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OPEN PEER REVIEW

Evaluation of Serum Zinc Levels in Children of 6 Months to 5 Years of Age Diagnosed with Simple Febrile Seizures

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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

2 comments · 26 Dec 2022 – 20 Jan 2023

Zahra Rezaei Reviewer

MAJOR REVISION 26 Dec 2022

Dear corresponding author/s,
Thank you for submitting your valuable study to IJP. There are some points that might be helpful in making your article more comprehensive, as follows:
1. Febrile seizure (FS) is commonly used instead of the previous terminology, febrile convulsion. Please mention it in your manuscript.
2. The aim of the abstract contains a definition of FS. Please note that all definitions related to seizure/epilepsy should follow ILAE guidelines. Besides, it is mentioned that in FS, a seizure is associated with infection. But keep in mind that fever induced by vaccination could lead to FS, although it is not an infectious process.
3. The part "material" should be rewritten in the abstract section. Please clarify the whole methodology in a clear and brief manner.
4. It should be mentioned which types of FS the study evaluates: simple FS, complex FS, febrile status epilepticus, and so on. The results should be revised accordingly.
5. Please clarify the "normal years of cases" that are used in the results part of the abstract.
6. The purpose of the study is mentioned as " the possible role of sink in the pathogenesis, prophylaxis, and treatment of Fs". Considering that the article is descriptive, this aim is not clearly addressed in the conclusion and discussion parts.
7. The sentence "...the body temperature of the patients.." is repeated twice.
8. The discussion part is too disorganized. Please summarize this part while focusing on the aim of the study.
9. In the discussion, the author/s claim that "... We believe low zinc levels are not only associated with .... But also....". As mentioned in the manuscript, there are only paraclinic data in favor of the above sentence. So you could simply propose a hypothesis that needs to be evaluated in detail later.
10. "The statistically negative correlation..." should be described with statistical evidence (P....).

Referee 1 Reviewer

MAJOR REVISION 20 Jan 2023

The authors present a cross-sectional descriptive study looking at the relationship between serum zinc levels and febrile convulsions. They performed a cross-sectional study on 85 pediatric patients, dividing them into 3 groups: 1- fever only, 2- fever and convulsions, and 3- control group. They checked whether low serum zinc levels were present in the fever-only and FC groups and whether there was an association. They found that serum zinc levels were significantly lower in patients with febrile convulsions and in the fever-only group.
Specific comments/questions:
1- The number of references is appropriate and their selection is judicious. But the references are not up to date, and recently published literature should be added and discussed. These include but are not limited to:

- Bakri AH, Hassan MH, Ahmed AE, Halim PR, El-Sawy SA, Mohamed MM, Rashwan NI. Biochemical Assessments of Neurotrophin-3 and Zinc Involvement in the Pathophysiology of Pediatric Febrile Seizures : Biochemical Markers in Febrile Seizures. Biol Trace Elem Res. 2022 Jun;200(6):2614-2619. doi: 10.1007/s12011-021-02886-w. Epub 2021 Aug 18. PMID: 34406624.

- Kumar M, Swarnim S, Khanam S. Zinc Supplementation for Prevention of Febrile Seizures Recurrences in Children: A Systematic Review and Meta-Analysis. Indian Pediatr. 2021 Sep 15;58(9):857-860. Epub 2021 Aug 2. PMID: 3433822

- Arul J, Kommu PPK, Kasinathan A, Ray L, Krishnan L. Zinc Status and Febrile Seizures: Results from a Cross-sectional Study. J Neurosci Rural Pract. 2020 Oct;11(4):597-600. doi: 10.1055/s-0040-1715992. Epub 2020 Sep 8. PMID: 33144797; PMCID: PMC7595794.

- Heydarian F, Nakhaei AA, Majd HM, Bakhtiari E. Zinc deficiency and febrile seizure: a systematic review and meta-analysis. Turk J Pediatr. 2020;62(3):347-358. doi: 10.24953/turkjped.2020.03.001. PMID: 32558408.

2- It would be interesting to see the relationship between serum zinc levels and seizure type and frequency. These data should be easily available to the authors (line 60-64) and would add interesting data on relationships that remain controversial.

3- The authors discuss the relationship between leukocytosis and fever in the 4th paragraph of the discussion (lines 165 -182). However, it should be mentioned and discussed that the increase in WBC and neutrophil counts in patients with febrile convulsions could also be a transient effect due to the demarginating effects of circulating catecholamines after a seizure.

4- I would suggest a more evidence-based discussion about the relationship between WBC count and zinc levels. (Lines 181 – 182)

5- While discussing the relationship between FC and CRP levels (lines 186-188), I think it should be changed to: “the reason for this is suggested that the inflammatory response is slower in children WITH FEBRILE CONCULSION”. I believe the cited literature (reference 31) is misplaced since it doesn’t have any content related to CRP and FC.

6- All abbreviations used in tables should be explained in the table footer.

7- The abstract conclusion is not very clear and needs rephrasing.

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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.

Response to Reviewer 1:

Dear reviewer, first of all, thank you very much for your comments and contributions on these values, these comments will shed light on our future studies.

1. Febrile seizure (FS) is commonly used instead of the previous terminology, febrile convulsion. Please mention it in your manuscript.

Response: In line with your suggestions, we used the new terminology, seizure, instead of convulsion.

2. Aim of the abstract, contains a definition of FS. Please note that all definitions related to seizure/epilepsy should follow ILAE guidelines. Besides, it is mentioned in FS, a seizure is relative to infection. But keep in mind that fever induced by vaccination could lead to FS but it is not an infectious process

Response: *We revised the definition of febrile seizure according to the ILAE Definition*

3. The part "material" should be rewritten in the abstract section. Please clarify the whole methodology in a clear and brief manner.

Response: The material part in the summary section has been revised

4. It should be mentioned the study evaluates simple FS, complex FS, febrile status epilepticus, and so on. The results should be revised based on it.

Response *:* ***Although we designed our study in this way, most of our patients had simple febrile seizures. therefore, we included only simple febrile convulsions in our study. accordingly, I reviewed the material and method and the title of the study. Your valuable contribution will be a guide for our future work.***

5. Please clarify the "normal years of cases" that are used in the result part of the abstract.

Response *:* ***Changed to "The mean age of the cases was 29.2±15.9 (6-60) months."***

6. The purpose of the study is mentioned as " the possible role of sink in the pathogenesis, prophylaxis, and treatment of Fs". Considering the article is a descriptive one, this aim is not truly mentioned in the conclusion and discussion parts.

Response: ***this part was rewritten***

The purpose of this research is to investigate the role of serum zinc in the possible pathogenesis of children aged 6 months -5 years who applied to the pediatric emergency department of our hospital and were diagnosed with febrile seizures.

7. The sentence "...the body temperature of the patients.." is repeated twice.

Response: this part was misspelled twice, we've corrected it, thank you for your understanding

8. Discussion part is too scrambled, please summarize this part while focusing on the aim of the study.

Response:

9. In discussion the author/s claim that "... We believe low zinc levels are not only associated with .... But also....". As it is mentioned in the manuscript, there is only a paraclinic data in favor of the above sentence. So you could simply make a hypothesis that needs to be evaluated in detail later.

Response : I have revised and simplified the discussion section.
10. "The statistically negative correlation...", should be described with statistical evidence (P....).

Response: *specified in table 3*

r: -0.572	**P:0.001**

Response to Reviewer 2:

Dear reviewer, first of all, I would like to thank you very much for your contribution and guidance for this study.

1- The number of references is appropriate and their selection is judicious. But references are not UpToDate and recent published literature should be added and discussed. These include but are not limited to:

Response:

I updated the references in line with your suggestions, I added the references you suggested to my article.

- Bakri AH, Hassan MH, Ahmed AE, Halim PR, El-Sawy SA, Mohamed MM, Rashwan NI. Biochemical Assessments of Neurotrophin-3 and Zinc Involvement in the Pathophysiology of Pediatric Febrile Seizures : Biochemical Markers in Febrile Seizures. Biol Trace Elem Res. 2022 Jun;200(6):2614-2619. doi: 10.1007/s12011-021-02886-w. Epub 2021 Aug 18. PMID: 34406624.

- Kumar M, Swarnim S, Khanam S. Zinc Supplementation for Prevention of Febrile Seizures Recurrences in Children: A Systematic Review and Meta-Analysis. Indian Pediatr. 2021 Sep 15;58(9):857-860. Epub 2021 Aug 2. PMID: 3433822

- Arul J, Kommu PPK, Kasinathan A, Ray L, Krishnan L. Zinc Status and Febrile Seizures: Results from a Cross-sectional Study. J Neurosci Rural Pract. 2020 Oct;11(4):597*-600. doi: 10.1055/s-0040-1715992. Epub 2020 Sep 8. PMID: 33144797; PMCID: PMC7595794.*

- Heydarian F, Nakhaei AA, Majd HM, Bakhtiari E. Zinc deficiency and febrile seizure: a systematic review and meta-analysis. Turk J Pediatr. 2020;62(3):347-358. doi: 10.24953/turkjped.2020.03.001. PMID: 32558408.

2- If would be interesting to see the relationship between serum zinc levels and seizure type and frequency. These data should be easily available for the authors (line 60-64) and would add interesting data which remain controversially discussed.

Response: your suggestion is very important, but there were only 3 patients with complex seizures in our study. Therefore, our study consists of only simple febrile convulsions. This information will be a guide for future studies.

3- The authors discuss the relationship between leukocytosis and fever in 4th paragraph of the discussion (lines 165 -182). However, it should be mentioned and discussed that the increase in WBC and neutrophil in febrile conclusion patients could also be a transient effect and due to demarginating effects of the circulating catecholamines after seizure.

Response: you are very right, there may be a possible increase in wbc due to convulsion. However, since CRP increased more in the febrile seizure group, secondary infections may have been added to viral infections due to late admissions due to the effect of the covid pandemic.

4- I would suggest a more evidence-based discussion about the relationship between WBC count and zinc levels. (Lines 181 – 182)

I mentioned two studies in line with your suggestion.

5- While discussing the relationship between FC and CRP levels (lines 186-188) I think it should be changed to: “the reason for this is suggested that the inflammatory response is slower in children WITH FEBRILE CONCULSION”. I believe the cited literature (reference 31) is misplaced since it doesn’t have any content related to CRP and FC.

This reference has been corrected, thank you very much for your contribution.

6- All abbreviations used in tables should be explained in the table footer

Response: Abbreviations in the article have been added under the table.

7- The abstract conclusion is not very clear and needs rephrasing.

Response: abstract has been revised again

2 Revision 1

1 comment · 10 Jul 2023

Zahra Rezaei Reviewer

MINOR REVISION 10 Jul 2023

Thanks, Dear Authors, for considering the comments. Based on the final results, it seems that you find that fever, with or without a seizure, leads to a decreased zinc level. This should be highlighted in your conclusion as a hypothesis that needs further evaluation.