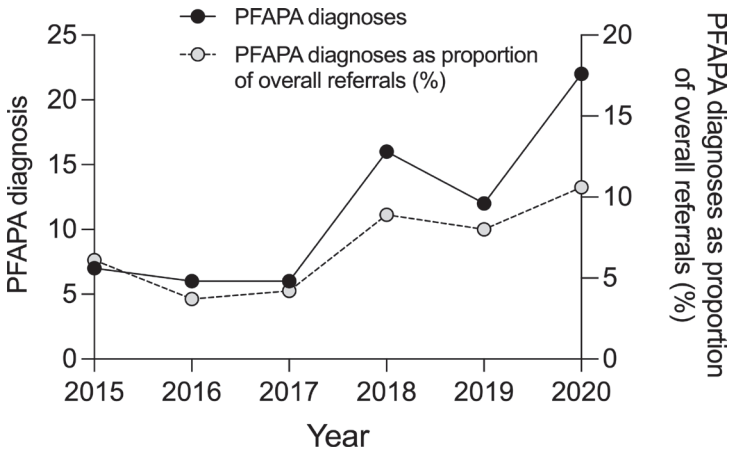

Figure 1 Rise in children presenting with PFAPA syndrome during the COVID-19 pandemic. Children with a new diagnosis of PFAPA syndrome as absolute number (black circles) and as proportion of overall referrals (grey circles) to the tertiary paediatric immunology and rheumatology outpatient clinics at Bristol Royal Hospital for Children (2015–2020).

Several factors could explain our data. The incidence of influenza and respiratory syncytial virus infections has decreased by over 90% in the UK likely as a result of COVID-19 public health control measures.[4] This reduction in respiratory viral transmission may have facilitated the recognition of children with non-infectious causes of fever by parents and healthcare practitioners, thereby increasing referrals to our service. Second, we observed a modest increase in PFAPA syndrome diagnoses before the COVID-19 pandemic, perhaps suggesting that awareness of this condition was already increasing. Third, many of our cohort underwent multiple SARS-CoV-2 tests, and the disruption associated with repeated periods of household self-isolation may have contributed to impetus for parents to seek medical attention. Finally, a biological hypothesis is possible involving autoinflammation provoked by (1) reduced viral infection or (2) SARS-CoV-2 infection itself, although there was limited evidence of COVID-19 among our cohort.

We present our data to alert clinicians that PFAPA syndrome may be more common than previously thought. Periodic fever during periods of low viral transmission should prompt clinicians to consider PFAPA syndrome as a differential diagnosis.

Table 1 Incidence rate of children diagnosed with PFAPA syndrome and their characteristics before and during the COVID-19 pandemic

	Pre-COVID-19 pandemic **Jan 2015 to Dec 2019 (n=51)**	COVID-19 pandemic **Jan 2020 to Mar 2021 (n=26)**
PFAPA incidence rate (per 1 000 000 person-years)*	9.85	24.67
Gender (male:female)	28:23 (55%:45%)	15:11 (58%:42%)
Age (years), median (range)	4.8 (1.3–12.8)	5.4 (1.3–15.5)
Colchicine treatment	25 (51%)	17 (65%)
Tonsillectomy	24 (49%)	Insufficient time elapsed to assess
Clinical resolution	41 (89%)	Insufficient time elapsed to assess

*Incidence rate calculated using population estimates for children aged 0–16 years from published data (Office for National Statistics).[5]

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