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OPEN PEER REVIEW

Fecal Calprotectin and the Complications of IgA-mediated Vasculitis: A Cohort Study

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1 Original submission

3 comments · 12 Apr 2024 – 24 Apr 2024

Referee 1 Reviewer

MINOR REVISION 12 Apr 2024

Thank you for this invitation.
The study design and concept are interesting. However, a few points could be considered:
1. How did you reach the final recommendation: "... considering the high cost of calprotectin test, the monthly follow-up with urine analysis seems to be a more logical approach..."?
What is the role of fecal calprotectin in IgA-associated vasculitis?
2. As a suggestion, the authors could include this valuable article in their work:
"Koninckx CR, Donat E, Benninga MA, Broekaert IJ, Gottrand F, Kolho KL, Lionetti P, Miele E, Papadopoulou A, Pienar C, Schäppi MG. The use of fecal calprotectin testing in paediatric disorders: a position paper of the European Society for Paediatric Gastroenterology and Nutrition Gastroenterology Committee. Journal of pediatric gastroenterology and nutrition. 2021 Apr 1;72(4):617-40."
3. Did you check all samples in the same laboratory?
4. When did you check the stool samples? On the 1st day of admission or diagnosis, or during follow-up?

Associate Editor

MINOR REVISION 24 Apr 2024

Dear EIC,
I thank the authors and express my appreciation to the researchers. The manuscript is a valuable piece of research. But some revisions are needed.
ABSTRACT:
1- The study design should be mentioned in the first line of the methods section of the ABSTRACT.
2- A summary of the statistical analysis results should be mentioned in the results section of the ABSTRACT.

Editor-in-Chief

MINOR REVISION 24 Apr 2024

Dear Author,
Thank you for submitting the article. It needs some revision. Please revise it based on the reviewers' and AE's comments.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear editor and dear reviewers,

Thank you very much for taking the time to review our manuscript. We are very thankful for your invaluable comments. We have provided answers to all of the comments and we are providing them in the following section. Moreover, the associated changes are marked by yellow highlight in the manuscript.

Reviewer 1:

1. How did you reach the final recommendation: "... considering the high cost of calprotectin test, the monthly follow-up with urine analysis seems to be a more logical approach..."

What is the role of fecal calprotectin in IgA-associated vasculitis?

Answer: As a matter of fact, answering this question was the goal of our study. We have discussed the studies that investigated the levels of calprotectin in HSP patients and tried to find the association with GI and renal manifestations of the disease. For instance, Kanik et al were able to find such an association between calprotectin and renal manifestation. In our study, we could not establish the correlation between renal involvement. This could also be attributable to the fact that we did not have many patients with hematuria and/or proteinuria, o elevated creatinine levels. However, we found a correlation between blood in stool and calprotectin levels. Therefore, we can suggest that calprotectin level is associated with GI involvement. It should be noted that in HSP, the major complication that we are worried about, can resent lately, and we need to do follow-up for, is renal involvement. Since we could not find any association between calprotectin level and renal involvement, we cannot suggest using this marker. On the other hand, there is a routine way for following up these patients, which is urine analysis, an easy and cheap test. That is why we concluded that we can suggest continuing the routine way of following up these patients with urine analysis rather that using an expensive test whose efficacy has not been proven.

We hope that this explanation satisfies the respected reviewer.

2. As a suggestion the authors could include this valuable article in their work:

"Koninckx CR, Donat E, Benninga MA, Broekaert IJ, Gottrand F, Kolho KL, Lionetti P, Miele E, Papadopoulou A, Pienar C, Schäppi MG. The use of fecal calprotectin testing in paediatric disorders: a position paper of the European Society for Paediatric Gastroenterology and Nutrition Gastroenterology

Committee. Journal of pediatric gastroenterology and nutrition. 2021 Apr 1;72(4):617-40."

Answer: Thanks to your invaluable comment, we added this sentence with the above reference to the introduction:

Fecal calprotectin is introduced as a better indicator of the possibility of inflammatory bowel disease (IBD) than serum inflammatory markers.

3. Did you check all samples in the same laboratory?

Answer: Yes, and thanks to your invaluable comment, we added it to methods:

All the samples were checked in the same laboratory.

4. When did you check stool samples? 1ts day of admission or diagnosis? or on their follow up?

Answer: We checked them on the first day of admission. We added this to the method:

The patients' fecal calprotectin levels were measured on the first day of admission using Biohit Calprotectin Elisa kit, …

Reviewer 2:

Fecal calprotectin (FC) elevation indicates intestinal inflammation, and is can be used as an indicator for other intestinal diseases. FC can be used as an indicator of GI involvement in HSP patients, and may be used as a prognostic factor of duration of GI symptoms or response of treatment. Please explain why serum calprotectin is not used for involvement of internal organs such as synovium or kidney?

Answer: Thank you very much for your invaluable comment. As a matter of fact, some studies have proposed that calprotectin can be used as a marker of renal involvement. We have explained this in our discussion in the following part:

Kanik et al reported that the level of calprotectin was higher in patients with renal complications of HSP, i.e., hematuria, proteinuria, and elevated creatinine(15). Kawasaki et al studied HSP patients with renal injury according to kidney biopsy in two groups of low and high calprotectin. Proteinuria was more frequent in the high calprotectin group, but there was not a significant difference in hematuria and creatinine levels. The frequency of International Study of Kidney Disease in Children (ISKDC) classification grades of 3, 4, or 5 was higher in the high calprotectin group(14). Ohara et al divided 37 patients in two groups of minimal change disease and

glomerulonephritis (GN) and compared their levels of MRP8/14, which was significantly higher in GN group(10). Conversely, we did not find any association between calprotectin level and hematuria or proteinuria. This might be due to the small sample size and therefore the low number of hematuria (10 patients) and proteinuria (8 patients). Furthermore, there was no indication to a renal biopsy in our patients to analyze the association of pathology with calprotectin level.

Regarding synovial involvement, Abidltrup at al. published a systematic review on he use of calprotectin as an indicator of disease activity, therapeutic response, and prognosis in rheumatoid arthritis (RA). They included 17 studies. Here is their result: Calprotectin levels were high in active disease and were particularly high in rheumatoid factor (RF)-positive patients. Levels fell with effective treatment. Longitudinal data showed that calprotectin was a significant and independent predictor of erosive progression and therapeutic responses, particularly in patients who received effective biological treatments.

As our study did not focus on musculoskeletal involvement, we have not discussed this in our article before. However, thanks to your invaluable comment, we added this reference to the introduction in this way:

Elevated levels of calprotectin were found in patients with rheumatoid arthritis, consistent with the disease activity(14).

Associate editor's comments:

1- Study design should be mentioned in first line of method section of ABSTRACT

Answer: We added this to the first line of method:

In this cohort study, …

2-Summary of Statistical analysis results should be mention in result section of ABSTRACT.

Answer: Some of the statistical analyses were already included, and we edited the result section in the following way:

Out of the 100 patients who began to participate, 47 were eventually enrolled (25% girls). The age ranged from 2 to 18 years, mean 6.5 ± 2.9. Hematuria was found in 21% and proteinuria in 17%. Mann-Whitney test found an association between calprotectin and blood in stool (P value=0.03). No association was found between calprotectin and abdominal pain, sonography findings, hematuria, or proteinuria. Pearson correlation test found a positive

correlation between calprotectin level and leukocyte count (P value=0.003), neutrophil count (P value=0.002), and CRP (P value=0.03).

2 Revision 1

3 comments · 15 May 2024 – 18 May 2024

Referee 1 Reviewer

ACCEPT 15 May 2024

Thanks a lot for the invitation to the second round of review.
The explanations were satisfactory. However, the recommended reference (9) explained the role of FC in HSP and other IgA vasculitis.

Associate Editor

ACCEPT 18 May 2024

Dear EIC.
Previous errors have been corrected, and there are no further recommendations.

Editor-in-Chief

ACCEPT 18 May 2024

Dear authors.
Thanks for your valuable efforts in carefully revising the manuscript.