LETTER

On the road to discovery in periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome

Although the condition is rare, every pediatrician is likely to encounter at least one case of periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome during her or his career (1). PFAPA primarily affects preschool-age children and has a major impact on the daily life of the entire family. It is a nonhereditary disease of unknown etiology in which autoinflammatory attacks occur with an often remarkable periodicity. In the absence of a genetic or molecular marker, diagnosis relies exclusively on clinical phenotype, detailed case history, and the exclusion of other diseases (2). Although previous works have improved the clinical picture and diagnosis of PFAPA, the diagnostic criteria still fails to definitively exclude other periodic fevers of hereditary or unknown etiology and may inadvertently conceal different diseases from a pathophysiological perspective. Improved diagnostic methods can shorten the diagnostic delay and advance the quality of care for patients and their families as well as ensure that research studies aimed to improve our understanding of PFAPA can enlist clinically well defined patients.

The report by Stojanov et al. in PNAS is the most comprehensive analysis to date of the molecular and cellular phenotype of PFAPA syndrome (3). Stojanov et al. identified gene expression patterns in PFAPA patients during febrile episodes that can be distinguished from gene expression in afebrile periods or hereditary periodic fevers and from gene expression in healthy children. Data extracted from the gene expression studies provided evidence that patients may benefit from anti–IL-1 receptor antagonist (Anakinra); indeed, the severity of fever and the expression of a fever-associated biomarker (IP-10) responded positively to this treatment. The identification of a potential biomarker of PFAPA marks a substantial advancement in the understanding of PFAPA syndrome and the pursuit of a definitive diagnosis of PFAPA. It may also prove useful in the development of novel treatments, in which it can be used to monitor drug efficacy.

This report (3) also described alterations in blood cell abundances and inflammatory markers that we identified in 2010 in a small cohort of children in Sweden with PFAPA syndrome (4). It has been suggested that PFAPA flares are caused by an environmental trigger such as an infectious agent. Similar findings in the geographically and genetically distinct cohorts (Sweden and United States) offers strong evidence that the pathophysiological mechanism in both groups is the same. Moreover, it argues for one infectious agent with worldwide prevalence or a number of different infectious agents that are all able to set PFAPA syndrome in motion. The innate immune system indeed responds to different infectious agents in a similar manner. A shortcoming of both cohort studies is the focus on PFAPA syndrome in Caucasian children. As PFAPA syndrome affects children of multiple ethnicities (5), and racial differences in inflammatory and infectious challenge have been identified, it will be imperative to extend PFAPA studies in this direction.

***Kelly L. Brown*[a], *Per Wekell*[b,c], *Anna Karlsson*[d,1], *and Stefan Berg*[b]**

[a]*Centre for Understanding and Preventing Infection in Children, Child and Family Research Institute, Vancouver, BC, Canada V5Z 4H4;* [b]*Department of Pediatrics, Sahlgrenska Academy at the University of Gothenburg and The Queen Silvia Children's Hospital, Gothenburg, SE-405 30 Gothenburg, Sweden;* [c]*Department of Pediatrics, NU-Hospital Organization, SE-451 80 Uddevalla, Sweden; and* [d]*Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at the University of Gothenburg, SE-405 30 Gothenburg, Sweden*

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[1]To whom correspondence should be addressed: E-mail: anna.karlsson@rheuma.gu.se.