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OPEN PEER REVIEW

Quantitative Brain MRI Signal Differences in Children with Congenital Portosystemic Shunt Based on 3D T1-Weighted Sequence

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About this report

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1 Original submission

4 comments · 15 Jan 2024 – 10 Feb 2024

Referee 1 Reviewer

MINOR REVISION 15 Jan 2024

Dear Authors,
I reviewed your valuable manuscript titled "Quantitative MRI assessment based on 3D T1-weighted sequence of congenital portosystemic shunt-related brain signal changes in children". I have some questions and comments as follows:
1- In the method section, did you have any exclusion criteria for control group cases? How did you exclude patients with metabolic and mitochondrial diseases that may have imaging findings similar to those of CPPS?
2- Some cases were evaluated by a second radiologist. Why were not all cases evaluated by two radiologists? Nothing is mentioned about interobserver variability. Please provide more detailed information and statistical analysis in this regard.
3- What do you mean by pulmonary artery fistula? (Did you mean arteriovenous fistula?)
4- In fig 1, PDA should be corrected to PDV.
5- In the results, you mentioned that you had a case with "aproctia navicular fossa fistula". I think there is a writing mistake; if not, please explain the condition.

Referee 2 Reviewer

MAJOR REVISION 17 Jan 2024

After careful review of your study, I would like to acknowledge the strengths of your research efforts and the valuable contributions they make to the scientific community's understanding of this field. However, I believe that the manuscript requires significant revisions to enhance its rigor and clarity. I kindly request that you consider the following points during your revision process:

Basic concerns
1. Lack of follow-up data: The research aimed to assess signal changes over time, necessitating a longitudinal study design. However, in this study, a case-control design was used, which only provided a snapshot of the brain signal in CPSS without patient follow-up to evaluate the stability, progression, or resolution of these changes over time. Incorporating longitudinal data would have yielded valuable insights into the natural history of CPSS-related brain signal changes and their clinical implications.
2. Limited clinical significance: While the study demonstrates statistically significant differences in the measured indices between the Case Group (CPSS patients) and Control Group (children without liver or structural diseases), the clinical significance of these differences is not clearly established. The study does not provide information on how these brain signal changes relate to the clinical presentation, prognosis, or management of CPSS in children.
3. Unclear diagnostic utility: The study does not establish the diagnostic utility of quantitative MRI assessment using the 3D T1-weighted sequence for CPSS-related brain signal changes in children. It does not provide information on the sensitivity, specificity, positive predictive value, or negative predictive value of the MRI indices in detecting CPSS or differentiating it from other conditions with similar brain signal changes.
4. Limited information on clinical correlations: The study briefly mentions correlation analysis between the MRI indices (GFI and API) and ammonia levels in the Case Group. However, the correlation coefficients reported (0.147 and 0.190) are relatively weak, suggesting a lack of strong association between these variables. The study does not explore potential correlations with other clinical parameters or laboratory markers

relevant to CPSS.
5. Lack of blinding: It is not clear whether the researchers performing the quantitative MRI measurements were blinded to the group assignments (Case Group vs. Control Group). This lack of blinding could introduce potential bias in the measurement and interpretation of the results.

Abstract
6. Lack of context: The abstract does not provide sufficient background information to understand the significance of the study. It briefly mentions increased T1-weighted signal intensities as characteristic features of CPSS, but it does not explain why these brain signal changes are important or what their potential clinical implications are.
7. Incomplete methods: The methods section of the abstract provides limited details regarding the methodology employed in the study. It briefly mentions that 32 patients with CPSS underwent standard brain MRI, but it does not mention the specific study design (case-control), sampling technique, inclusion and exclusion criteria, imaging protocol, the duration of the study, or any additional assessments conducted.
8. Inconsistent tense usage: The abstract switches between past tense and present tense in describing the methods and results. Maintaining a consistent tense throughout the abstract would improve the overall coherence and readability.
9. Ambiguity in statistical analysis: The abstract mentions that the GFI and API were measured and statistically analyzed between the Case Group and the Control Group, but it does not provide information on the specific statistical tests used or the adjustment for potential confounding factors.
10. Incomplete conclusion: The conclusion of the abstract suggests that quantitative MRI assessment is an effective method for evaluating uncertain portosystemic brain signal changes. It also states that the 3D T1W sequence is more suitable than the standard T1W sequence for evaluating GFI. However, the conclusion falls short in discussing the clinical implications of these findings, considering the study's limitations, and offering suggestions for further research.

Introduction
11. Insufficient context and rationale: The introduction mentions that children with CPSS may present with certain symptoms and brain signal changes, but it does not explain the clinical importance of detecting these changes or how quantitative assessment can contribute to diagnosis, prognosis, or treatment decisions.
12. Lack of logical flow: The introduction lacks a smooth and logical flow between sentences and paragraphs. The information jumps from discussing the classification of CPSS to the increasing reports in children, and then abruptly shifts to discussing T1-weighted high signal intensity in the brain. The transitions between these ideas are not clear, making it difficult for the reader to follow the line of reasoning.
13. Inadequate literature review: The introduction does not provide a comprehensive literature review to establish the current knowledge and gaps in the field of CPSS.
14. Lack of a clear research objective: The introduction does not clearly state the research objective or research question of the study. It briefly mentions retrospective review and quantitative assessment of brain MRI images in patients with CPSS, but it does not provide a clear statement of the study's purpose and the clinical application of its results.

Methods
15. Lack of subtitles: The Methods section suffers from the absence of subheadings, as it is composed of cohesive sentences without appropriate subtitles such as study design, samples and sampling, data collection, imaging protocol, imaging analysis, ethical considerations, and statistical analysis. This lack of subheadings hinders the reader's comprehension and understanding of the different components and procedures involved in the study.
16. Inadequate description of study design: The Methods section does not clearly state that this is a case-control study. It should explicitly mention the study design and explain how cases and controls were selected.

17. Lack of sample size justification: The Methods section does not provide a rationale for the sample size of 32 patients with CPSS and 30 children in the control group.
18. Incomplete description of patient selection: The section mentions Digital Subtraction Angiography (DSA) and/or Computed Tomography (CT) as diagnostic methods, but it does not specify the inclusion and exclusion criteria for patient selection.
19. Insufficient details on data collection: The Methods section should provide detailed information on how the data were collected, including the procedures and instruments used.
20. Lack of blinding and independent assessment: The section does not mention whether the researchers assessing the brain MRI images were blinded to the case-control status. Blinding is important to minimize bias in the assessment process.
21. Incomplete description of statistical correlation coefficient analysis: The section mentions conducting correlation analysis between GFI ratios and ammonia levels, but it does not provide details on the statistical methods used to assess the correlation.
22. Incomplete information on software and statistical package: The provided text mentions the use of IBM SPSS 26 but does not include the manufacturer's name.
23. Absence of ethical considerations: While the section briefly mentions obtaining informed consent and following ethical standards, it lacks important details about the ethical approval.

Results
24. Incomplete results presentation: The presentation of sample characteristics is incomplete as only partial demographic information, such as age and gender distribution, is provided. However, the characteristics of the control group are not mentioned. It is crucial to provide a comprehensive description of both the cases and controls, including relevant demographic and clinical information. Additionally, including the p-value for the comparison between the two groups would further enhance the understanding of the findings.
25. The interpretation of the results is inappropriate. The statement suggests that there is a significant increase in GFI and API in the Case Group compared to the Control Group, which is attributed to portosystemic brain signal changes. However, it's important to note that this study has a case-control design, which provides only a snapshot view and does not allow conclusions to be drawn about changes or increases over time. To accurately assess such changes, a longitudinal study with multiple measurements would be necessary.
26. Lack of clarity in figure references: Figures are mentioned in the text (e.g., Fig.1A-1C) without providing a clear explanation of what these figures represent.
27. Inappropriate design of Table 1: The way variables are presented in Table 1, illustrating the case series study on a case-by-case basis, is deemed inappropriate. To enhance the clarity and rigor of the presentation, it is recommended that Table 1 be redesigned to organize the data in a grouped manner. This revision should involve incorporating control group data and including p-values to facilitate effective comparisons. By implementing these changes, the overall quality of the table will be improved, allowing for a more comprehensive analysis and interpretation of the study findings.

Discussion
28. Lack of critical analysis: The discussion primarily focuses on presenting findings and observations without critically analyzing the results or discussing potential limitations or alternative explanations.
29. Inadequate discussion of limitations: The discussion briefly mentions some limitations of the study, such as retrospective analysis and inadequate brain MRI data. However, it does not elaborate on these limitations or discuss their potential impact on the results and conclusions.
30. Absence of future directions: The conclusion does not provide suggestions for future research directions or areas that require further investigation.

I appreciate your commitment to improving your work and look forward to reviewing the revised version.

Associate Editor MAJOR REVISION 9 Feb 2024

Dear authors, your manuscript needs major revision.
Please follow and respond to all questions and comments from the IJR reviewers.

Editor-in-Chief MAJOR REVISION 10 Feb 2024

Dear authors,
Your article needs Major Revision.
Regards

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.

Reply to Reviewers' Letter

Dear Editor and Reviewers:

I would like to thank the authors for addressing the comments. Here I will reply the comments of the reviewers as follow:

Reviewer 1:

1- In method, did you had any exclusion criteria for control group cases? How did you excluded patients with metabolic and mitochondrial diseases which may have similar imaging findings with CPSS?

Reply: Yes, we had some exclusion criteria for control group cases. First, the control group cases must have no liver or structural brain diseases. Some medical examinations were utilized to rule out these diseases such as abdominal and cardiac ultrasound, brain MRI, liver function tests, development assessments and so on. And then, as our study was a retrospective study starting from January 2017, we tried to select control group cases which underwent brain MRI in our hospital from 2017 to 2018. This way, we could have enough time (nearly 5-6 years) for follow-up to rule out the possibility of any structural or metabolic brain diseases. Also, patients would be excluded due to unavailable pre-therapy brain MRI.

Actually, genetic metabolic and mitochondrial diseases were not uncommon in our hospital. Considering that certain underlying diseases, such as metabolic and mitochondrial diseases may have similar imaging manifestations, some brain MRI sequences such as DWI and MRS were used to differentiate these diseases. In fact, in our hospital, these two sequences were our routine brain MRI sequences. In addition, abdominal ultrasound or abdominal enhancement CT could detect the abnormal portosystemic shunt. If necessary, we would also recommend genetic study to rule out the metabolic and mitochondrial diseases.

2- Some cases had been evaluated by second radiologist, why all cases were not evaluated by two radiologist? Nothing in mentioned about the interobserver variability, please provide more detail information and statistic analysis bin this regard.

Reply: In this study, we took into account the differences in radiologists and the placements of ROI due to a lack of sufficient measurement experience, these may lead to deviations in the data. Meanwhile, we need to maintain the data continuity. Therefore, only one radiologist measured GFI on axial 3D T1W sequence and standard T1W sequence, API on sagittal 3D T1W sequence of both

the Case Group and the Control Group. To test the reliability of the data, we asked another radiologist to measured GFI on axial 3D T1W sequence of both groups. These cases account for approximately 30% of all measurement values. An independent-sample T-test was applied for the comparison of the data from two radiologists, it showed that there is no significant difference in the index values differences between two radiologists. This is a sampling inspection method as a judgment of the reliability of measurement results.

Here is the reference:

Ritz A, Kolorz J, Hubertus J, Ley-Zaporozhan J, von Schweinitz D, Koletzko S, et al. Sarcopenia is a prognostic outcome marker in children with high-risk hepatoblastoma. Pediatr Blood Cancer. 2021 May;68(5): e28862. doi: 10.1002/pbc.28862.

3- What do you mean by pulmonary artery fistula? (Did you mean arteriovenous fistula?)

Reply: Dear reviewer: Thank you for your question. We found PAF through the electronic case record system of our institution. We discussed with our cardiologist about this case. He told us that PAF was not correct, the accurate complication of this case was PAVF.

4- In fig 1, PDA should be corrected to PDV.

Reply: Dear reviewer: Yes, I have made a mistake. PDA has been corrected to PDV.

5- In results you mentioned that you had a case with “aproctia navicular fossa fistula”, I think there is a writing mistake, if not please explain about the condition.

Reply: Dear reviewer: “aproctia navicular fossa fistula” should be corrected to “aproctia with navicular fossa fistula”. It refers to a patient who has congenital imperforation anus and also has a rectal navicular fistula.

Reviewer 2:

1. Lack of follow-up data: The research aimed to assess signal changes over time, necessitating a longitudinal study design. However, in this study, a case-control design was used, which only provided a snapshot of the brain signal in CPSS without conducting patient follow-up to evaluate the stability, progression, or resolution of these changes over time. Incorporating longitudinal data would have yielded valuable insights into the natural history of CPSS-related brain signal changes and their clinical implications.

Reply: Dear reviewer: In the discussion section, we have noticed the limitations of our study. It was a retrospective analysis rather than a prospective research. Congenital portosystemic shunts are rare vascular malformations. Though our hospital is a well-known pediatric cardiovascular hospital in our country, our recognition of this disease is still gradually improving with the accumulation of experience and the advancement in imaging modalities in the past 10-15 years. The initial purpose of this study was to conduct a preliminary analysis of brain signal changes in the cases over the past 5 years. We have designed a project to conduct a further prospective study of this disease. Next, we plan to collaborate with the cardiology department to follow up a series of cases for evaluating the stability, progression, or resolution of these brain signal changes over time. We think incorporating longitudinal data will definitely yield valuable insights into the natural history of CPSS-related brain signal changes and their clinical implications, I think we can discuss our research insights in the next manuscript.

2. Limited clinical significance: While the study demonstrates statistically significant differences in the measured indices between the Case Group (CPSS patients) and Control Group (children without liver or structural diseases), the clinical significance of these differences is not clearly established. The study does not provide information on how these brain signal changes relate to the clinical presentation, prognosis, or management of CPSS in children.

Reply: Dear reviewer: Before we start to write this manuscript, we searched for papers related to portosystemic shunting, we found that the majority of papers focused on the types of portosystemic shunting, the complications of the cardiovascular system and liver, while there was less analysis of neurological involvement because this is a longitudinal study over time. Actually, in our study, a variable degree of increased T1-weighted (T1W) signal intensities in some locations on brain MRI could be detected in all CPSS cases, which suggest an augmented accumulation of Manganese, but

only one patient presented occasional unconscious and lethargy, the others have no evident neurological symptoms. Sometimes, minor signal changes and no neurological symptoms may be ignored and lead to irreversible brain damage in children with CPSS.

Based on our experience, quantitative MRI assessment especially the 3D T1W sequence could be used to evaluate uncertain portosystemic brain signal changes, it was suitable for a longitudinal study of CPSS over time. By this quantitative way, even if we had some doubts about minor signal changes, we would suggest an abdominal or cardiac ultrasound to further clarify the presence of CPSS. We believed that it was helpful to reduce complications, improve the prognosis, and better management of CPSS in children.

3. Unclear diagnostic utility: The study does not establish the diagnostic utility of quantitative MRI assessment using the 3D T1-weighted sequence for CPSS-related brain signal changes in children. It does not provide information on the sensitivity, specificity, positive predictive value, or negative predictive value of the MRI indices in detecting CPSS or differentiating it from other conditions with similar brain signal changes.

Reply: Dear reviewer: With the advanced of MRI equipment, the 3D T1W sequence, which has a high spatial resolution has become a routine sequence in brain MRI diagnosis in children. The typical clinical routine 3D T1W protocols have an isotropic resolution of 1 mm and require a data acquisition time ranging from 4 to 5 minutes. In our study, through quantitative analysis, we found that there was a difference between the ratio's looking in the cases between the 3D T1W sequence and the standard T1W sequence. That means the 3D sequence is more sensitive to detecting signal anomalies than the standard T1W sequence. We believe it has diagnostic value. Therefore, we recommend using 3D T1W sequence for quantitative analysis for children suspected of CPSS.

In the results section, we recorded the range of the mean GFI of both the Case Group (1.001 to 1.494) and the Control Group (0.906-1.049), it showed that if the mean GFI value was greater than 1.000, we should suspect the possibility of CPSS, abdominal or cardiac US was recommended, as well as the venous ammonia testing.

Considering that certain underlying diseases, such as metabolic and mitochondrial diseases may have similar imaging manifestations, some brain MRI sequences such as T2-FLAIR, DWI and MRS can be utilized as a supplementary sequence to the 3D sequence to differentiate among these diseases. In fact, in our hospital, these sequences are our routine brain MRI sequences. In addition,

abdominal ultrasound or abdominal enhancement CT can detect the abnormal portosystemic shunt. If necessary, we will also recommend genetic study to rule out the metabolic and mitochondrial diseases.

4. Limited information on clinical correlations: The study briefly mentions correlation analysis between the MRI indices (GFI and API) and ammonia levels in the Case Group. However, the correlation coefficients reported (0.147 and 0.190) are relatively weak, suggesting a lack of strong association between these variables. The study does not explore potential correlations with other clinical parameters or laboratory markers relevant to CPSS.

Reply: Dear reviewer: As ammonia levels are a characteristic of this disease, it is necessary to analyze the correlation between the MRI indices (GFI and API) and ammonia levels in the Case Group. After the Pearson's correlation, it showed that the correlation coefficients were relatively weak. This was consistent with the literature that the blood ammonia levels were not reliably correlated with the degree of encephalopathy instead of peak and duration of hyperammonemia. In the future work, more adequately cases need to be collected to explore any potential correlations with other clinical parameters such as the different classifications of CPSS.

5. Lack of blinding: It is not clear whether the researchers performing the quantitative MRI measurements were blinded to the group assignments (Case Group vs. Control Group). This lack of blinding could introduce potential bias in the measurement and interpretation of the results.

Reply: Dear reviewer: Yes, the radiologists performing the quantitative MRI measurements were all blinded to the group assignments (Case Group vs. Control Group). We have added this opinion into the paper.

Abstract

6. Lack of context: The abstract does not provide sufficient background information to understand the significance of the study. It briefly mentions increased T1-weighted signal intensities as characteristic features of CPSS, but it does not explain why these brain signal changes are important or the potential clinical implications.

Reply: Dear reviewer: According to your suggestion, we added a sentence “which may lead to brain damage” in the background section.

7. Incomplete methods: The abstract method provides limited details regarding the methodology employed in the study. It briefly mentions that 32 patients with CPSS underwent standard brain

MRI, but it does not mention the specific study design (case-control), sampling technique, inclusion and exclusion criteria, imaging protocol, the duration of the study, or any additional assessments conducted.

Reply: Dear reviewer: Thank you very much for your opinion. As most abstracts were limited to 250 words or less, these contents were not included in the abstract. Now we have revised the methods of abstract in the manuscript.

We had inclusion and exclusion criteria for the patients. We reviewed the electronic medical records and corresponding available image data, those patients who identified as the diagnosis of CPSS by Digital Subtraction Angiography (DSA) and/or Computed Tomography(CT) and underwent brain MRI before interventional treatment or surgery can be included in this study. Meanwhile, as some small intrahepatic shunts located between the portal branches and hepatic veins may regress and close spontaneously by the age of 1 to 3 years, we excluded the cases of intrahepatic CPSS under 2 years of age. Patients were excluded due to unavailable pre-therapy brain MRI.

We also had some inclusion and exclusion criteria for control group cases. First, the control group cases must have no liver or structural brain diseases. Some medical examinations were used to rule out these diseases such as abdominal and cardiac ultrasound, brain MRI, liver function tests, development assessments and so on. And then, as our study was a retrospective study starting from January 2017, we tried to select control group cases which underwent brain MRI in our hospital from 2017 to 2018. This way, we could have enough time (nearly 5-6 years) for follow-up to rule out the possibility of any structural or metabolic brain diseases.

Because this was a retrospective study, we selected all the patients and control group cases from January 2017 to August 2023. We spent more than 3 months on measurement, statistics and manuscript writing.

8. Inconsistent tense usage: The abstract switches between past tense and present tense in describing the methods and results. Maintaining a consistent tense throughout the abstract would improve the overall coherence and readability.

Reply: Dear reviewer: Thank you very much for your opinion. We have revised the tense to maintain a consistent past tense.

9. Ambiguity in statistical analysis: The abstract mentions that the GFI and API were measured and statistically analyzed between the Case Group and the Control Group, but it does not provide

information on the specific statistical tests used or the adjustment for potential confounding factors.

Reply: Dear reviewer: Thank you very much for your opinion. As most abstracts were limited to 250 words or less, these contents were not included in the abstract. Now we have revised the statistical methods of abstract in the manuscript.

We used the statistical software package (IBM spss26, IBM Corporation, Chicago, Illinois, 2019) for statistical analysis. A single Kolmogorov-Smirnov Test (K-S test) was implemented in order to take appropriate data adjustment or corrective action. Then an independent-sample T-test was applied for the comparison of GFI and API on 3D T1W sequence between the Case Group and the Control Group. A paired-sample T-test was applied to compare the GFI of the Case Group on 3D T1W sequence with that on standard T1W sequence. Meanwhile, a correlation analysis was conducted between the GFI ratios and the ammonia levels, as well as the API ratios and the ammonia levels in the Case Group.

10. Incomplete conclusion: The abstract conclusion of the study suggests that quantitative MRI assessment is an effective method for evaluating uncertain portosystemic brain signal changes. It also states that the 3D T1W sequence is more suitable than the standard T1W sequence for evaluating GFI. However, the conclusion falls short in discussing the clinical implications of these findings, considering the study's limitations, and offering suggestions for further research.

Reply: Dear reviewer: Thank you for your opinion. According to your comments, we revised the abstract conclusion as follows: Quantitative MRI assessment based on 3D T1-weighted sequence could be used to evaluate portosystemic shunt-related brain signal changes. A longitudinal study with multiple measurements would be necessary.

Introduction

11. Insufficient context and rationale: The introduction mentions that children with CPSS may present with certain symptoms and brain signal changes, but it does not explain the clinical importance of detecting these changes or how quantitative assessment can contribute to diagnosis, prognosis, or treatment decisions.

Reply: Dear reviewer: Thank you for your opinion. According to your comments, we have revised the introduction of the manuscript.

12. Lack of logical flow: The introduction lacks a smooth and logical flow between sentences and paragraphs. The information jumps from discussing the classification of CPSS to the increasing

reports in children, and then abruptly shifts to discussing T1-weighted high signal intensity in the brain. The transitions between these ideas are not clear, making it difficult for the reader to follow the line of reasoning.

Reply: Dear reviewer: Thank you for your opinion. According to your comments, we have revised the introduction of the manuscript.

13. Inadequate literature review: The introduction does not provide a comprehensive literature review to establish the current knowledge and gaps in the field of CPSS.

Reply: Dear reviewer: Thank you for your opinion. According to your comments, we have adjusted and added some references in the introduction section.

14. Lack of a clear research objective: The introduction does not clearly state the research objective or research question of the study. It briefly mentions retrospective review and quantitative assessment of brain MRI images in patients with CPSS, but it does not provide a clear statement of the study's purpose and its clinical application of the results.

Reply: Dear reviewer: Thank you for your opinion. According to your comments, we have provided our study's purpose and its clinical application of the results in the introduction section.

Methods

15. Lack of subtitle: The Methods section suffers from the absence of subheadings, as it is composed of cohesive sentences without appropriate subtitles such as study design, samples and sampling, data collection, imaging protocol, imaging analysis, ethical considerations, and statistical analysis. This lack of subheadings hinders the reader's comprehension and understanding of the different components and procedures involved in the study.

Reply: Dear reviewer: Dear reviewer: Thank you for your opinion. According to your comments, we have added subheadings in the methods section.

16. Inadequate description of study design: The Methods section does not clearly state that this is a case-control study. It should explicitly mention the study design and explain how cases and controls were selected.

Reply: Dear reviewer: We have added the study design in the study design section. We have revised and explained how cases and controls were selected in data collection section and study design section.

17. Lack of sample size justification: The Methods section does not provide a rationale for the

sample size of 32 patients with CPSS and 30 children in the control group.

Reply: Dear reviewer: Portosystemic shunt is a rare disease, and also there are not numerous children undergoing brain MRI, in order to save the sample size, according to case-control study protocols, we designed this case-control study with a case-control ratio of 1:1 in a paired design.

18. Incomplete description of patient selection: The section mentions Digital Subtraction Angiography (DSA) and/or Computed Tomography (CT) as diagnostic methods, but it does not specify the inclusion and exclusion criteria for patient selection.

Reply: Dear reviewer: We have revised the inclusion and exclusion criteria for patient selection.

19. Insufficient details on data collection: The Methods section should provide detailed information on how the data were collected, including the procedures and instruments used.

Reply: Dear reviewer: The detailed information on how the data were collected, including the procedures and instruments used is in the imaging analysis section.

20. Lack of blinding and independent assessment: The section does not mention whether the researchers assessing the brain MRI images were blinded to the case-control status. Blinding is important to minimize bias in the assessment process.

Reply: Dear reviewer: We agreed on the importance of blinding in the assessment process. Yes, the radiologists performing the quantitative MRI measurements were all blinded to the group assignments (Case Group vs. Control Group). We have added this opinion into the methods section.

21. Incomplete description of statistical correlation coefficient analysis: The section mentions conducting correlation analysis between GFI ratios and ammonia levels, but it does not provide details on the statistical methods used to assess the correlation.

Reply: Dear reviewer: Thank you for your opinion. We have provided details on the statistical methods used to assess the correlation in the methods section.

22. Incomplete information on software and statistical package: The provided text mentions the use of IBM SPSS 26 but does not include the manufacturer's name.

Reply: Dear reviewer: Thank you for your opinion. We have provided the manufacturer's name of IBM SPSS 26 in the methods section.

23. Absence of ethical considerations: While the section briefly mentions obtaining informed consent and following ethical standards, it lacks important details about the ethical approval.

Reply: Dear reviewer: Thank you for your opinion. We have provided the ethical approval Number

in the methods section.

Results

24. Incomplete results presentation: The presentation of sample characteristics is incomplete as only partial demographic information, such as age and gender distribution, is provided. However, the characteristics of the control group are not mentioned. It is crucial to provide a comprehensive description of both the cases and controls, including relevant demographic and clinical information. Additionally, including the p-value for the comparison between the two groups would further enhance the understanding of the findings.

Reply: Dear reviewer: Thank you for your comments. We have added the relevant demographic and clinical information of the Control Group.

25. The interpretation of the results is inappropriate. The statement suggests that there is a significant increase in GFI and API in the Case Group compared to the Control Group, which is attributed to portosystemic brain signal changes. However, it's important to note that this study is a case-control design, which provides only a snapshot view and cannot draw conclusions about changes or increases over time. To accurately assess such changes, a longitudinal study with multiple measurements would be necessary.

Reply: Dear reviewer: Thank for your comments. We have revised the interpretation of the results “It was considered that there is a correlation between portosystemic shunt and increased brain signals.”. Meanwhile, we also revised the limitations of our study in the discussion section.

26. Lack of clarity in figure references: Figures are mentioned in the text (e.g., Fig.1A-1C) without providing a clear explanation of what these figures represent.

Reply: Dear reviewer: Thank you for your comments. We have adjusted the position of the figures in the text to provide a better explanation of what these figures represent.

27. Inappropriate design of Table 1: The way variables are presented in Table 1, illustrating the case series study on a case-by-case basis, is deemed inappropriate. To enhance the clarity and rigor of the presentation, it is recommended that Table 1 be redesigned to organize the data in a grouped manner. This revision should involve incorporating control group data and including p-values to facilitate effective comparisons. By implementing these changes, the overall quality of the table will be improved, allowing for a more comprehensive analysis and interpretation of the study findings.

Reply: Dear reviewer: Thank you for your comments. I think you are referring to Table 2, not Table1.

Actually, I've never been very satisfied with my Table 2, but I am not sure how to revise it. Now I have revised it according to your suggestion, thank you very very much.

Discussion

28. Lack of critical analysis: The discussion primarily focuses on presenting findings and observations without critically analyzing the results or discussing potential limitations or alternative explanations.

Reply: Dear reviewer: Thank you very much. According to your comments, we have critically analyzed the results and discussed the potential limitations.

29. Inadequate discussion of limitations: The discussion briefly mentions some limitations of the study, such as retrospective analysis and inadequate brain MRI data. However, it does not elaborate on these limitations or discuss their potential impact on the results and conclusions.

Reply: Dear reviewer: Thank you very much. According to your comments, we have revised the limitations of our study in the discussion section.

30. Absence of future directions: The conclusion does not provide suggestions for future research directions or areas that require further investigation.

Reply: Dear reviewer: Thank you very much. According to your comments, we have provided suggestions for future research directions in the discussion section.

2 Revision 1

3 comments · 28 Feb 2024 – 23 Mar 2024

Referee 2 Reviewer

MAJOR REVISION 28 Feb 2024

I appreciate your thorough response to the comments and questions raised during the review process. It is evident that you have made efforts to address the concerns and improve the manuscript accordingly.
However, I would like to reiterate the initial concern regarding the suitability of the data for the objectives of the study.
As previously mentioned, the data presented in the study, with each sample having only one measurement, may not be sufficient to adequately assess brain signal changes in children with congenital portosystemic shunt (CPSS). While the clinical relevance of the topic is acknowledged, it may be more appropriate to present the findings as a case series, similar to other published papers in the field. This approach would provide valuable insights into the specific characteristics and outcomes of the CPSS group.
Additionally, I would like to emphasize that the scientific writing structure of the manuscript, particularly the abstract, is not appropriate and requires basic revision. The abstract should provide a concise and clear summary of the study's objectives, methods, results, and conclusions. Currently, the abstract contains excessive details about patient selection criteria, statistical methods, and study duration, which are better suited for the main body of the paper.
Thank you for your attention to this matter, and I look forward to reviewing the revised version of your manuscript.

Associate Editor

MAJOR REVISION 18 Mar 2024

According to the methodological reviewer's comments, the manuscript needs major revision.

Editor-in-Chief

MAJOR REVISION 23 Mar 2024

Dear authors,
Your article needs Major Revision.
Regards

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.

Reply to Reviewers' Letter

Dear Editor and Reviewers:

I would like to thank the reviewers for addressing the comments. Here I will reply the comments of the reviewers as follow:

Reviewer 2:

1. I appreciate your thorough response to the comments and questions raised during the review process. It is evident that you have made efforts to address the concerns and improve the manuscript accordingly. However, I would like to reiterate the initial concern regarding the suitability of the data for the objectives of the study.

As previously mentioned, the data presented in the study, with each sample having only one measurement, may not be sufficient to adequately assess brain signal changes in children with congenital portosystemic shunt (CPSS). While the clinical relevance of the topic is acknowledged, it may be more appropriate to present the findings as a case series, similar to other published papers in the field. This approach would provide valuable insights into the specific characteristics and outcomes of the CPSS group.

Reply: Dear reviewer: Thank you very much for your comments. Meanwhile, I also appreciate your understanding. Actually, when I received your first review comments on Feb 9th, 2024, it was our Chinese Lunar New Year and I happened to have about 5 days off. During this holiday, I replied to your and another reviewer's comments day and night, because I knew it was very important for me to made efforts to address the concerns and improve my manuscript.

About the data presented in this study, I drew some experience from other papers, for example:

* Ritz A, Kolorz J, Hubertus J, Ley-Zaporozhan J, von Schweinitz D, Koletzko S, et al. Sarcopenia is a prognostic outcome marker in children with high-risk hepatoblastoma. Pediatr Blood Cancer. 2021 May;68(5): e28862. PubMed ID: 33438330.

With each sample, taking the average of three measurements for each location could reflect the measurement values of that location. Our method was, because the globus pallidus, frontal lobe, AP, and pons were in different sizes, we used ROI measurement tool with different areas to measure these regions. This was also what the reviewer of another journal suggested to me. As the globus pallidus and frontal lobes were bilateral structures, we measured the sum of bilateral values three times, worked out the average values of the globus pallidus and the frontal lobes, then calculated the GFI. Similarly, we used

ROI measurement tool with different areas for measurements of anterior pituitary and pons on sagittal 3D T1W sequence, repeated the same method three times and took the average value, then calculated the API. We considered that this should be sufficient to adequately assess brain signal changes in children with congenital portosystemic shunt (CPSS). We also hope that this approach could provide valuable insights into the specific characteristics and outcomes of the CPSS group.

2. Additionally, I would like to emphasize that the scientific writing structure of the manuscript, particularly the abstract, is not appropriate and requires basic revision. The abstract should provide a concise and clear summary of the study's objectives, methods, results, and conclusions. Currently, the abstract contains excessive details about patient selection criteria, statistical methods, and study duration, which are better suited for the main body of the paper.

Reply: Dear reviewer: Thank you for your opinion. According to your comments this time, combined with the 7th comment you proposed during the first major revision, in order to make the abstract more concise and clear, we have revised the study's methods including (1) the specific study design (case-control), (2) imaging protocol, (3) sampling technique. We have moved some details including (1) the patient inclusion and exclusion criteria, (2) statistical methods, and (3) study duration to the main body of the paper.

Thank you very much for your comments.

Yours sincerely

Ying Zhou

Mar 28th,2024

3 Revision 2

3 comments · 6 Apr 2024 – 9 Apr 2024

Referee 2 Reviewer

MINOR REVISION 6 Apr 2024

Thank you to the authors for appropriately editing the manuscript and responding to the questions. However, as previously mentioned, to assess changes, at least two measurements are required. In this instance, only one measurement has been taken. Therefore, it is not possible to evaluate change, and there may be a measured difference between the case and control groups. Consequently, terms such as change, increase, and decrease should be replaced with 'difference' throughout the entire manuscript.

Associate Editor

MINOR REVISION 8 Apr 2024

The manuscript is ready for finalization after minor revision as described by the reviewer.

Editor-in-Chief

MINOR REVISION 9 Apr 2024

Dear authors,
Your article needs Minor Revision.
Regards

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Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

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Reply to Reviewers' Letter

Dear Editor and Reviewers:

I would like to thank the reviewers for addressing the comments. Here I will reply the comments of the reviewers as follow:

Reviewer 2:

1. **Reviewer 1:** Thank you to the authors for appropriately editing the manuscript and responding to the questions. However, as previously mentioned, to assess changes, at least two measurements are required. In this instance, only one measurement has been taken. Therefore, it is not possible to evaluate change, and there may be a measured difference between the case and control groups. Consequently, terms such as change, increase, and decrease should be replaced with 'difference' throughout the entire manuscript.

Reply: Dear reviewer: Thank you very much for your comments. We completely agree with your point of view. Therefore, throughout the entire manuscript, we have replaced terms such as change, increase, and decrease with 'difference'. We highlighted all the revised words in blue. Thank you very much for your comments.

Sincerely Yours

Ying Zhou

April 9th,2024

4 Revision 3

2 comments · 21 Apr 2024 – 1 May 2024

Associate Editor

ACCEPT 21 Apr 2024

Dear Editor-in-Chief,

I am pleased to inform you that the authors have effectively addressed all the comments raised by the reviewers during the editing process.
As the Associate Editor, I have conducted a comprehensive review of the revised manuscript, and I am delighted to report that it is now suitable for publication in IJ Radiology.

Editor-in-Chief

MINOR REVISION 1 May 2024

Dear authors,
Your article needs Minor Revision.
Regards

5

Revision 4

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.

Reply to Reviewers' Letter

Dear Editor and Reviewers:

I would like to thank the reviewers and the associate editors for addressing the comments. Here I will reply the comments of the Reviewer 1 and Associate Editor 3 as follows:

Reviewers' Comments:

Reviewer 1:

1-Please cite figures in sequential order in the manuscript.

Reply: Dear Reviewer 1: Thank you very much for your comments. I have adjusted the figures to keep the citation in sequential order.

Associate Editors' Comments:

Associate Editor 3:

Thanks to authors for sending their paper to IJR. there are some points that should be addressed.

1-the title is unclear. It should be improved for more clarity. [For example: "Quantitative Brain MRI Signal Changes in Children with Congenital Portosystemic Shunt based on 3D T1-weighted Sequence" [or something like this]

Reply: Dear Editor 3: Thank you very much for your comments. I have improved the title according to your comments. Here, we use the term "differences" instead of "changes" , because Reviewer 1 suggested us that"terms such as change, increase, and decrease should be replaced with 'difference' throughout the entire manuscript" during the second revision.

2-in the objective of abstract, I can not see the word children that is not appropriate. Please correct. The aim should inform the reader that the study has been done on children.

Reply: Dear Editor 3: Thank you very much for your comments. I have added the word "children" in the objective of abstract.

3-please add objective part to paper according to journal format.

Reply: Dear Editor 3: Thank you very much for your comments. I have added the objective part to paper according to journal format.

4-please add sequential numbers to title and sub-titles: 1-Background. 2-Objectives. 3-Patients and methods. 3-1-Ethical review. 3-2-Data collection …..

Reply: Dear Editor 3: Thank you very much for your comments. I have added sequential numbers to title and sub-titles.

5-there is a single sentience in lines 86-9. The sentence is too long and unclear. It is better you split this sentence into smaller sentences for more clarity. [Considering that ages can affect the T1W signals in the brain ….]

Reply: Dear Editor 3: Thank you very much for your comments. I have split this sentence into some smaller sentences for more clarity.

6-in line 90 and 155, the term premature long-term follow-up seems to be wrong. It is better as prematurity long-term follow-up.

Reply: Dear Editor 3: Thank you very much for your comments. Yes, I have made a mistake, the term premature is an adjective word, the prematurity is a noun. I have revised this word.

7-this part seems wrong: in children under three-year-old patients it is better as in children under three-year-old of age.

Reply: Dear Editor 3: Thank you very much for your comments. I have revised “in children under three-year-old patients” to “in children under three-year-old of age”.

8-it is better you mention the full term of abbreviations in first location in which they are mentioned for example FLAIR, …..

Reply: Dear Editor 3: Thank you very much for your comments. I have added the full term of abbreviation of FLAIR and 3D.

9-what is the meaning of or not in line 100?

Reply: Dear Editor 3: Thank you very much for your comments. I have revised this sentence “with a gap of 1-2 mm or no gap”.

10-line 104, please correct as The contrast media was

Reply: Dear Editor 3: Thank you very much for your comments. Yes, I have corrected.

11-what is the meaning of “following the protocol”? by “following protocol?

Reply: Dear Editor 3: Thank you very much for your comments. I have made a mistake. It should be “the following protocol” instead of “following the protocol”.

12-this sentence seems to be connected to previous one but it has been written independently: “Assuming that there was no significant difference in the index values between two independent samples and that between two paired samples” please correct.

Reply: Dear Editor 3: Thank you very much for your comments. I have adjusted the place of this sentence forward.

13-please delete this part: “P-value > 0.05 indicated no significant correlation between the two variables.”

Reply: Dear Editor 3: Thank you very much for your comments. I have deleted this sentence.

14-please correct the following sentence: “Statistical analysis was carried out using the statistical software package for Windows. (IBM spss26, International Business Machines Corporation, Chicago, Illinois, 2019)” with this one: “Statistical analyses were carried out using SPSS ver. 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp)”

Reply: Dear Editor 3: Thank you very much for your comments. Yes, I have used the new sentence.

15-what is the logic of this sentence in paper: “The duration of the study from the study design to the final completion of the manuscript was more than three months.”

Reply: Dear Editor 3: Thank you very much for your comments. I wrote this sentence because during the first revision, the Reviewer 2 suggested that the duration of the study should be mentioned in the manuscript. I deleted this sentence in the part of Patients and Methods and moved it to the Abstract.

16-please correct in line 69: “, digital subtraction angiography (DSA) and computed tomography(CT).”

Reply: Dear Editor 3: Thank you very much for your comments. Yes, I have corrected.

17-what is the meaning of the position papers in line 72?

Reply: Dear Editor 3: Thank you very much for your comments. The “position papers” here was based on the title of Reference 12.

Reference 12:



PRACTICE GUIDELINES

Congenital portosystemic shunts
Vascular liver diseases: Position papers from the francophone network for vascular liver diseases, the French Association for the Study of the Liver (AFEF), and ERN-rare liver

Florent Guérin[a,b,*], Stéphanie Franchi Abella[c], Valérie McLin[d], Oanez Ackermann[b,e,f], Muriel Girard[f,g], Jean Paul Cervoni[h], Laurent Savale[i], Virginia Hernandez-Gea[j], Dominique Valla[f,k,l], Sophie Hillaire[m], Danielle Dutheil[n], Christophe Bureau[o], Emmanuel Gonzales[b,e,f,†], Aurélie Plessier[f,k,†]

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[f] French Network for Rare Liver Diseases (FILFOIE), European Reference Network (ERN) “Rare-Liver” Saint Antoine Hospital, AP–HP, 184, rue du Faubourg Saint Antoine, 75012 Paris, France
[g] Department of Pediatric Hepatology, Hôpital Necker - enfants malades, AP–HP, 149, rue de Sèvres, 75743 Paris cedex 15, France

Abbreviations: AaO2, Alveolar Arterial Oxygen Gradient; APTT, Activated Partial Thromboplastin Time; CEPS, Congenital Extrahepatic Portosystemic Shunt; CPSS, Congenital Porto Systemic Shunt; CT, Computerized Tomography; FNH, Focal Nodular Hyperplasia; gGT, Gamma-Glutamyltransferase; HCA, hepatocellular Adenoma; HCC, hepatocellular Carcinoma; HE, hepatic Encephalopathy; HPS, hepatopulmonary Syndrome; IVC, inferior Cava Vein; MPAP, mean Pulmonary Artery Pressure; MRI, magnetic Resonance Imaging; PaHT, Pulmonary Arterial Hypertension; PaO2, Partial Pressure Of Oxygen; PASP, Pulmonary Artery Systolic Pressure; PT, Prothrombin Time.

* Corresponding author at: Department of Visceral Pediatric surgery, FHU Hépatinov, Bicêtre Hospital, AP–HP, Paris-Saclay, 78, rue du Général-Leclerc, 94270 Le Kremlin-Bicêtre, France.
E-mail address: florent.guerin@aphp.fr (F. Guérin).
† Equally participated.

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2210-7401/© 2020 Elsevier Masson SAS. All rights reserved.

18-please change involved to included in line 75.

Reply: Dear Editor 3: Thank you very much for your carefulness. I have changed “involved” to “included” in line 75.

19-lines 81-4: please delete: “To investigate the value of quantitative MRI in assessing brain signal differences with portosystemic shunt in children, we designed this case-control study.” Instead, replace mentioned part with this one: “In this case control study, 32 patients with diagnosis of CPSS, including12 females and 20 males were enrolled as case group (median age: 6 years and 5 months, age range: 22 months-15 years old,.).”

Reply: Dear Editor 3: Thank you very much for your comments. I have replaced mentioned part with the new part.

20-in line 149, it is better the gender distribution of IHPS and EHPS will be compared with statistical test [chi square] and P-Value will be mentioned.

Reply: Dear Editor 3: Thank you very much for your comments. I have compared the gender distribution of IHPS and EHPS with statistical test ~Fisher's exact probability tests ((P-Value 0.062).

Fisher's exact probability tests:

Because n<40, we utilized Fisher's exact probability tests instead of Chi square test.

个案处理摘要

	个案					
	有效		缺失		总计	
	N	百分比	N	百分比	N	百分比
组别 * 结局	32	100.0%	0	0.0%	32	100.0%

组别 * 结局 交叉表

计数

		结局		
		男	女	总计
组别	EHPS	9	10	19
	IHPS	11	2	13

卡方检验

	值	自由度	渐进显著性（双侧）	精确显著性（双侧）	精确显著性（单侧）
皮尔逊卡方	4.569[a]	1	.033		
连续性修正[b]	3.118	1	.077		
似然比	4.891	1	.027		
费希尔精确检验				.062	.036
有效个案数	32				

a. 1 个单元格（25.0%）的期望计数小于 5。最小期望计数为 4.88。

b. 仅针对 2x2 表进行计算

21-you mentioned the control group are 2-15 years old (A total of thirty children aged 2 to 15 years), while you mentioned then Age at performing brain MRI ranged from 1 year to adolescent. These are not in accordance [what is minimum age?] please note that for control group, the age is the time that the subject has shared the clinical and MRI data, so minimum age is 1 year.

Reply: Dear Editor 3: Thank you very much for your comments. This patient was selected as the Control Group at the age of 2, but he underwent brain MRI at the age of 12 months. I have revised this inconsistency.

22-in line 163, (RDM) could be deleted as it has been mentioned only one time in paper.

Reply: Dear Editor 3: Thank you very much for your comments. I have deleted the abbreviation "(RDM)".

23-table 2 legend is not appropriate. It could be: "Demographic, Clinical and Imaging Characteristics of the congenital portosystemic shunts Group and the Control Group" please correct the line 164 accordingly. [Sample Characteristics …]

Reply: Dear Editor 3: Thank you very much for your comments. I have revised the table 2 legend and revised the line 164 accordingly.

24-in line 168, the part "Therefore, the assumption is not established," is meaningless and could be deleted.

Reply: Dear Editor 3: Thank you very much for your comments. I have deleted this sentence.

25-The lines 166-170 could be written as: "The mean GFI of Cases in 3D T1-weighted sequence was 1.278±0.132 (range=1.001-1.494), while this figure was 0.969±0.036 (range=0.906-1.049) in controls. (P<0.01) (Fig.1A-1B, Fig.2A-2B, Fig.3A) The mean API of cases in 3D T1-weighted sequence was 1.316±0.233 (range 0.804-1.761), while this figure was 0.941±0.103 (range=0.745-1.152) in controls. (P<0.01) (Fig.1C, Fig.2C, Fig. 3B)

Reply: Dear Editor 3: Thank you very much for your revision. I have changed this part. Meanwhile, I adjusted the figures to keep the citation in sequential order according to Reviewer 1's comments.

26-figure 4A, Y axis of plot, it is frontal not rrontal. In addition it is better as "Globus Pallidus to White Matter of Frontal Lobe Index" , part B in Y axis of plot "Anterior Pituitary to Pons Index" part C Y axis is better as "Globus Pallidus to White Matter of Frontal Lobe Index"

Reply: Dear Editor 3: Thank you very much for your revision and carefulness. I have revised the Y axis of plot from Fig.4A to Fig.4C.

27-figure 4 legend is better as: "A-Comparison of GFI between Cases and Controls. B- Comparison of API between Cases and Controls. C- Comparison of GFI between 3D T1W sequence and the standard T1W sequence in Cases (GFI: Globus pallidus to white matter of frontal lobe index. API: Anterior pituitary to pons index.)

Reply: Dear Editor 3: Thank you very much for your revision. I have revised the figure 4 legend.

28-sentences in lines 172-5 could be written as: "In case group, mean GFI of on the 3D T1W sequence was 1.278±0.132 (range=1.001-1.494), while this figure was 1.111±0.085 (range=0.967

-1.265) on standard T1W sequence. (P<0.01) (Figs.1A,B, 2A,B)”

Reply: Dear Editor 3: Thank you very much for your revision. I have changed this part. Meanwhile, I adjusted the figures to keep the citation in sequential order according to Reviewer 1’s comments.

29-please delete (P>0.05) in lines 178 and 179.

Reply: Dear Editor 3: Thank you very much for your comments. I have deleted “(P>0.05) in lines 178 and 179”.

30-please change speedy to rapid in line 183.

Reply: Dear Editor 3: Thank you very much for your comments. I have changed “speedy” to “rapid” in line 183.

31-The following part, “.. were the most common presentations and complications, pulmonary involvement included HPS (44%), PHTN (31%) and pulmonary arteriovenous fistula (PAVF, 22%).” is unclear. [may be, if we change, to full stop, the sentence will be better (change into 2 sentences)]

Reply: Dear Editor 3: Thank you very much for your comments. We have changed this sentence into 2 sentences.

32-this part seems unclear: “these often delayed referral and diagnosis” please clarify.

Reply: Dear Editor 3: Thank you very much for your comments. This sentence was quoted from Reference 19. “In the early course of this congenital disease there are few, if any symptoms. Those symptoms are usually not liver related, which delays referral and diagnosis.” We have revised some sentences in this part.

Reference 19 ➡

HEPATOLOGY

Congenital veno-venous malformations of the liver: Widely variable clinical presentations

Peter Witters,*† Geert Maleux,‡ Christophe George,§ Marion Delcroix,¶ Ilse Hoffman,† Marc Gewillig,† Chris Verslype,*§ Diethard Monbaliu,*** Raymond Aerts,** Jacques Pirenne,** Werner Van Steenbergen,§ Frederik Nevens,*§ Johan Fevery*§ and David Cassiman*§

*Laboratory of Hepatology, Catholic University of Leuven, Leuven, and Departments of †Paediatrics, ‡Radiology, §Hepatology, ¶Pulmonology and **Transplantation Surgery, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium

Discussion

Portosystemic shunts are increasingly recognized due to the evolution and expansion of medical imaging. However, the total number of reports remains small. Early recognition of portosystemic shunts is important, given the detrimental effects of shunting on the liver and on other organs. This damage can be prevented if a timely diagnosis is made. In the early course of this congenital disease there are few, if any symptoms. Those symptoms are usually not liver related, which delays referral and diagnosis. Furthermore, a clinical suspicion will alert the radiologist and increase the diagnostic yield of for instance echo Doppler, allowing a diagnosis to be made. Here we review the possible clinical presentations.

The liver’s synthetic functions are usually well preserved and symptoms secondary to portal hypertension (splenomegaly, ascites, varices) are typically absent. This is due to the fact that portal

33-in line 219, the word subthalamic is incomplete. It should be for example subthalamic region.

Reply: Dear Editor 3: Thank you very much for your comments. We have revised this word.

34-the word difference in line 223 is meaningless: “Abnormal MR signal differences” it could be signal intensity

Reply: Dear Editor 3: Thank you very much for your comments. I wrote this sentence because during the second revision, the Reviewer 2 suggested that “terms such as change, increase, and decrease should be replaced with 'difference' throughout the entire manuscript”, so I changed the “Abnormal MR signal changes” into “Abnormal MR signal differences”. I revised the part “Abnormal MR signal differences” to “Abnormal MR signal intensities” this time.

35-line 228 it is area not areas.

Reply: Dear Editor 3: Thank you very much for your comments. I have revised this word.

36-this sentence is unclear: “Wide age range also influenced the ratios of the results, although there were positive age-matched controls.” Please clarify.

Reply: Dear Editor 3: Thank you very much for your comments. When designing this study, we have considered that ages can affect the T1 signals in the brain, especially in the young children. The age range of the case group was wide (1-15 years old). Such a wide age range may influence the ratios of the results. Our main response method was to select age-matched controls to minimize the impact of age on brain signal changes as much as possible.

37-what is the meaning of DA in line 228? What is IR in line 263?

Reply: Dear Editor 3: Thank you very much for your comments. The meaning of DA is dopamine. The meaning of IR is interventional angiography, here I revised “IR” into “DSA”.

38-in line 271, please correct: “… children with CPSS compared to controls.”

Reply: Dear Editor 3: Thank you very much for your comments. I have corrected this sentence.

39-line 272, please correct: A longitudinal

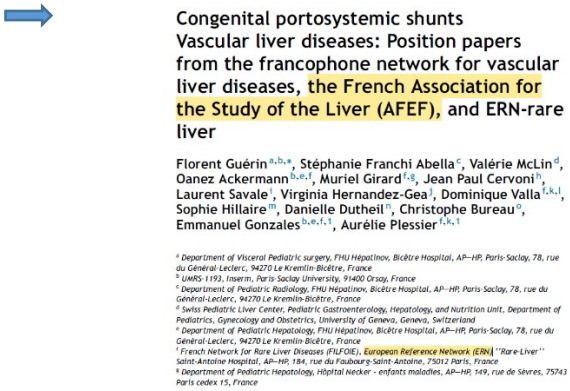
Reply: Dear Editor 3: Thank you very much for your comments. I have corrected “a longitudinal” to “A longitudinal”.

40-what are AFEF and ERN in table 1 legend? Please add in footnote of table.

Reply: Dear Editor 3: Thank you very much for your comments. I have added the full term of abbreviations in the footnote of table 1. (AFEF: French Association for the Study of the Liver, ERN:

European Reference Network.)

Reference 12:



Congenital portosystemic shunts
Vascular liver diseases: Position papers from the francophone network for vascular liver diseases, the French Association for the Study of the Liver (AFEF), and ERN-rare liver

Florent Guérin[a,b,*], Stéphanie Franchi Abella[c], Valérie McLin[d], Oanez Ackermann[b,e,f], Muriel Girard[f,g], Jean Paul Cervoni[h], Laurent Savale[i], Virginia Hernandez-Gea[j], Dominique Valla[f,k,l], Sophie Hillaire[m], Danielle Dutheil[n], Christophe Bureau[o], Emmanuel Gonzales[b,e,f,†], Aurélie Plessier[f,k,†]

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41-please add full term of abbreviations in table 2 footnote for example EHPS, IHPS, PDV

Reply: Dear Editor 3: Thank you very much for your comments. I have added the full term of abbreviations in table 2 footnote.

42-in figures legend, you are reporting a single case so the word difference that denote difference between two groups are inappropriate. it would better with change. For example: “Fig 1. Portosystemic shunt-related brain signal changes in a 11 years old girl with a patent ductus venosus (PDV) shunt(IHPS)” and: “Fig 2. Portosystemic shunt-related brain signal changes in a 13 years old girl with an Upstream of the portal vein type (EHPS)”

Reply: Dear Editor 3: Thank you very much for your comments. I understand what you mean. That is in the part of figures legend, it is a single case, the word “change” that denote difference between two groups is better than the word “difference”. So I changed the word “differences” into “changes” in Fig 1 and Fig 2.

43-in fig 2 legend please correct: “Abdominal enhanced CT scan …”

Reply: Dear Editor 3: Thank you very much for your comments. I have corrected “Abdominal enhanced CT scan …”.

44-Please cite figures in sequential order in the manuscript.

Reply: Dear Editor 3: Thank you very much for your comments. Your suggestion is consistent with the comments of Reviewer 2. I have adjusted the figures and keep the citation in sequential order.

I highlighted all the revised parts in yellow. Thank you very much for your comments.

Sincerely Yours

Ying Zhou

May 5th,2024

5 Revision 4

1 comment · 11 May 2024

Editor-in-Chief

ACCEPT 11 May 2024

Dear authors,
Your article is acceptable for publication in IJR.
Regards