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OPEN PEER REVIEW

IL-17 Producing T cells as Predictors of Primary Immunodeficiencies in Patients with *Candida* Infections

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

3 comments · 4 Mar 2021 – 19 Apr 2021

Associate Editor

MINOR REVISION 4 Mar 2021

Dear author
1- Please add "the number" in the following sentence (line 8):
The purpose of this study is to evaluate the role of (the number) of Th17 cells as the predictor of…
2- Please describe the role of the questionnaire filled out by the physician (lines 61-63).
3- Please provide a complete report of the results of statistical analysis related to the comparison of Th17 cells in the two groups.
Regards

Referee 1 Reviewer

MAJOR REVISION 4 Apr 2021

1- Candida should be capitalized and italicized in the manuscript.
2- Th17 should be written in a consistent format (TH17 or Th17).
3- How did the authors detect the fungal infection? The laboratory tests must be specified in the manuscript.
4- The authors are required to explain how they ruled out combined immunodeficiency and neutrophil disorders.
5- The flow cytometry methods should be explained completely.
6- The concentration of Ionomycin should be specified in the manuscript.
7- Please specify the color and company name of the flow cytometry antibodies.
8- Flow cytometry graphs showing the gating of Th17 should be included in the manuscript.
9- The quality of figure 1 is low, and it should be replaced with a high-quality one.
10- The age range of the patients is very wide, and it may affect the frequency of Th17. How can the authors explain this?
11- Why was immunophenotyping by flow cytometry not performed for all the patients?
12- Language editing is required.

Referee 2 Reviewer

MAJOR REVISION 19 Apr 2021

Dear Author ,

Thank you for submitting your work to Archives of Pediatric Infectious Diseases.
I read the manuscript. It is not clear why you consider a low number of Th17 to be a predictive factor for PID. It is known that Th17 are decreased or functionally abnormal in immunodeficiency syndromes that manifest with recurrent fungal infections. Therefore, the key message and novelty of this study remain unclear.
In the discussion, you need to emphasize the study of the functional assay and the limitation you encountered.

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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.

Point-to-Point Answers

Reviewer 1

Dear Reviewer 1

Thank you very much for your detailed comments. We believe your comments help promoting the quality of our manuscript.

- We have changed all the "*Candida*"s through the text with the format you recommended.
- All the Th17 cells are written with the same format.
- Fungal infections are detected and confirmed by culture in appropriate media.
- We ruled out combined and phagocytic immunodeficiencies after performing immunologic screening for the patients which is now mentioned and yellow highlighted.
- The flowcytometry method is now added to the text and highlighted.
- The concentration of ionomycin is added to the text.
- The color and the company name is added to the "Methods".
- Th17-gated flowcytometry graphs are added.
- The quality of figure 1 is improved.
- As you know CMC is a disease of all ages. Because many patients do not present with their skin disorder to physicians and the disease remains undiagnosed. Unfortunately, many physicians are not aware of immunodeficiency states which may accompany refractory/relapsing dermatoses. Therefore, many patients may remain undiagnosed until adulthood.
- It is true that a wide range exists among the patients in this study but we tried to overcome the variety in the count of Th17 cells by selecting a sex and age-matched normal healthy control for each patient. So, I assume we had fixed this possible bias in this way.
- Immunophenotyping has been performed for all the patients. But after ruling out the combined immunodeficiencies they were no longer collected in their records. So, they were not available for us at the time of writing the manuscript. While, all the patients had undergone this test before entering the study.
- The text is edited by a native English this time.

Point-to-Point answers Reviewer 2

Dear reviewer

Below, we are going to respond the reason why we chose Th17 as a biomarker for specific types of primary immunodeficiencies which are associated with mucocutaneous candidiasis, discussed in this manuscript.

- "**Th17 cells produce the IL-17 family of cytokines on epithelium, which resist dermal opportunistic infections. Th17 cell dysfunction is associated with chronic muco-cutaneous candidiasis**".
  Cited from: Lower T regulatory and Th17 cell populations predicted by RT-PCR-Amplified *FOXP3* and *ROR*γt changes are not rare in patients with primary immunodeficiency diseases. **Frontiers in Immunology, 25 June 2020.**

- We added the functional assay to the "Method" section.
- We added the limitations of the study.
- The key message of this study was in regard to selecting targeted panels of genetic tests in patients with low counts of Th17 cells instead of performing Whole Exome Sequencing. So, in this way the results of the genetic testing became more precise than doing as a whole exome sequencing.

Point-to-Point responses to Associate Editor 1:

Dear Associate Editor 1

Thank you for your detailed comments. We made the following changes according to your recommendations:

- We added the "number" in the 8th line and green-highlighted it.
- We explained the role of the acquisition of data in confirming the eligibility of the participants and green-highlighted it.
- We provided a complete report of the statistical analysis of the Th17 cells in the two studied groups in Table 3.

Point-to-point answers to Associate Editor 2

Dear Associate Editor 2

You criticized our manuscript because of the small number of the patients participated in this study. But as you know primary immunodeficiencies are rare disorders. In order to have a big sample size, multicenter studies are required. Since CMCs are very rare primary immunodeficiency disorders we have asked other immunodeficiency centers in Tehran to refer their patients to us and finally we have collected these seven patients by asking other colleagues from other medical universities.

Point-to-point answers to Associate Editor 3

- The enumeration of CD3 cells has been performed after stimulation.
- Cell permeability has been done for measurement of Th17 cells.
- The diagnosis of primary immunodeficiencies were suggested after ruling out other differential diagnosis not only by lab findings but also with the specific clinical course and the relapsing nature of fungal infections in mucocutaneous sites.

- We made the changes in Table 1 as you recommended.

2 Revision 1

2 comments · 26 Aug 2021 – 8 Nov 2021

Mahdi Kalani Reviewer

MINOR REVISION 26 Aug 2021

Dear Editor-in-Chief
Archives of Pediatric Infectious Diseases

Respectfully, I would like to inform you that the authors addressed all comments in accordance with my suggestion. However, based on their responses, in the title and elsewhere in the manuscript, they should replace TH17 with IL-17 producing T cells because they used only anti CD3 and anti IL-17 antibodies to detect TH17. With these antibodies, some other T cells, like CD8+ T cells as well as gamma-delta T cells, may be considered TH17, which can affect the results.
If they used anti CD4 antibodies with anti-IL-17, they could confirm TH17.
Best Regards,

Associate Editor

MINOR REVISION 8 Nov 2021

Dear authors
The manuscript's overall presentation improved after amendments; however, some correction is warranted based on the reviewer's comments.
Thanks

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Revision 2

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.

Point-to-Point Answers

Dear Editor-in-Chief

We have made the following changes according to the reviewer 1 comments:

Reviewer 1: The authors should replace IL-17 producing T cells instead of TH17.

Answer: We changed all Th17 cells throughout the text to IL-17 producing T cells. The changes are made in the following lines of the text:

Lines number: 1, 5, 8, 10, 17, 20, 24, 26, 30, 35, 38, 39, 45, 47, 50, 53, 55, 68, 82, 90, 95, 97, 99, 102, 113, 116, 120, 121, 123, 125, 127, 128, 130, 132, 133, 146, 148, 243, 252.

We also changed TH17 cells to IL-17 producing T cells in Table 3 (in caption and the first two columns from the left) and highlighted them.

We also changed the TH17 cells to IL-17 producing T cells in Figure 1.

Reviewer 2: All the points mentioned in the first review have been modified.

Answer: Please consider that reviewer 2 has accepted the modified manuscript.

3 Revision 2

0 comments

No public comments in this round.