Reviewer's report

Title: Profile of Blood Cells and Inflammatory Mediators in Periodic Fever, Aphthous Stomatitis, Pharyngitis and Adenitis (PFAPA) syndrome

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Reviewer: isabelle kone paut

Reviewer's report:

Review article Brown et al BMC/PFAPA

This study is an attempt to identify modification in cells, serum acute phase reactants, cytokines and chemokines in PFAPA syndrome, that could help to understand the pathogenesis.

Three small groups of children have been studied: controls, PFAPA afebrile and PFAPA febrile

The study is limited due to the low number of patients, the lack of information on patient’s selection and the absence of “febrile” control group: MKD patients for example.

Patients and methods
1. How were these patients selected for the study?
2. The authors say that PFAPA was diagnosed in accordance to clinical criteria of Thomas et al…and that they ruled out patients from Mediterranean countries Netherlands and Belgium were excluded to avoid FMF and MKD. For this reviewer the only way to rule out MKD is to measure the mevalonic acid in the urine during acute episodes. It is not guaranteed that Swedish patients may not have MKD.
3. It is not clear if the patients have received steroids in both the febrile and afebrile group.

Results
1. SAA: It is interesting to note that SAA levels are not completely normal in the control group in contrast to the CRP levels. The same observation is present in the afebrile PFAPA group even SAA is markedly elevated in the febrile PFAPA group. What happened with patient 3?
2. Thrombocytosis in between febrile episodes is of interest (not observed in 2 patients). The problem is that if we compare the values in the same patients afebrile and febrile, for example patient 5 and 8, we do not find differences…..So is there a possible bias regarding patient selection.? 
3. The control group seems to have higher eosinophils count than PFAPA patients. There is a decrease in eosinophils count in between attacks, however the variation is within a range of 40 to 190/mm3 which is in the normal values? Is there a role in steroids administration to PFAPA febrile and afebrile patients?
Indeed there is an hypothesis for a link between this syndrome and atopia and it is well known than eosinophils from atopic patients bear high levels of receptor to steroids.

4. As the biological pattern of PFAPA is very proinflammatory, it is not clear why IL-1b is not elevated. One reason could be that IL-1b is generally undetectable in the serum even in clear IL1b linked disorders. Probably in vitro experiments with patient’s stimulated monocytes could show increased release of this cytokine. The concomitant elevation of the IL1RA and IL-6 in febrile patients could support this hypothesis

Discussion

1. Methodological limitations cited previously should be included in this section
2. As the classification of auto-inflammatory disorder is a challenging task, the authors should state if after this study they can give their opinion as classifying PFAPA in this category of disorders.
3. Moreover are the findings in accordance with an “immuno-allergic” mechanism?

Global assessment:

Is the question posed by the authors well defined? Yes and no
2. Are the methods appropriate and well described? Methods are ok. Limitation on patients are exposed in the patient section above
3. Are the data sound? yes
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? yes
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Are limitations of the work clearly stated? no
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? N\A
8. Do the title and abstract accurately convey what has been found? Yes
9. Is the writing acceptable? Yes