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OPEN PEER REVIEW

Seroprevalence of Toxocariasis Among Hypereosinophilic Children: A Single Center Study, Tehran, Iran

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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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Contents

1 Original submission 2
2 Revision 1 Associate Editor 3
Authors' reply to reviewers 4
Reviewer and editor comments 13
3 Revision 2 Associate Editor 15
Authors' reply to reviewers 16
Reviewer and editor comments 21
4 Revision 3 Associate Editor 22
Authors' reply to reviewers 23
Reviewer and editor comments 25

1 Original submission

0 comments

No public comments in this round.

2

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-in-Chief of Archives of Pediatric Infectious Diseases,

Thank you for giving us the opportunity to submit a revised draft of the manuscript, 123107, "Seroprevalence of toxocariasis among hypereosinophilic children in Iran; a closer look into risk factors" for publication in "*Archives of Pediatric Infectious Diseases"* journal.

We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments on and valuable improvements to our paper.

We have incorporated the suggestions made by the reviewers. Those changes are highlighted in yellow within the manuscript.

Yours Sincerely,

Reviewer #1:

We appreciate the reviewers for their precious time in reviewing our paper and providing valuable comments. It was your valuable and insightful comments that led to possible improvements in the current version. The authors have carefully considered the comments and tried our best to address every one of them. Below we provide the point-by-point responses. All modifications in the manuscript have been highlighted in yellow.

Comment 1:

The author is suggested to delete the word objective (Line 7).

Response:

This word has been deleted in the text.

Comment 2:

The author is suggested to change the first line to this one: Variatious factors, including toxocariasis, can cause Hypereosinophilis (Line 8).

Response:

This comment has been changed in the text.

Comment 3:

Line 9: The study aims to instead of "*The goal of this study is*"

Response:

This comment has been done in the text.

Comment 4:

Line 10: Mention the name of the hospital instead of saying only the Iranian hospital

Response:

The haspital name has been mentioned in the text.

Comment 5:

Line 10: Children's instead of children

Response:

This comment has been done in the text.

Comment 6:

Line 14: Consider spelling out 282 because it appears at the beginning of your sentence.

Response:

This comment was considered in the manuscript.

Comment 7:

Line 15: Erase "an" before informed

Response:

The deletion was done in the text.

Comment 8:

Line 16: Write "the" before "Serological ELISA"

Response:

"the" was included in mentioned section.

Comment 9:

Line 17: Delete "in order"

Response:

The deletion was done in the manuscript.

Comment 10:

Line 23: "reported to be" is unnecessary, so delete it

Response:

The comment was done in the manuscript.

Comment 11:

Line 27: The word “nonspecific” has been written in the manuscript with and without a hyphen. Both ways are acceptable, but it is best to be consistent.

Response:

The comment was considered in the manuscript.

Comment 12:

Line 31: Display alphabetically

Response:

The comment was applied in the manuscript.

Comment 13:

Line 34: Check the journal guideline to see if it is needed to write “Background & Objectives” or “introduction”

Response:

The necessary change has applied in the manuscript.

Comment 14:

Line 35: Delete the word “ that is”

Response:

The deletion was done in the manuscript.

Comment 15:

Line 36: Toxocara canis instead of Toxocaracanis

Response:

The comment was considered in the manuscript.

Comment 16:

Line 36: Rewrite this sentence in a way that needs not to be explained in parenthesis

Response:

The comment was considered in the manuscript.

Comment 17:

Line 37: Socioeconomic instead of socio-economic, change accordingly throughout the manuscript

Response:

The comment was considered in the manuscript.

Comment 18:

Line 40: Antibodies instead of the antibody

Response:

The comment was applied in the text.

Comment 19:

Line 41: Delete the “reported to be”

Response:

The deletion was done in the manuscript.

Comment 20:

Line 49: There are instead of “there is”

Response:

This comment has been done in the text.

Comment 21:

Line 53: Eosinophilia is a sign, not a symptom

Response:

Thank you for your precious comment. The comment was considered in the manuscript.

Comment 22:

Line 56: Microliter, not millilitre; change accordingly throughout the manuscript

Response:

The comment has been changed in the manuscript.

Comment 23:

Line 56: Delete the word “of them”

Response:

The word has been deleted in the manuscript.

Comment 24:

Line 57-59: A count of more than 0.5 × 109/L eosinophils of blood is generally considered eosinophilia in adults which is divided into mild, moderate, and severe according to the eosinophil counts. Hypereosinophilia (HE) is defined as persistent prominent eosinophilia (absolute eosinophils ≥1.5 × 109/L) in peripheral blood.

Response:

The values mentioned in the text are based on the exist references. If 1500 eosinophile cells/mm^3 were considered as hypereosinophilia, sensitivity of the study was lowere and there was a possibility of missing positive cases that were in early stages of the disease or did not have very high number of eosinophile.

Comment 25:

Line 64: are (instead of is)

Response:

This comment has been changed in the text.

Comment 26:

Line 71: Again check the journal guideline to see what has to be written here

Response:

This comment has been considered in the manuscript.

Comment 27:

Line 72-73: In this section, the authors have written that the participants were related to the year 2016 while in the last paragraph of the introduction section something else was written.

Response:

This comment has been corrected in the manuscript.

Comment 28:

Line 77: environmental blood factors

Response:

It was changed to peripheral blood factors

Comment 29:

Line 77: Measured instead of “administered”

Response:

The change has been applied in the text.

Comment 30:

Line 78-80: Children with an eosinophil count of more than 1500/dl should be considered hypereosinophilia

Response:

This comment has been considered in the manuscript.

Comment 31:

Line 86: Sera instead of “serums”

Response:

The change has been done in the text.

Comment 32:

Line 86: Instead of writing light absorption, write absorbance was measured]

Response:

The comment has been done in the text.

Comment 33:

Line 93: This mean age plus and minus the standard deviation (3.65 ± 7.31)does not seem to be correct unless the data distribution is very high. So recheck is suggested.

Response:

Thanks for your valuable comment. Unfortunately the age of some paticipatns were input wrongly which were rectified and analysed again..

Comment 34:

Line 93: The eosinophilia unit should be mentioned

Response:

This comment has been done in the text.

Comment 35:

Line 94: There is no figure in the text

Response:

The figure is presented on page 13 of PDF file.

Comment 36:

Line 100: The same comment as line 93 goes for this line

Response:

This comment has been considered in the manuscript.

Comment 37:

Line 112: In line 111 authors mentioned that none of the children with toxocariasis had any contact with animals while in line 112 they have said such contact was higher in children with toxocariasis compared to those who weren’t suffering from toxocariasis

Response:

In the line 111 "keeping of animals in house" but in line 112 "dog and cat contact" was mentioned. Theses issues are different.

Comment 38:

Line 165-167: What is the explanation of the authors for the high rate of infection in Ahvaz (50% in Ref:11) since they attributed the low prevalence of infection in Iran to religious issues? Meanwhile, the authors said that having contact with dogs is prohibited in Iran? What about cats?

Response:

You are right but there may be multifactorial causes for high prevalence of toxocariasis in this region such as climate, food culture or presence of a large number of stray dogs and cats.

Comment 39:

Line 188-190: This should be the part of the result, not a discussion

Response:

The comment has been performed in the manuscript.

....

Comment 40:

Line 193-195: What is the relationship of this statement with the study's conclusion? How checking the IgE can help this kind of patient when there is hypereosinophilia with a positive Toxocara antibody test?

Response:

The sentence was removed from the text.

Comment 41:

Line 196-197: This is already been known. When a child suffers from eosinophilia, the first thing that should come to a physician's mind must be toxocariasis.

Response:

You are right and our study comfirmed this issue.

Comment 42:

Line 199-200: ESR and CRP elevate in any inflammation and infection, not only toxocariasis.

Response:

You are right, the sentence was deleted.

Comment 43:

Line 237: Reference number 9 is not completed.

Response:

The mentioned reference was completed.

Reviewer #2:

We appreciate the reviewers for taking the time to read our paper and many helpful suggestions. The changes have been highlighted in yellow within the manuscript. The followings are our point-by-point responses:

Comment 1:

In the row No 73, the date is not correct (2016 instead of 2020).

Response:.

This comment was considered in manuscript.

Comment 2:

In the row No 102, mean eosinophilic count is better to completely mention with unit

Response:

The comment has been done in the text.

Reviewer #3:

I would like to thank the reviewer for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript.The changes have been highlighted in yellow within the manuscript. The followings are our point-by-point responses:

Comment 1:

Please write mean ± SD for age.

Response:

The comment has been considered in the text.

Comment 2:

Please write exact p-value for comparison of ESR and CRP between two groups. Results

Response:

The comment has been done in the manuscript.

Comment 3:

Please only mention that is there any association between positive serology and risk factors or not and refer it to your table.

Response:

As it has been mentioned in result section, there is not a significant correlation (p- values are mentioned in the table) between risk factors and serological positive people.

Comment 4:

Please report that the residential area (rural vs. urban) is associated with seropositivity or not.

Response:

The comment has been done in the text.

Comment 5:

Table-1 should be deleted and only report it in your results.

Response:

The comment has been done in the text.

Comment 6:

Table-2: If there is normal distribution in your cases mean ± SD is enough and median ± IQR should be deleted. Figure-1 should be deleted and only report it in your results.

Respons

As some variable were non- normal, both mean and median are reported.

The figure 1 has been deleted.

2 Revision 1

1 comment · 18 Aug 2022

Associate Editor

MAJOR REVISION 18 Aug 2022

Editorial comments
Dear authors
The manuscript's overall presentation improved after amendments. Although your replies to the concerns of the reviewers are satisfactory, the authors should consider the following shortcomings:

In cross-sectional studies, association and correlation could be investigated, but not risk factors; accordingly, the title should be corrected. Your study is an example of a seroprevalence study.
Suggestion for the title: "Seroprevalence of toxocariasis among hypereosinophilic children, a single center study, Tehran, Iran"

Line 7: replace the first sentence: "Toxocariasis is a parasitic cause of hypereosinophilia."
Line 34: remove "parasites"
Dear authors, first, the exact definitions of eosinophilia and hypereosinophilia should be written based on valid references. If you have another cutoff in mind, explain it in the methods section. Your answer to Reviewer 1, comment 24 was not acceptable. Also, move the definitions of "eosinophilia and hypereosinophilia" to follow this statement: "Toxocariasis or VLM is a known cause of eosinophilia and hypereosinophilia (HE)".

Lines 74-75 should be replaced with: "Inclusion criteria were children referring to the Children's Hospital Medical Center for blood testing."

Regarding reviewer 1, comment 34: the correct unit is "per microliter of blood". Consider correcting this throughout the manuscript.

Lines 78-79: "Children with eosinophil count less than 1000 per microliter of blood were excluded."
Replace "eosinophilia" with "eosinophil count" throughout the text when reporting counts.

Figure 1 needs corrections. First, the study year should be corrected. Second, the title should be rewritten with the correct words: "Age distribution of children with hypereosinophilia who visited the Children's Hospital Medical Center for blood testing as an outpatient." Third, the mean age and SD are not similar to the values reported in the text. Finally, use an Excel graph for a better illustration of age units. Remove decimals.

Line 100: "The mean eosinophil count was 1.4±2.3 per microliter ..." is correct.

Line 112: remove: "than non-infected children"

Lines 186-188 should be replaced with: "In our study, there was no significant association between toxocariasis seropositivity and liver function tests."
Add the following statement to the end of the results section: "There was no significant association between SGOT, SGPT and ALKP values and toxocariasis seropositivity in our study ($p > 0.05$)."

The title of Table 1 should be revised. My suggestion: "Laboratory characteristics of children with hypereosinophilia who visited the Children's Hospital Medical Center for blood testing as an outpatient".

The title of Table 2 should be revised. My suggestion: "Investigated exposures of children with hypereosinophilia who visited the Children's Hospital Medical Center for blood testing as an outpatient".

The discussion section should be improved.
Add study limitations/advantages to the end of the discussion section.

One of the main objections to the obtained results is selection bias. Increased ESR and CRP also may be surrogate markers for bacteremia and sepsis. So, researchers may encounter unwanted bacteremia/sepsis-induced eosinophilia in this study (pseudo-eosinophilia). The presence of an immunology clinic in the study center and the inclusion of patients referred for immunological workups constitute another important issue for which no useful information is provided in the paper for clarification. Accordingly, the discussion should be focused on these points and the possible causes of the low seropositivity in the study.
The conclusion should be revised entirely. The conclusion is not informative and does not correctly summarize the study results.

The titles of Tables 1 and 2 should be corrected. Consider the correct study year. Separate the last column of Table 2 into two distinct columns: OR (95%CI) and P-value.

To ensure the Editor will be able to recommend that your revised manuscript is accepted, please pay careful attention to each of the comments that have been posted. This way we can avoid future rounds of clarifications and revisions, moving swiftly to a decision.

1. Please provide a point-by-point response to the comments
2. Please highlight all the amendments in your manuscript
3. Use line numbering and page numbers in the next submission

3

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.

Dear Editor-in-Chief of Archives of Pediatric Infectious Diseases,

Thank you for giving us the opportunity to submit a revised draft of the manuscript, 123107, “Seroprevalence of toxocariasis among hypereosinophilic children in Iran; a closer look into risk factors” for publication in “*Archives of Pediatric Infectious Diseases”* journal.

We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments on and valuable improvements to our paper.

We have incorporated the suggestions made by the reviewers. Those changes are highlighted in yellow within the manuscript.

Yours Sincerely,

* Corresponding author:

Dr Bahram Nikmanesh

Zoonosis Research Center, Tehran University of Medical Sciences, Tehran, Iran.

Department of Medical Laboratory Sciences, School of Allied Medical Sciences, Tehran University of Medical Sciences, Tehran, Iran.

Reviewer #1:

We appreciate the reviewers for their precious time in reviewing our paper and providing valuable comments. It was your valuable and insightful comments that led to possible improvements in the current version. The authors have carefully considered the comments and tried our best to address every one of them. Below we provide the point-by-point responses. All modifications in the manuscript have been highlighted in yellow.

Comment 1:

In cross-sectional studies, association and correlation could be investigated not risk factors, accordingly title should be corrected. Your study is an example of a seroprevalence study. Suggestion for the title: "Seroprevalence of toxocariasis among hypereosinophilic children, a single center study, Tehran, Iran"

Response: Thanks for the invaluable comment. The modification was done (line 1)

Comment 2:

Line 7: replace the first sentence: "Toxocariasis is a parasitic cause of hypereosinophilia."(Line 7).

Response: Thanks for the invaluable comment. The modification was done (line 8).

Comment 3:

Line 34: remove "parasites"

Response: Thanks for the invaluable comment. The modification was done.

Comment 4:

Dear authors, first, the exact definition of eosinophilia and hypereosinophilia should be written based on valid references. If you have another cut-off in mind, explain it in the method. Your answer to Reviewer 1, comment 24 was not acceptable. Also, move definitions of "eosinophilia and hypereosinophilia" following this statement: "Toxocariasis or VLM is a known cause of eosinophilia and hypereosinophilia (HE)".

Response: Thanks for the invaluable comment. The modification was done (line 57-59)

Comment 5:

Lines 74-75: should be replaced with: "Inclusion criteria were children referring to the Children's Hospital Medical Center for blood testing."

Response: Thanks for the invaluable comment. The modification was done (line 75-76)

Comment 6:

Regarding reviewer 1, comment 34: correct unit is "per microliter of blood". Consider correction in the whole manuscript.

Response: Thanks for the invaluable comment. The modification was done.

Comment 7:

Lines 78-79: "Children with eosinophil count less than 1000 per microliter of blood were excluded.

Response: Thanks for the invaluable comment. The modification was done (line 78-79)

Comment 8:

Replace "eosinophilia" with "eosinophil count" in the whole text when reporting counts.

Response: Thank you very much for the pointer to this paper. The modification was done.

Comment 9:

Figure 1 needs corrections. First, the study year should be corrected. Second, the title should be rewritten with the correct words: "Age distribution of children with hypereosinophilia who visited the Children's Hospital Medical Center for blood testing as an outpatient." Third, mean age and SD is not similar to values reported in the text. Finally, use an excel graph for a better illustration of age units. remove decimals.

Response: Thank you very much for the pointer to this paper. The modifications were done. The mentioned figure deleted according to comment 35 of previous referee.

Comment 10:

Line 100: "The mean eosinophil count was 1.4±2.3 per microliter ..." is correct.

Response: Thank you very much for the pointer to this paper. The modification was done.

Comment 11:

Line 112: remove: "than non-infected children"

Response: Thank you very much for the pointer to this paper. The modification was done.

Comment 12:

Lines 186-188 should be replaced with: "In our study, there was no significant association between toxocariasis seropositivity and liver function tests."

Response:Thank you very much for the pointer to this paper. The modification was done.

Comment 13:

Add the following statement to the end of the results section: "There was no significant association between SGOT, SGPT and ALKP values and toxocariasis seropositivity in our study (p> 0.05)."

Response: Thank you very much for the pointer to this paper. The modification was done.

Comment 14:

Table 1 title should be revised. My suggestion: "Laboratory characteristics of children with hypereosinophilia who visited the Children's Hospital Medical Center for blood testing as an outpatient".

Response: Thank you very much for the pointer to this paper. The modification was done.

Comment 15:

Table 2 title should be revised. My suggestion: "Investigated exposures of children with hypereosinophilia who visited the Children's Hospital Medical Center for blood testing as an outpatient".

Response: Thank you very much for the pointer to this paper. The modification was done.

Comment 16:

The discussion section should be improved. ….

Response: Thank you very much for the pointer to this paper. The modification was done (line 180-184 and 196-202).

Comment 17:

Add study limitations/advantages to the end of the discussion part.manuscript

Response: Thank you very much for the pointer to this paper. The modification was done (line 196-202).

Comment 18:

One of the main objections to the obtained results is selection bias. Increased ESR and CRP also may be surrogate markers for bacteremia and sepsis. So, researchers may encounter unwanted bacteremia/sepsis-induced eosinophilia in this study (pseudo-eosinophilia). The presence of an immunology clinic in the study center and including patients referred for immunological workups is another important issue which no useful information is provided in the paper for clarification. Accordingly, the discussion should be focused on these points and the possible causes of the low seropositivity in the study.

Response: Thank you very much for the pointer to this paper. The modification was done (line 180-184 and 196-202).

Comment 19:

The conclusion should be revised totally. The conclusion is not informative and does not correctly conclude the study results.

Response: Thank you very much for the pointer to this paper. The modification was done (line 206-210).

Comment 20:

Tables 1 and 2 titles should be corrected. Consider the correct study year. Separate the last column of Table 2 into two distinct columns: OR (95%CI) and P-value.

Response: Thank you very much for the pointer to this paper. The modification was done (Table 2).

3 Revision 2

1 comment · 23 Sep 2022

Associate Editor

MINOR REVISION 23 Sep 2022

Editorial comments
Dear authors
The manuscript's overall presentation improved after amendments and is now more readable. Although your replies to the reviewers' concerns are satisfactory, the manuscript still needs to be improved.

Line 64: "per microliter" is correct.
Line 65: "per microliter" is correct.
Line 119: remove "than non-infected children".
Line 182-183: "If seroprevalence is associated with other associated factors to toxocariasis including eosinophilia, pica behavior and consumption of raw meat the prevalence is statistically higher" is difficult to read and understand.
Line 183-184: "Toxocariasis should always be considered in any child with hypereosinophilia and compatible clinical signs and symptoms, even in low endemic regions."

4

Revision 3

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.

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We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments on and valuable improvements to our paper.

We have incorporated the suggestions made by the reviewers. Those changes are highlighted in yellow within the manuscript.

Yours Sincerely,

Reviewer #1:

We appreciate the reviewers for their precious time in reviewing our paper and providing valuable comments. It was your valuable and insightful comments that led to possible improvements in the current version. The authors have carefully considered the comments and tried our best to address every one of them. Below we provide the point-by-point responses. All modifications in the manuscript have been highlighted in yellow.

1. **Comment 1:**

Line 64: "per microliter" is correct.

Response to comment 1:

Thanks for the invaluable comment. The modification was done (Line 64).

2. **Comment 2:**

Line 65: "per microliter" is correct.

Response to comment 2:

Thanks for the invaluable comment. The modification was done (Line 65).

3. **Comment 3:**

Line 119: remove "than non-infected children".

Response to comment 3:

Thanks for the invaluable comment. The modification was done (Line 119).

4. **Comment 4:**

Line 182-183: "If seroprevalence is associated with other associated factors to toxocariasis including eosinophilia, pica behavior and consumption of raw meat the prevalence is statistically higher", is difficult for reading and understanding.

Response to comment 4:

Thanks for the invaluable comment. The modification was done (Line 182-183).

5. **Comment 5:**

Line 183-184: "Toxocariasis should always be considered in any child with hypereosinophilia and compatible clinical signs and symptoms, even in low endemic regions.".

Response to comment 5: Thanks for the invaluable comment. The modification was done (Line 183-184).

4 Revision 3

1 comment · 25 Oct 2022

Associate Editor

ACCEPT 25 Oct 2022

I read the revised manuscript.
I have no further comments to add. I thank the authors for their very detailed replies to my comments.