Author’s response to reviews

Title: MR Imaging Features of Orbital Langerhans Cell Histiocytosis

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Version: 2 Date: 04 Jun 2019

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Response to the comments:
(Reviewer 1) Jian Li, MD, PhD: The authors should be congratulated as they did a lot of hard work to document the clinical manifestations and MRI findings of 23 patients with histology-confirmed orbital Langerhans Cell Histiocytosis (LCH), which is a rare disease all over the world. However, there are several points need to be clarified before considering for publication. Many thanks for your comments.

1. No control subjects were recruited for this study. Most of the results were descriptive. Few quantitative analyses of the images were presented. Thus, article type of case series report could be more appropriate for this manuscript.
   Response: The LCH is a rare disease, so the data of 23 patients with the orbit provide precious information to readers. In this article, our main purpose was analyzed the MRI features of the orbital LCH. And in fact, according to our research, we found orbital LCH posses some specific manifestations on MRI, and these performances have not been reported in previous literatures. We suggest the results of the analysis have important value, which can improve the diagnostic accuracy of the orbital LCH for radiologists, and can provide valuable information for clinicians to understanding the disease better and clearer. Therefore, we consider that our study has clinical application value, it can be considered as the research article, and we hope to get your understanding and support. In the following work, we will recruit control subjects to continue the in-depth study.

2. Discussion section could be refined to emphasize the crucial features of MRI in LCH.
   Response: In the revised manuscript, we have made adjustment in this section, replenish some information of the MRI feature.
3. As concluded in this manuscript, "MRI characteristic features can improve the diagnostic accuracy of the orbital LCH". Authors are encouraged to evaluate the diagnostic accuracy of LCH by using MRI.

Response:
In the discussion of revised manuscript, we emphasized the significance of the MRI characteristic features of the orbital, which can provide key point for radiologist to improve the diagnostic accuracy.

4. The writing needs to be improved to avoid typos and grammar mistakes.
Response:
In the revised manuscript, we have corrected the typos and grammar mistakes try our best.

(Reviewer 2) Sentaro Kusuhara, M.D., Ph.D.: The manuscript written by Wu C et al. is a retrospective study to examine the MR imaging characteristics of orbital Langerhans cell histiocytosis (LCH). As the authors stated, LCH is a rare disease and the data of 23 patients with LCH in the orbit surely provide precious information to the readers. Accordingly, I strongly recommend for publication pending adequate responses to the following concerns.

Many thanks for your comments.

Major points
1) In Results of Abstract, hemorrhage cannot be identified on MRI as its appearance depends on the type of hemoglobin present. Please be noted that we only know MRI images of several stage of hematoma meaning we are unable to define hemorrhage solely by MR imaging.
Response:
In the revised manuscript, we have corrected this sentence.
2) The latter part of 'Clinical characteristics of the patients' is reiteration of Tables 1 and can be omitted. In addition, I do not think that 'misdiagnosed as inflammatory pseudotumor is a clinical sign.
Response:
In the revised manuscript, we have deleted that table 1. And, deleted the “misdiagnosed as inflammatory pseudotumor” from the clinical sign.
3) In subsection 'Pre-contrast MRI presentation along with the pathological results', the authors presented the characteristics of MRI on each imaging technique. However, in clinical practice, the combinatory use of MR images is required (e.g., a tumor exhibits T1 high, T2 low, and positive Gd enhancement). Therefore, a table would be helpful which summarizes MRI findings of all 23 cases including location, shape and size, and signals on T1WI, T2WI, and enhanced image.
Response:
In the revised manuscript, we add two tables, one is about location, shape and boundary, and the other is about the signals on T1WI, T2WI and enhanced image.
4) BCVA data before and after treatment should be provided.
Response:
In the revised manuscript, we add the information of the visual acuity. Because the lesions of LCH rarely affect the optic never or orbital apex, most patients’ vision is unaffected.
5) In the second paragraph of the subsection 'The differential diagnosis of orbital LCH', most of descriptions are explanations of each disease raised as a candidate for differential
diagnosis. As this is a discussion part, the authors should describe what characteristics of LCH is useful in the differential diagnosis.

Response:
In the revised manuscript, we have corrected this section, we added the MRI feature of the disease that need to be identified, through comparing with the characteristics of LCH to differential diagnosis.

6) Figure 4 does not contain novel information because no link was given to patient's characteristics including MR images.

Response:
The figure 4 is used to confirm the pathological of the LCH for our cases. The images shows the hemorrhage and necrosis in the lesions, which is match with the appearance on MRI, play the role of mutual verification. In addition, we added the images of IHC in the revised manuscript.

Minor points
1) Professional English editing is mandatory.

Response:
In fact, this article has been professionally edited by AJE before.

2) There are so many typos. For example, an extra comma is present in the first sentence in Results of Abstract.

Response:
I’m terribly sorry for these mistakes, I have examined the whole text carefully and corrected it.

3) Ambiguous words such as 'most' and 'some' seem unsuitable in the description of the results (in Results of Abstract).

Response:
In the revised manuscript, we have corrected these two words. “most” change to “majority”, “some” change to “several”.

(Reviewer 3)Anton Lennikov, M.D., Ph.D.: Manuscript BOPH-D-19-00089R1 "MR Imaging Features of Orbital Langerhans Cell Histiocytosis" by Wu et al., is a research article on the topic of diagnostic of Langerhans cell histiocytosis in orbit, manuscript present and summarises different localization and appearance of MRI findings during LCH. The findings of scientific interest and clinical relevance. However, the manuscript requires additional editing, proofreading, and addition of specific histological stainings to be considered for publication.

Many thanks for your comments.

General comments:
1. The manuscript requires significant editing and proofreading by a native speaker or scientific editing company or preferably both as there are many spelling mistakes, several sentences sound disjointed or involve unusual phrasing and word choices in a multitude of instances across the manuscript.

Response:
I apologized to you for my mistake, I have examined the whole text carefully. And in fact, In fact, this article has been professionally edited by AJE before.

2. Authors should carefully re-read the manuscript paying extra attention to the usage of spaces between words and sentences in many sentences spaces are missing in some places; there are unnecessary spaces introduced.

Response:
I’m terribly sorry for these mistakes, I have corrected it.
3. If authors have taken the photographs of the patients' eyes during initial visit and have the authorization from the patients and/or patients' legal guardians it would be good to present images of the eyes overall look to further support MRI findings as it will benefit the manuscript primary goal to provide the reference for clinicians who may encounter orbital LCH patients.

Response:
In the revised manuscript, we added two child patients’ photographs, which have the authorization from the patients’ parents.

4. As it a retrospective study authors may include the treatment strategy for orbital LCH and its outcome.

Response:
In the revised manuscript, we added the treatment strategy and outcome. Since this study mainly analyzed the MRI features of orbital LCH, the treatment strategy and prognosis were not elaborated in detail.

Specific comments:
Page 1, lines 30-32
As the mean age of the patients was 6.3 years old authors should mention that written informed consent was obtained from patients' parents or legal guardians where applicable. Which authors do in the declarations at the end of the article, but not in the statement at the beginning of the article.

Response:
In the revised manuscript, we added this information.

Page 3, line 54
I do not think using word short in conjunction with the word diameter is correct.

Response:
In the revised manuscript, we have corrected this sentence.

Page 4, lines 16
"bolus injection of 0.2 mg/kg" - of what? The description and the sources of the contrast are missing.

Response:
In the revised manuscript, we have replenished the information.

Page 4, Results
Authors suggested reworking the description of patients’ age, sex, diseases duration into the table.

Response:
We appended a table about all patients age, sex and disease duration.

Page 5, Location and morphology of lesions
Authors encouraged to add visual cues such as arrows or dotted margins to indicate the exact position of lesions on the MRI images. It will improve the understanding of the article by non-specialists in the field.

Response:
In the revised figures, we added the arrows to indicate the lesions.

Page 5, Pre-contrast MRI presentation along with the pathological results
Authors describe hemosiderin and macrophages but only present H&E histology to support their statements. See additional experiments.

Response:
We added the figures of IHC.
Page 6, line 54
"0.2-2.0% cases" - is it worldwide or in some locality? Please clarify.
Response:
In the revised manuscript, we have replenished the information.

Page 6, line 57 - "High incidence of the orbital involvement." Where is this data is coming from please provide the reference and please indicate percentage if available regarding the incidence of orbital involvement?
Response:
In the revised manuscript, we have replenished the information.

Page 7, line 9 - "boys" - male at or pre-adolescent males. "Boys" is not an appropriate word in the scientific text.
Response:
In the revised manuscript, we have corrected the “boy” to “pre-adolescent males”.

Page 7, lines 6-42 - please revise this fragment of text avoiding using vague terms such as "this group."
Response:
In the revised manuscript, we have corrected this fragment.

Page 7, 42-44 - "Regrettably we could not determined the specific type of rest cases because of the lack of whole body systemic details" - Please rework this sentence as it is confusing to the reader of what exactly authors meant. "Whole body systemic details" is even more confusing statement. Please be more specific of what are you referring to also appropriate grammar is required for sentence to be understandable.
Response:
In the revised manuscript, we have corrected this sentence.

Page 7, line 55 - Coincident - I assume intended meaning is "not consistent."
Response:
In the revised manuscript, we have corrected this word.

Page 7, line 58 - actually - Please rework this whole sentence.
Response:
In the revised manuscript, we have corrected this sentence.

Page 8, line 8 - were mostly "crumb or triangular" - I do not understand authors terminology here. Was intended meaning triangular? Is the intended meaning for crumb is porous in structure?
Response:
In the revised manuscript, we have corrected this sentence.

Page 9, line 17 - Authors talk about S100 and CD1a in differential diagnostics of LCH but only present general H&E staining in the figures. See additional experiments.
Response:
We added the images of IHC, include S100, CD 1a and CD 68.

Page 9, line 32 "general conditions of the patients is poorer" - please revise this sentence to "Patients demonstrate symptoms outside the orbital region, consistent with primary tumor localization, along with typical malignancy associated general symptoms."
Response:
In the revised manuscript, we have corrected this sentence.

Page 9, line 36 - "abdominal primary tumors been found can help diagnosis" - Please revise this sentence to "Presence of the primary tumor is the main finding in the differential diagnostic of the condition."
Response:
In the revised manuscript, we have corrected this sentence.
Page 9, line 43 "worm-eaten" - While I understand what authors try to say, try to use a different synonym to this term such as deteriorated.
Response:
In the revised manuscript, we have corrected this sentence.
Page 10, lines 10-13 - "Osteomyelitis... ...can be repaired if anti-inflammatory treatment timely" please revise this sentence it is just disjointed set of words especially in the second part of the sentence.
Response:
In the revised manuscript, we have deleted this sentence for this disease could be ignored.
Page 10, lines 19 - Please spell the acronyms on the first use "Diffusion-weighted magnetic resonance imaging," and since authors have introduced the list of abbreviation, please put it in there. At the same time, the authors did not abbreviate dynamic enhanced scanning.
Response:
In the revised manuscript, we have added the information of the DWI. But “dynamic enhanced scanning” is not usually abbreviated in routine duties.
Figures:
Figure 1-3 Normal MRI should be introduced for comparison.
Dotted plot or arrows should indicate the abnormal findings on MRI images for ease of the readers.
Response:
In the revised figures, we added the arrows to indicate the lesions. Because the lesion mostly involved unilateral orbit, contralateral unaffected orbit can be used as the normal control.
It would significantly improve the ease of following the MRI images if authors could introduce drawn or 3D rendered artwork of the skull with the localization of abnormalities based on the MRI data.
Response:
Due to the lack of 3D data on MRI, 3D image could not be reconstructed, however, we added 3D image on CT data of patient, which can show the lesion site very well.
Figure 4 - Specific stainings are required to make statements regarding cell populations, hemosiderin, and macrophages. H&E staining gives only general information as it not specific staining for these cell types. Please introduce the scale bar into the images rather than staining the magnification.
Response:
We added the images of IHC, include S100, CD 1a and CD 68. Limited by the function of the device, we cannot add the scale bar into the images.
Additional experiments:
Authors mention in the background of the article that distinctive marker for LCH is CD1a+ cells, CD1a+ indeed along with CD207 CD1a are specific markers for Langerhans cells, however, only present H&E staining to support their statements regarding the presence of Langerhans cells and hemosiderin in their work. Authors strongly encouraged to perform the IHC with patients' histological samples using DAPI/CD1a, DAPI/CD207 (triple DAPI/CD1a/CD207 is preferable) and Prussian blue to accurately detect hemosiderin, i.e. using Iron Stain Kit (such as ab150674). This IHC is easy to perform as authors already have histological sections. If authors have no access to florescent microscopy of suitable quality DAB staining with visible light microscopy
demonstrated by H&E figure is acceptable. If authors want to demonstrate the macrophages in their samples, they need to use CD14 or CD16 to identify the population positively. Moreover, the combination of CD14/Prussian blue or CD16/Prussian blue is required to identify the phagocytosis of hemosiderin by the macrophages. If possible authors also need to present a healthy orbital material biopsy (or post mortem tissue sample) as a control as well as metastatic orbital biopsy (or post-mortem tissue sample) for comparison.

Response:
We added the images of IHC, include S100, CD 1a and CD 68. Because of the lack of the CD14 and CD16, we do the CD 68, it also can identify the phagocytosis of hemosiderin by the macrophages.