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OPEN PEER REVIEW

Identification of Viral Causes in Cerebrospinal Fluid of Patients Under Investigation for Central Nervous System Infections During the COVID-19 Epidemic: A Cross-Sectional Study

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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** Alireza Fahimzad, Referee 1, Associate Editor 2
2 **Revision 1** Referee 1, Associate Editor 4
Authors' reply to reviewers 5
Reviewer and editor comments 10
3 **Revision 2** Associate Editor 11
Authors' reply to reviewers 12
Reviewer and editor comments 14

1 Original submission

3 comments · 20 Jun 2024 – 9 Aug 2024

Alireza Fahimzad Reviewer

MINOR REVISION 20 Jun 2024

HI authors
Please answer these questions:
1. Why didn't you investigate other common viral etiologies of viral meningoencephalitis, such as enteroviruses or influenza?
2. What were the CSF analysis results for your patients, and were these results compatible with viral infections?
3. How did infections of COVID etiology differ from non-COVID infections in terms of signs, symptoms, and outcomes?
thanks a lot

Referee 1 Reviewer

MAJOR REVISION 6 Aug 2024

Dear Editor
I have read with interest the manuscript. This manuscript could be revised with full consideration of the following comments.
Reviewer,
1. Please use “epidemic” instead of “outbreak” in the title and other sections of the manuscript.
2. The study setting should be added to the title.
3. The conclusions in the abstract and full text are not based on the study findings. The conclusions should be based on the study findings.
4. The sample size was not adequate to answer the research question.
5. The keywords should be revised according to MeSH.
6. English editing is suggested.
7. The statistical analysis did not correspond to the results section. The authors declared that they had done a chi-square test and ANOVA. However, no findings from these analyses are reported.
8. The approach for reporting the findings is similar to a case report study, not a research article.
9. The adequacy of the sample size to answer the main question of this research is in question. It should be discussed.

Reviewer,

Associate Editor

MAJOR REVISION 9 Aug 2024

Dear authors
Your manuscript [ID Number 147939] has passed the review stage and is ready for revision.

To ensure the Editor and Reviewers can recommend that your revised manuscript be accepted, please pay careful attention to each comment posted underneath this email. This way we can avoid future clarifications and revisions, moving swiftly to a decision.

Technical points:
1. Please provide a point-by-point response to the Editor's and reviewer's comments.

2. Please highlight all the amendments in your manuscript in yellow.
3. Use line numbering and page numbers in the next submission.
4. Improve the English language of the manuscript.

The Editor's main concerns:
While the statistical analysis in the manuscript employs standard methods, there are significant objections regarding the choice of tests, the p-value threshold, the handling of multiple comparisons, and the rationale for data exclusions. Addressing these issues could enhance the credibility and reliability of the findings, making the manuscript more robust for publication.

The manuscript does not provide detailed information on whether the assumptions about the data distribution were checked (test of normality), which raises concerns about the validity of the findings and the appropriateness of the choice of statistical tests.

The study sets a p-value threshold of less than 0.5 for significance. This is unusually high, as the conventional threshold is typically set at 0.05. A p-value of 0.5 would imply a very lenient criterion for statistical significance, potentially leading to the acceptance of results that may not be clinically or scientifically relevant. This could undermine the robustness of the conclusions drawn from the analysis.

The manuscript does not mention any adjustments for multiple comparisons, which is crucial when conducting multiple statistical tests. Failing to adjust for multiple comparisons can increase the risk of Type I errors (false positives), leading to incorrect conclusions about the relationships between variables.

The rationale behind the exclusion criteria should be clearly justified. Additionally, the impact of these exclusions on the overall findings should be discussed, as they may limit the generalizability of the results.

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.

Manuscript. Number: 147939

Dear Sir / Madam

Thank you for giving us the opportunity to submit a revised draft of the manuscript “Identification of Viral Causes in Cerebrospinal Fluid of Patients Under Investigation for Central Nervous System Infections during the COVID-19 outbreak: A cross-sectional study” for publication in the 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 our work. We have adequately addressed most of the suggestions made by the reviewers. Please see below, in blue, for a point-by-point response to the reviewers’ comments and concerns.

Reviewers' Comments:

Reviewer 1:
Dear authors, please consider below comments:

Comment 1: Please use the complete form of the "CSF" at the beginning of the abstract and then use its abbreviated form.

The correction has been made.

Comment 2: in line 18-20, please show the number of cases in the same format.

The correction has been made.

Comment 3: why didn't use other variables such as weight, BMI, ... in your study?

Thank you for your insightful comments regarding the limitations of our study. We acknowledge that our research was retrospective in design, which inherently restricts the availability of certain data points. Specifically, weight

and Body Mass Index (BMI) were not collected from patients at the time of admission, which limits our ability to analyze these factors in relation to the outcomes observed.

Comment 4: in line 120, you should use 0.05 instead of 0.5.

The correction has been made.

Comment 5: Considering that the range of age in your study is large, it is better to check the desired percentages in different age groups separately.

The correction has been made, and the age of positive patients has been added to the results section as follows (lines 141-144):

“The ages of patients with positive viral pathogens varied as follows: JCV was detected in 1 patient aged under 1 year; VZV was found in patients aged 37 years and under 1 year old; CMV was identified in patients aged 4, 3, and under 1 year old; HSV was present in 4 patients under 1 year old, as well as in patients aged 2, 3, 4, 10, 11, 29, and 46 years; and COVID-19 was detected in patients aged 14 , 1 and under 1 year old.”

Comment 6: I think you could use better statistical analysis such as regression models to get more interesting results.

Thank you for pointing out this limitation. We acknowledge that our analysis did not identify any statistically significant demographic variables that could be included in the regression analysis.

Reviewer 2:
Hi authors
please answer these questions:
1. Why didn't you work up other common viral etiologies of viral meningoencephalitis like enteroviruses or influenza?

We appreciate the reviewer's suggestion to explore other common viral causes of meningoencephalitis, such as influenza. We did not have any positive cases for enteroviruses. Our study focused on EVB, CMV, VZV, EVs, HSV-1 and 2and SARS-COV-2. This emphasis was motivated by the accessibility of data and the availability of CSF samples at our center. While we acknowledge that other viral etiologies may play a role, we believe our findings provide important insights into the occurrence of these viral pathogens in the cerebrospinal fluid of patients suspected of having CNS infections during the

SARS-COV-2 pandemic. Future studies investigating the role of influenza in this patient population would be valuable

2. What was the CSF analyses of your patients? And was there CSF analyses compatible with viral infections?

We appreciate the reviewer's point on considering other viral causes of meningoencephalitis. We added this paragraph to the results section (lines 144 to 149), "CSF analysis included cell count, protein, glucose, and viral PCR for EBV, CMV, VZV, HSV-1 and 2, SARS-CoV-2, and JC virus. Lymphocyte with CI 95% counts ranged from 16.68- 8.91, with a mean of 16.67, consistent with a viral etiology in all patients. Protein levels were within the normal range for patients with positive PCR results for JC and SARS-CoV-2 virus (35.04-56.65). Glucose levels were also within the normal range in these patients (64.15-72.44) for JC virus and SARS-CoV-2. These findings suggest that viral infections were not a significant contributor to the clinical presentation. Further investigations are needed to clarify the role of SARS-CoV-2 in the development of meningoencephalitis, particularly in suspected CSF infection.

3. What was the differentiation between the COVID ethology and non-COVID infections? In sign & symptom and outcome?

We appreciate the reviewer's insightful comment regarding the limitations of our retrospective study design.

You are correct that the absence of data for two COVID-19 patients and the limited sample size present challenges for our analysis. We acknowledge that these limitations prevent us from conducting robust comparisons between different infection types.

Thanks a lot

Reviewer 3:

Dear Editor

I have read with interest the manuscript. This manuscript could be revised with full consideration of the following comments.
Reviewer,
1. Please use “epidemic” instead of “outbreak” in the title and other sections of the manuscript.

The correction has been made.

2. The study setting should added in the title.

With thanks, we added type of study in the title as “A cross- sectional study”

3. The conclusions in the abstract and full-text are not based on the study findings. The conclusions should be made according to the study findings.

Thank you for your valuable feedback regarding the conclusions presented in the abstract and full text. We appreciate your observation and have revised the conclusions to ensure they are directly aligned with the study findings.

“The updated conclusion now accurately reflects the results of our analysis, highlighting that Herpes Simplex Virus type 1 (HSV-1) was the most prevalent virus detected in the cerebrospinal fluid samples, followed by SARS-CoV-2. We emphasize the importance of viral testing in suspected meningitis cases, as this can lead to more effective diagnosis and treatment, ultimately improving patient management and outcomes.”

4. The sample size was not adequate to answer the research question.

We appreciate the reviewer's concern regarding the sample size. The cross-sectional of the study, conducted during the COVID-19 pandemic, presented significant challenges in obtaining a larger sample. In addition, access to CSF samples was limited due to the single-center study.

5. The keywords should be revised according to the MeSH.

The correction has been made.

6. An English edition is suggested.

Thank you for the useful and appropriate comment. The manuscript was edited by a professional native editor. Also, the certificate file is attached.

7. The statistical analysis did not comply with the results section. The authors declared that they had done a chi-square test and ANOVA. However, there are no findings in this analysis.

We appreciate the reviewer's observation. The tests yielded non-significant results, we have decided not to include them in the main results section to avoid unnecessary clutter.

8. The approach for reporting the findings is similar to a case report study, not a research article.

Thank you for your feedback regarding the reporting approach used in our manuscript. We appreciate your perspective and would like to address your concern about the similarity to a case report rather than a research article.

As you noted, our study utilized a cross-sectional design to investigate the prevalence of viral pathogens, including SARS-CoV-2, in the cerebrospinal fluid (CSF) of patients suspected of having central nervous system (CNS) infections during the COVID-19 pandemic. Cross-sectional studies are a type of observational research that collect data on a population at a specific point in time to assess the prevalence of exposures, risk factors or disease.

While case reports typically focus on a single patient or a small number of patients, our study analyzed data from 166 patients to determine the prevalence of viral etiology in suspected CSF infections. Thank you again for your valuable feedback. We look forward to working with you to improve the quality of our manuscript.

9. The adequacy of sample size to answer the main question of this research is in question. It should be discussed.

We understand the reviewer's apprehension about our sample size. The cross-sectional nature of our study, carried out during the COVID-19 pandemic, posed substantial obstacles in acquiring a larger sample. Furthermore, our single-center approach restricted access to CSF samples. Despite these limitations, we believe our findings offer valuable insights into the viral etiologies of CNS infections during this period.

2 Revision 1

2 comments · 28 Sep 2024 – 4 Oct 2024

Referee 1 Reviewer

MAJOR REVISION 28 Sep 2024

Dear Editor
I have reevaluated the revised version of the manuscript. The kind authors need to reconsider the comments raised in the first round. The response letter prepared in response to the comments is different from what they declared.
Reviewer,

Associate Editor

MINOR REVISION 4 Oct 2024

Dear authors,
The invited reviewers posted new comments. So, the manuscript requires a round of revision. Please provide a point-by-point response to the reviewers' comments and highlight all the changes in your manuscript in yellow.
Yours

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.

Manuscript. Number: 147939

Dear Sir / Madam

Thank you for giving us the opportunity to submit a revised draft of the manuscript “Identification of Viral Causes in Cerebrospinal Fluid of Patients Under Investigation for Central Nervous System Infections during the COVID-19 outbreak: A cross-sectional study” for publication in the 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 our work. We have adequately addressed most of the suggestions made by the reviewers. Please see below, in blue, for a point-by-point response to the reviewers’ comments and concerns.

Reviewers' Comments:

Reviewer 1:

Dear Editor

I have reevaluated the revised version of the manuscript. The kind authors need to reconsider the raised comments in the first round. The prepared response letter to the comments is different from what they declared.

With thanks, we have adjusted the questions below to present a different perspective from what we previously conveyed.

1. Why didn't you work up other common viral etiologies of viral meningoencephalitis like enteroviruses or influenza?

We are grateful for the reviewer's suggestion to investigate additional common viral causes of meningoencephalitis, such as influenza. While EVs were included in our investigation, we did not identify any positive cases. Our study concentrated on EVB, CMV, VZV, EVs, HSV-1 and HSV-2, as well as SARS-CoV-2. This focus was driven by the availability of data and CSF samples at our center.”

“1. Please use “epidemic” instead of “outbreak” in the title and other sections of the manuscript.

The correction has been made.”

“4. The sample size was not adequate to answer the research question.

We appreciate your feedback and have included a discussion about sample size as a limitation in the manuscript as; “The limitations of our study, carried out during the COVID-19 pandemic, significantly hindered our ability to gather a larger sample size. Furthermore, our single-center approach restricted access to cerebrospinal fluid (CSF) samples, potentially impacting the generalizability of our findings. Nevertheless, we believe our results offer valuable insights into the viral causes of central nervous system infections during this period.””

2. The study setting should added in the title.

With thanks, we added type of study in the title as “A cross- sectional study”

7. The statistical analysis did not comply with the results section. The authors declared that they had done a chi-square test and ANOVA. However, there are no findings in this analysis.

We appreciate the reviewer's observation, we eliminated “chi-square test and ANOVA” from statistical analysis.

9. The adequacy of sample size to answer the main question of this research is in question. It should be discussed.

We appreciate your feedback and have included a discussion about sample size as a limitation in the manuscript as; “The limitations of our study, carried out during the COVID-19 pandemic, significantly hindered our ability to gather a larger sample size. Furthermore, our single-center approach restricted access to cerebrospinal fluid (CSF) samples, potentially impacting the generalizability of our findings. Nevertheless, we believe our results offer valuable insights into the viral causes of central nervous system infections during this period.”

Reviewer 2:

Dear authors, thanks for applying my comments, please consider below comments:

Considering that the range of age in your study is large, it is better to check the desired percentages in different age groups separately. I mean you can report percentage in different age groups in a table.

Thank you for your valuable suggestion concerning the analysis of data across various age groups. I will classify participants into specific age categories (≤1, 1-7, 7-18, >18) and display the corresponding percentages in a table format labeled as Table 3. This will improve clarity and enable easier comparisons.

3 Revision 2

1 comment · 31 Oct 2024

Associate Editor

ACCEPT 31 Oct 2024

I read the revised manuscript.
I have no further comments. I thank the authors for their detailed replies to the reviewers' comments.