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OPEN PEER REVIEW

Neuropsychiatric Manifestations of COVID-19 in Hospitalized Pediatrics: A Multicenter 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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1 Original submission

2 comments · 21 Sep 2022 – 20 Oct 2022

Referee 1 Reviewer

MAJOR REVISION 21 Sep 2022

Thanks for your manuscript. There are some comments:
Abstract
-The study is cross-sectional, not observational.
Introduction
-This isn't an observational study; it is cross-sectional.
Results
-The results should be concise and comprehensive. Please delete many parts of this section and report your results briefly.
Discussion
-The discussion is discrete and inconclusive. Please organize it.
Footnotes
-The author's contributions and conflicts of interest should be added.
Tables
-Tables 1 and 3 should be deleted. The table legends should be written above the tables, not below them.

Referee 2 Reviewer

ACCEPT 20 Oct 2022

Dear author
Thank you for the manuscript.

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,

We thank you and the reviewers for giving us the opportunity of revising our manuscript and a chance to publish our paper in your prestigious journal.

As a result, we have provided our replies to the reviewers' comments in the best way we could. We have responded to all of the comments as a rebuttal letter and submitted it.

Dear reviewers,

Thank you for your sincere efforts in reviewing our manuscript and allowing us to revise our work. Hereby, we have provided our replies to your comments in the best way we could. Please let us know if we should clarify or modify any other parts.

Reviewer 1:
Dear author
Thank you for the manuscript

We appreciate you for the detailed and thoughtful review.

Reviewer 2:
Thanks for your manuscript. There are some comments:

We appreciate you for the detailed and thoughtful review.

Abstract
-The study is cross-sectional not observational.

We corrected this part.

Introduction
-This isn't observational study, it is cross-sectional.

We corrected this part.

Results
-Should be concise and comprehensive. Please delete many parts of it and report your results briefly.

All findings in this study are significant, and considering the paper's word count, we could not delete any parts of the findings. Please let us know if you consider a particular part for deletion.

Discussion
-Is discrete and inconclusive. Please organize it.

We organized this part.

Footnotes

-Author's contributions, conflict of interests should be added.

We implemented these items in the website according to the author's guidelines.

-Tables of 1 and 3 should be deleted. The legend of Tables should be written in upper part of Tables not in below.

Tables 1 and 3 have essential variables in the final analysis, which can be considered risk factors and confounding factors. The legends of the tables were corrected.

Reviewer 3:
Thank you very much for referring this article to me.
This is a prospective study on n important issue in clinical setting which could be potentially important for prevention of psychiatric sequels of COVID 19 in children.

Thanks for your sincere efforts in reviewing our manuscript and allowing us to revise our work.

However there are many problems with the study which makes the results questionable:
1. evaluation of symptoms after a few weeks of disease seems very late

According to the DSM-5, time criteria (at least one month) must be fulfilled to diagnose most psychiatric disorders. Therefore, this period was considered.

2. there is a mixture of neurological and psychiatric complications in the study, I could not understand which pathogenetic mechanisms are underway.

"Neuropsychiatric Disorders" is a general scientific term used in several studies[1]. We defined both of them in separate topic like other studies. However, there are multiple theories for the neurological and psychiatric complications of COVID-19, with not specific consensus on them. So, we mentioned these theories, and other studies should confirm them.

1-Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *The Lancet Psychiatry*. 2020;**7**(7):611-27.

3.included cases are not quite clear, the authors claim that they excluded previous psychological cases,but when you look at underlying problems,it seems very confusing if they didn't have such problems.

During the evaluation and history taking from each caregiver and patient, no notable point was found in the past psychiatric history. Confounder factors for the psychiatric manifestations were evaluated to eliminate their effects (table3).

4. the incidence of psychiatric disorders after COVID is near the rates in general population.

If you mean that we mentioned this sentence in our study, we highlighted this part in the discussion and pointed out that the incidence of Anxiety/mood disorders is more in our study in comparison with the general population. The incidence in other studies showed similar findings.

5. regarding the SAD as a common problem ,how can we accept that admission in PICU is not important?

Thank you for this point. This is an exciting point for us too because not only ICU admission was not related to psychiatric manifestations, but also other risk factors, i.e., death from COVID-19 in the family and history of neurologic problems, were not significantly related. Slomski ‘s study showed similar results.

2 Revision 1

1 comment · 18 Nov 2022

Associate Editor

MAJOR REVISION 18 Nov 2022

Thank you for submitting your revised manuscript to the “Archives of Pediatric Infectious Diseases”. After careful consideration, we feel that it has merit but does not fully meet the publication criteria of the “Archives of Pediatric Infectious Diseases” as it currently stands. Therefore, we invite you to submit a revised version of the manuscript that addresses the points raised during the review process. Note that the article will not be accepted without consideration of all the corrections. Pay special attention to the comments given in the discussion section and apply them all. 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 changes in your manuscript in a different color.
3. Use line numbering and page numbers in the next submission.
4. Improve the English language of the manuscript.

Other shortcomings
Spell out all abbreviations at first use.

It is important to mention that this study investigates hospitalized pediatric patients, not all pediatric populations with COVID-19. Therefore, the title should be corrected to include "hospitalized pediatric patients".

Line 60: "cross-sectional study" is correct.
Line 78: State the exact timing of the neurologic examination during admission. Did you perform a neurologic examination only on admission? What was the final outcome for patients who developed CNS signs and symptoms after the first examination? You should discuss this as a study limitation.

Lines 80-81: Remove this part: "and all patients with a past psychiatric history were excluded from our study". Avoid repetition (see lines 75-76).

Line 86-87: Each term should be spelled out at first use.

Line 105: Report 45% with a ratio (such as x/y).

Authors should provide additional information regarding different clinical presentations during illness (the most common S & S in each group, for example, GI manifestations in patients whose symptoms last for 2-3 weeks, ...). This is important for interpreting neuropsychiatric findings.

Lines 118-121: Use lowercase in the middle of a sentence: "antivirals", "anti-malarial", ...

Lines 130-131: The data provided are uninformative [were more frequent (???) and longer (how many days?)]. At what frequency? Compared with whom, and at what frequency?

Line 149: What is the most common EEG finding?

Line 158: "ischemic stroke" is correct. Use lowercase.

Lines 164-165: Use the abbreviation after spelling out the term at first use.
Line 168: What was the final outcome for the other 9 cases?

Line 172-175: The following statement is completely meaningless: "Six patients could not walk due to MIS-C, four patients had a history of seizures, one patient with a possibility of neurometabolic disease

(mitochondrial disorders), and one patient with a history of diabetes mellitus."
Did you confirm that DM caused the inability to walk, or was there only a co-occurrence? If yes, why? Also, regarding MIS-C, more description is needed. Use scientific writing.

Lines 185-193: Use lowercase in the middle of a sentence for all disease names. It is better to use abbreviations for psychiatric disorders in this section.

Line 193: Remove "respectively".

Line 195: Remove: "some important risk factors including". For this claim, you need more advanced statistical analysis. At this stage, you can only assess the relationship.

Line 196: What about neuropsychiatric signs and symptoms in severe versus non-severe cases? You should provide more information in this regard. A comparative analysis summarized in a new table would be helpful.

Line 202: Remove all reported p-values from this section.

Line 204: "hospitalized children and adolescents"

Lines 219-220: Remove the following part: "On the other hand, a large number of admitted patients (45%) had past medial history, either neurological, or other medical disorders (Supplementary table)."

Line 221: What about your study? I have not found any comparison between severe and non-severe cases.

Line 222: Remove the following statement: "To our knowledge, there are not specific studies for the neurological complications in children with pre-exciting disorders (15)."

Line 225-227: Remove the following statement: "So, the pre-existing disorders could be the risk factor for more severe disease and hospitalization. However, a cohort study with a control group is needed."

Line 230-237: Remove the following part: "Seizures are generally common in viral infections, particularly with adenovirus, influenza, rhinovirus, and respiratory syncytial virus (RSV) in children six years and younger (17). In the pediatric COVID-19 patients, there are a few case reports for new-onset seizures (17, 24). Some of them are related to febrile seizures (17, 25). However, a few studies reported afebrile seizures in adolescent patients (24, 26). These studies showed that patients in the younger age group had more febrile seizure patterns. However, adolescent patients had afebrile seizure patterns, and EEGs in both groups (child and adolescent) were reported normal (17, 19, 24, 27)."

Line 244: Remove the following part: "Some studies have discussed the potential neurotropism of COVID-19 and suggested that the neuropsychiatric manifestations in the pre-existing patient are greater and more severe (14, 15). The entry of pro-inflammatory cytokines into the central nervous system or the production of these cytokines by microglia and astrocytes have been considered for the neurological manifestations of COVID-19 in the brain. Several potential mechanisms mentioned for these processes including Cytokine storm by Angiotensin-converting enzyme 2 (ACE2) receptor, abnormal coagulation, mitochondrial disturbance, electrolyte imbalance and blood-brain barrier (BBB) permeability breakdown by COVID-19 (29)."

Lines 257-263: Use lowercase in the middle of a sentence.

Line 276-280: Remove the following part: "Aging is one of the factors affecting the activity level of pro-inflammatory cytokines in the central nervous system (TNF-α and IL-6). Therefore, in older patients, we encounter a broader and more acute range of mental disorders and maybe neurological complications. On the other hand, systemic infections such as COVID-19 can increase the serum level of IL-6 and may be a stimulus for more acute form of mental disorders in older patients (34)."

Line 284: "The frequency of psychiatric symptoms" is correct.
Lines 292-312: Remove these lines.

The incidence and prevalence of mood disorders vary by province, so this may affect the results and should be discussed in the discussion section as a limitation.

Lines 482-485 should be moved to the bottom of the table as footnotes.
Line 497: The title of Table 3 should be corrected.
Table 3. Investigation of the patient's demographics and COVID-19-related clinical characteristics by the onset of psychiatric symptoms.

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,

We thank you and the reviewers for giving us the opportunity of revising our manuscript and a chance to publish our paper in your prestigious journal.

As a result, we have provided our replies to the reviewer's comments in the best way we could. We have responded to all of the comments and submitted it.

Dear reviewer,

Thank you for your sincere efforts in reviewing our manuscript and allowing us to revise our work. Hereby, we have provided our replies to your comments in the best way we could. Please let us know if we should clarify or modify any other parts.

Associate Editor 1:
Thank you for submitting your revised manuscript to the "Archives of Pediatric Infectious Diseases". After careful consideration, we feel that it has merit but does not fully meet the "Archives of Pediatric Infectious Diseases" publication criteria as it currently stands. Therefore, we invite you to submit a revised version of the manuscript that addresses the points raised during the review process. Note that the article will not be accepted without considering all the corrections. Pay special attention to the comments given in the discussion section and apply them all. 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 amends on your manuscript with different color
3. Use line numbering and page number in the next submission
4. Improve the English language of the manuscript

Other shortcomings
Spell out all abbreviations on the first occasion.
We corrected all of them.

It is important to mention that this study investigates hospitalized pediatric patients not all pediatric populations with COVID-19. So, the title should be corrected with "hospitalized pediatric patients".

It was corrected.

Line 60: "cross-sectional study" is correct.

Thank you for your point. It was revised.

Line 78: Declare the exact time of the neurologic examination during admission.

Did you perform a neurologic examination only on admission? What's the final fate of patients who developed CNS signs and symptoms after the first examination? You should discuss this fact as a study limitation.

This is an important point; however, we could not evaluate them after first visit, due to study design. We mentioned it as our limitation study.

Lines 80-81:remove this part: "and all patients with a past psychiatric history were excluded from our study". Avoid repetition (see lines 75-76).

We apologize for this repetition. It was removed.

Line 86-87: Each term should be spelled out on the first occasion.

We corrected all of them.

Line 105: Report 45% with a ratio (like x/y)

This ratio was added. *(*171/375)

Authors should provide additional information regarding different clinical presentations that exist during illness (the most common S & S in each group, for example, GI manifestation in whom their symptoms last for 2-3 weeks, ...). It is important for interpreting neuropsychiatric findings.

Unfortunately, this evaluation was not considered at the design of study. So, we could not report these findings.

Lines 118-121: use a lesser case in the middle sentence: "antivirals", "anti-malarial", ...

Thank you for your comment. They were corrected.

Lines 130-131: uninformative data provided [were more frequent (???) and longer (how many days?)]. By what frequency? compare with whom by what frequency??

Thank you for your point, we revised this paragraph.

Line 149: what is the most EEG finding?

We added these findings in the text.

Line 158: "ischemic stroke" is correct. use lesser case.

Thank you for your comment. It was corrected.

Lines 164-165: use abbreviation after the first occasion spelled out.

They were spelled out.

Line 168: what is the final fate of the other 9 cases?

They had normal gait. It was added to the sentence.

Line 172-175: the following statement is completely meaningless: "Six patients could not walk due to MIS-C, four patients had a history of seizures, one patient with a possibility of neurometabolic disease (mitochondrial disorders), and one patient with a history of diabetes mellitus."

This is the etiology of patients who could not walk with normal developmental history. The sentences were revised grammatically.

Did you confirm the causality of DM for the disability of walking or there is only a co-occurrence? If yes, why? Also, regarding MIS-C more description is needed. Use scientific writing.

Yes, because he had axonal peripheral polyneuropathy too and walking problem is related to this complication.

The MIS-C description was added with reference.

Lines 185-193: use a lesser case in the middle sentence for all disease names. It is better to use the abbreviation of psychiatric disorders in this section.

Thank you for your comment. They were corrected.

Line 193: remove "respectively"

It was removed.

Line 195: remove: "some important risk factors including". For this claim, you need more advance statistical analysis. In this step, you can only assess the relationship.

we removed word “risk” from sentence too. however, In the first step of risk factor evaluation, primary statistical analysis is used and advanced statistical analysis is considered when primary statistical analysis showed positive result.

Line 196: what about neuropsychiatric signs and symptoms in severe versus non-severe cases? You should provide more information in this regard. A comparative analysis which is summarized in the new table is helpful.

Thank you for your valuable comment. All Patients with COVID-19 were admitted when they were in the moderate to severe disease stage and we could not compare the severe and non-severe patients(outpatient) in this situation.

Line 202: remove all reported p.values from this section.
It was removed.

Line 204: "hospitalized children and adolescents"

It was corrected.

Lines 219-220: remove the following part: "On the other hand, a large number of admitted patients (45%) had past medial history, either neurological, or other medical disorders (Supplementary table)."

It was removed.

Line 221: what about your study? I have not found any comparison between severe and non-severe cases.

Thank you for your valuable comment. All Patients with COVID-19 were admitted when they were in the moderate to severe disease stage and we could not compare the severe and non-severe patients(outpatient) in this situation.

Line 222: remove the following statement "To our knowledge, there are not specific studies for the neurological complications in children with pre-exciting disorders (15)."

It was removed.

Line 225-227: remove the following statement: "So, the pre-existing disorders could be the risk factor for more severe disease and hospitalization. However, a cohort study with a control group is needed."

It was removed.

Line 230-237: remove the following part: "Seizures are generally common in viral infections, particularly with adenovirus, influenza, rhinovirus, and respiratory syncytial virus (RSV) in children six years and younger (17). In the pediatric COVID-19 patients, there are a few case reports for new-onset seizures (17, 24). Some of them are related to febrile seizures (17, 25). However, a few studies reported afebrile seizures in adolescent patients (24, 26). These studies showed that patients in the younger age group had more febrile seizure patterns. However, adolescent patients had afebrile seizure patterns, and EEGs in both groups (child and adolescent) were reported normal (17, 19, 24, 27)."

This paragraph compares our data on seizure and other studies. Therefore, we revised and summarized it.

Line 244: remove the following part "Some studies have discussed the potential neurotropism of COVID-19 and suggested that the neuropsychiatric manifestations in the pre-existing patient are greater and more severe (14, 15). The entry of pro-inflammatory cytokines into the central nervous system or the production of these cytokines by microglia and astrocytes have been considered for the neurological manifestations of COVID-19 in the brain. Several potential mechanisms mentioned for these processes including Cytokine storm by Angiotensin-converting enzyme 2 (ACE2) receptor, abnormal coagulation, mitochondrial disturbance, electrolyte imbalance and blood-brain barrier (BBB) permeability breakdown by COVID-19 (29)."

Most part of this paragraph was removed.

Lines 257-263: use a lesser case in the middle sentence.

It was corrected.

Line 276-280: remove the following part "Aging is one of the factors affecting the activity level of pro-inflammatory cytokines in the central nervous system (TNF-α

and IL-6). Therefore, in older patients, we encounter a broader and more acute range of mental disorders and maybe neurological complications. On the other hand, systemic infections such as COVID-19 can increase the serum level of IL-6 and may be a stimulus for more acute form of mental disorders in older patients (34)."

It was removed.

Line 284: "The frequency of psychiatric symptoms" is correct.

It was revised.

Lines 292-312: remove these lines.

This paragraph explains possible mechanisms of neuropsychiatric symptoms. Therefore, we revised and summarized it.

The incidence and prevalence of mood disorders are varied by province, so this may affect results and should be discussed in the discussion as a limitation.

Generally, the aim of our study was the evaluation of neuropsychiatric disorders caused by COVID-19. Besides, to report these data, a comparison with provinces before COVID-19 pandemic is required. Therefore, reporting these findings without comparison does not add valuable data.

Lines 482-485 should be moved to the bottom of the table as footnotes.

It was corrected.

Line 497: Table 3 title should be corrected.
Table 3. Investigation of the patient's demographics and COVID-19-related clinical characteristics by the onset of the psychiatric symptoms.

It was revised.

3 Revision 2

1 comment · 8 Dec 2022

Associate Editor

MINOR REVISION 8 Dec 2022

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

Editor's comments
Lines 103-107: How did you obtain these results? Statistics (or an analytical description) should be provided for these statements.

Lines 151-153 should be written as follows: "We found MISC (what is the possible cause????????), seizure disorders, neurometabolic disease (mitochondrial disease), and diabetes mellitus (axonal peripheral polyneuropathy) as possible causes for abnormal gait in 6, 4, 1, and 1 of cases, respectively."

Remove the following statements in the discussion: "Studies showed that patients 209 in the younger age group had more febrile seizure patterns(25). However, adolescent patients had 210 afebrile seizure patterns, and EEGs in both groups (child and adolescent) were reported normal 211 (18, 20, 26, 27)".

Lines 272-274 need correction.
"Besides, neurological examination was considered only on admission for the studied cases and we did not evaluate CNS complications which possibly developed later in the course of hospitalization."

Remove "P-value <0.05 were considered significant." from the titles of tables 1 and 2.

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.

Dear Editor in Chief, Dear reviewers,

Thank you for your sincere efforts in reviewing our manuscript and allowing us to revise our work. Hereby, we have provided our replies to your comments in the best way we could. Please let us know if we should clarify or modify any other parts.

Associate Editor 1:
Dear authors
The manuscript's overall presentation improved after amendments and is now more readable. Although your replies to the editors' concerns are satisfactory, the manuscript still needs to be improved.

We thank you for giving us the opportunity of revising our manuscript.

Editor's comments
Lines 103-107: How did you obtain these results? Statistics (or analytical description) should be provided for these statements.

We removed this part, due to unsatisfactory analysis.

Lines 151-153 should be written with the following phrases: "We found MISC (what is the possible cause????????), seizure disorders, neurometabolic disease (mitochondrial disease), and diabetes mellitus (axonal peripheral polyneuropathy) as possible causes for abnormal gait in 6, 4, 1, and 1 of cases, respectively."

This part has been revised.

Remove the following statements in the discussion: "Studies showed that patients 209 in the younger age group had more febrile seizure patterns (25). However, adolescent patients had 210 afebrile seizure patterns, and EEGs in both groups (child and adolescent) were reported normal 211 (18, 20, 26, 27)".

We removed this part.

Lines 272-274 need correction.
'Besides, neurological examination was considered only on admission for the studied cases and we did not evaluate CNS complications which possibly developed later in the course of hospitalization."

This part has been revised.

Remove 'P-value <0.05 were considered significant." from the tables 1 and 2 titles.

These parts has been removed.

4 Revision 3

0 comments

No public comments in this round.