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**Title**

Hiding in plain sight: how the COVID-19 pandemic unmasked the autoinflammatory PFAPA syndrome lurking in our midst

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## **Hiding in plain sight: how the COVID-19 pandemic unmasked the autoinflammatory PFAPA syndrome lurking in our midst**

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Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome is the most common autoinflammatory syndrome of childhood, particularly amongst non-Mediterranean populations.[1] The condition is characterised by recurrent and periodic episodes of unprovoked systemic inflammation (fevers and raised acute phase reactants) lasting 3-7 days that are often accompanied by localised inflammation (stomatitis, pharyngitis and adenitis). The underlying aetiopathogenesis of PFAPA syndrome remains a mystery, but various patterns of dysregulated innate and T-cell immune responses have been described.[1] Approximately one quarter of children with PFAPA syndrome have a positive (usually undiagnosed) family history, however whole exome sequencing is yet to identify a monogenic genetic aetiology for PFAPA.[1, 2] Individuals with PFAPA syndrome share minor genetic susceptibility loci with Behçet's disease and recurrent aphthous stomatitis, suggesting these conditions may lie on a common spectrum.[2] Typically, PFAPA begins in early childhood (1-5 years old), with episodes occurring every 2-8 weeks, before gradually and completely resolving in adolescence in most patients.[1] Between episodes, children are clinically well, with typical growth and development. Management approaches include watchful waiting, treatment with prednisolone at symptom onset (abrupt abortive effect on fever), regular colchicine (can reduce frequency and intensity of episodes) and tonsillectomy (can be curative).[1]

The diagnosis of PFAPA syndrome is challenging, as febrile episodes are often misinterpreted as viral infections. PFAPA episodes can be distinguished from infections by the absence of sick contacts, recurrent failure to isolate causative pathogens and the "clockwork" periodicity of the episodes, with parents often able to predict precisely the date their child will experience their next attack.[1] The epidemiology of PFAPA syndrome is poorly defined, owing to the challenges in diagnosis and under-recognition of the condition. The cumulative incidence has been reported as 2.3 per 10,000 children (up to age 5 years) in a Norwegian cohort from 2013.[1] It is increasingly felt that paediatricians will encounter PFAPA syndrome several times through the course of their career.[1]

In the current issue, Fiorito et al performed a retrospective case-control study at the New York University Langone Hospital to compare how long it took clinicians to diagnose PFAPA syndrome in periods before and during the COVID-19 pandemic.[3] Stay-at-home public health control measures to reduce SARS-CoV-2 transmission have been associated with a generalised reduction in the

transmission of all common viruses, which theoretically would illuminate the distinct fever episodes of PFAPA syndrome. If a child were to continue to have periodic fever episodes during a full-scale community lockdown, in the absence of sick contacts, parents and primary care physicians would possibly consider alternate diagnoses. The authors identified PFAPA patients diagnosed prior to lockdown (“control cohort”) and those diagnosed during lockdown (“quarantine cohort”). They found that cases of PFAPA syndrome identified during quarantine had a shorter time to diagnosis than in the control cohort (24 days vs 31 days), defined as the duration from first appointment with the infectious disease service to prescription of abortive corticosteroid therapy. Having adjusted for the number of fever recurrences prior to the initial visit, they concluded that the quarantine cohort was 2.7-fold more likely to be diagnosed with PFAPA syndrome, compared to the control cohort, representing a meaningfully increased risk of diagnostic delay.[3]

This study illustrates precisely what might be anticipated for a disease such as PFAPA syndrome: when the clouding differential of viral infections is eliminated, a recurrent febrile illness with clockwork periodicity and a distinct clinical phenotype should (and did) arouse suspicion in parents and clinicians. As acknowledged by the authors, the study is limited by its retrospective and chart review design, which is prone to biases found in information collected for clinical rather than research purposes. As with many published cohorts of PFAPA syndrome, the sample size is also small. At our centre, we also noted increased recognition of PFAPA syndrome during COVID-19 lockdown, compared with the pre-pandemic era (incidence rate ratio of 2.5).[4]

PFAPA syndrome has been shown to negatively impact the quality of life of patients and their families, despite its perception as a benign self-resolving condition.[5, 6] The fever episodes result in daycare and school absence, hinder activities of daily living and disrupt overall family functioning.[6] Children with PFAPA syndrome have reported a lower global mean Paediatric Quality of Life inventory score compared with those living with familial Mediterranean fever (FMF) (62.7 vs 76.4,  $p < 0.01$ ).[6] The impact of fever episodes has been heightened during the COVID-19 pandemic, given the consequence of repeated mandatory periods of isolation for children and their carers, and the associated sick leave from school/work, as well as multiple SARS-CoV-2 tests. Children with PFAPA syndrome at our centre underwent a median of five SARS-CoV-2 polymerase chain reaction tests during the first year of the pandemic, with only 13% recording 1 positive result, suggesting the majority of fever episodes were related to PFAPA syndrome.[4] PFAPA syndrome is also not without financial implications. After summing the costs of hospital visits, sick leave and carer’s leave, a study from Italy calculated that their PFAPA cohort had a higher overall economic burden than asthma, recurrent respiratory

infections or coeliac disease.[5] Diagnostic delay further exacerbates the impact of PFAPA syndrome on children and families, given that the median duration from symptom onset to diagnosis was reported as 14.5 months in the same Italian cohort.[5] They also report that 40% of their patients received over five courses of antibiotics per year for fever episodes, with primary care physicians prescribing antibiotics even following the diagnosis of PFAPA syndrome.[5]

There is therefore an urgent need to improve the awareness of PFAPA syndrome among child health professionals, and to develop an accurate diagnostic test. Currently, PFAPA is a diagnosis of exclusion, usually based on the modified Marshall's criteria proposed in 1999 (Table 1).[1, 7] Whilst sensitive, these criteria lack specificity.[1] More specific diagnostic criteria developed by a Delphi study in 2018 would have resulted in a significant number of cases being missed, compared with Marshall's criteria.[7] The nomenclature of PFAPA syndrome also often creates confusion for families and clinicians, because aphthous stomatitis, pharyngitis and adenitis are relatively inconsistent findings.[5] Unsurprisingly, there has been significant interest in developing new classification criteria as well as elucidating novel biomarkers that could accurately differentiate PFAPA syndrome from infectious causes of fever, and other autoinflammatory diseases.[5] During fever episodes, a modest rise in non-specific acute phase reactants such as C-reactive protein and serum amyloid A is commonly observed, but is not specific to PFAPA syndrome (although both should return to normal between flares in PFAPA, which may not reliably occur in other autoinflammatory disease). More specific candidate biomarkers have been proposed, including galectin-3, a member of the  $\beta$ -galactoside-binding lectin family with broad cellular and inflammatory functions, which has been found to differentiate PFAPA from FMF in both disease flare and quiescence.[1, 8] Although raised in other autoinflammatory diseases, serum procalcitonin may assist in differentiating PFAPA syndrome from bacterial illness.[1]

PFAPA syndrome is an important and under-recognised condition. As demonstrated by Fiorito et al's study, the COVID-19 pandemic lockdown inadvertently helped focus our eyes on children with PFAPA syndrome who were otherwise 'hiding in plain sight'. With the easing of pandemic restrictions and the returned transmission of common viruses, we can expect that the challenges of identifying PFAPA will also return. For now, we must raise awareness of this condition among clinicians, and focus our efforts on developing accurate diagnostic criteria and novel biomarkers.

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## Table

Table 1: Modified Marshall's criteria for diagnosis of PFAPA [1, 7]

Age of onset < 5 years
Regular fevers
Associated with at least one of: <ul style="list-style-type: none"><li>• Aphthous stomatitis</li><li>• Cervical lymphadenitis</li><li>• Pharyngitis</li></ul>
Asymptomatic between episodes
Normal growth and development
Exclusion of: <ul style="list-style-type: none"><li>• Cyclic neutropenia</li><li>• Respiratory tract infection</li></ul>