Comments to the Author:

Dear Authors,

Thank you for writing and submitting this manuscript entitled, "BLINDED."

The subject of bifocal germinomas (BFG) is of interest to AJNR and its readers. This was a retrospective review of 21 cases and the published literature on bifocal germinomas of the pineal region and hypothalamoneurohypophyseal axis (HNA) in an attempt to develop diagnostic criteria differentiating 'true BFG' – ie. primary tumors of both the pineal region and HNA' from 'false BFG' – ie. primary tumor of pineal region and metastatic lesion of HNA on the basis of both MRI and clinical features, with a potential implication on radiatiotherapy strategy.

Introduction:

1. This section primarily focuses on the definition of bifocal germinomas currently established in the literature. However, a more detailed explanation of characteristic MRI and clinical findings would also be of value.

2. The sentence 'The authors considered for these patients omission of spinal irradiation appeared to be a reasonable approach' should be rephrased/clarified. For example, 'The authors considered that omission of spinal irradiation was a reasonable approach in these patients.'

3. Please correct 'should alert clinicians to the possibility of a disseminated disease' to 'should alert clinicians to the possibility of disseminated disease.'

4. The final sentence in the Introduction, 'The results of our analysis suggest that dual-origin BFGs do exist, and that a distinct differential diagnosis of primary vs. metastatic BFG can be achieved, and that the existence of metastasis to other locations is not a diagnostic criteria for true or false bifocal germinomas,' has a 'comma' instead of 'period' at the end. It should also be rewritten in a clear manner. For example, 'The results of our analysis suggest that dual-origin BFGs do exist, and that a distinct differential diagnosis of primary vs. metastatic BFG can be achieved. Furthermore, the existence of metastasis to other locations is not a diagnostic criterium in differentiating true and false bifocal germinomas.'

Materials and Methods:

5. Please correct 'We searched PubMed with the following terms or combinations: (infundibulum OR stalk OR hypothalamus OR neurohypophysis OR "posterior pituitary" OR "posterior lobe" OR suprasellar OR intrasellar) AND (germinoma OR germinomas)' to 'We searched PubMed with the following terms or combinations: ("infundibulum" OR "stalk" OR "hypothalamus" OR "neurohypophysis" OR "posterior pituitary" OR "posterior lobe" OR "suprasellar" OR "intrasellar") AND ("germinoma" OR "germinomas")."

6. The statement ‘Normal inferior pituitary stalk has the minimum size of <3.0mm’ is confusing, since it is associated with reference #22 in the Materials and Methods and reference #18 in the Discussion. Furthermore, as per reference #18 (Maghnie M, Cosi G, Genovese E, et al. Central diabetes insipidus in children and young adults. N Engl J Med 2000;343:998-1007), an abnormally thickened pituitary stalk is greater than 3.0 mm. Please rephrase/adjust accordingly.

7. Please correct ‘both the pineal region and HNA with or without metastasis of other locations’ to ‘both the pineal region and HNA with or without metastasis to other locations.’

8. Please correct ‘All analysis were performed using IBM SPSS Version 20’ to ‘All analyses were performed using IBM SPSS Version 20.’

Results:

9. This section does not adequately discuss the MRI and clinical findings of ‘true’ versus ‘false BFGs.’ The types of tumors need to be clarified, and the presence versus absence of metastatic spread needs to be clearly defined / discussed in greater depth. Additional images, zoomed to the region of interest might be helpful.

10. Table 1 contains author identifiers ‘Our cases from Nanfang hospital (unpublished)’ – perhaps a better way of phrasing this would be ‘cases from our institution.’

11. Please correct ‘Of the 95 cases, there were only72 case whose posterior pituitary signal of MRI were reported, but none presented with high intensity signal (HIS)’ to ‘Of the 95 cases, there were only72 cases whose posterior pituitary signal of MRI was reported, but none presented with high intensity signal (HIS).

12. As per reference 18 (Maghnie M, Cosi G, Genovese E, et al. Central diabetes insipidus in children and young adults. N Engl J Med 2000;343:998-1007), an abnormally thickened pituitary stalk is greater than 3.0mm. Therefore, please correct/rephrase ‘According to the normal minimum size of the inferior pituitary stalk may < 3.0 mm.’ For example, ‘According to the normal maximum size of the inferior pituitary stalk of 3.0 mm’.

13. Statistical analysis is adequate.

Discussion:

14. The Discussion focused primarily on the findings previously described in the literature and needs to be rewritten in a more concise manner. Focus should be placed on the current results and diagnostic criteria for differentiating ‘true’ from false BFGs’ that the authors are trying to validate.

15. Limitations of the study (including rather small sample size) need to be outlined in detail.

16. Please correct ‘and 41.7% (5/12) remote metastasis,’ to ‘and 41.7% (5/12) remote metastasis.’

17. The sentence ‘Thus, our results suggest these variables do not support their view’ is confusing and should be rephrased in a more coherent manner, such as ‘Thus, our findings are in contradiction with the previously published results in the literature.’

18. The sentence ‘’suggesting that no ventricular or CSF disease does not exclude the possibility of metastasis’ is confusing and should be rephrased. For example ‘suggesting that the absence of ventricular or CSF disease does not exclude the possibility of metastasis.’

19. Please correct ‘it is inappropriate to categorize’ to ‘It is inappropriate to categorize’.

20. Please correct ‘with metastasis of the third ventricular floor’ to ‘with metastasis to the third ventricular floor.’

21. Please adjust ‘Cuccia and Alderete thought that bifocal lesions should have not metastasis of other locations’ to a more coherent phrase. For example ‘Cuccia and Alderete suggested that bifocal lesions shouldn’t have metastasis to other locations.’

22. Please correct ‘with other location metastasis’ to ‘with metastases to other locations.’

23. Please rephrase ‘The definition of Cuccia and Alderetre was too narrow.’ For example, ‘The definition provided/outlined by Cuccia and Alderete was too narrow.’

24. Please correct ‘Moreover, our data show that’ to ‘Moreover, our data shows that.’

25. Please correct ‘we are not able differentiate these patients with our method’ to ‘we are not able to differentiate these patients with our method.’

26. Please correct ‘neurohypophyseal germinomas with metastatic pineal region tumor’ to ‘neurohypophyseal germinoma with metastatic pineal region tumor.’

27. Please change ‘In fact, primary germinomas of the pineal gland or the neurohypophysis is totally different from the germinomas easily seeded at the ependyma of the third ventricular floor or of the suprapineal recess’ to ‘In fact, primary germinomas of the pineal gland or the neurohypophysis are totally different from the germinomas easily seeded to the ependyma of the third ventricular floor or of the suprapineal recess’.

28. Please change ‘while metastatic lesions first seeded at the ventricular side of the ependyma and then grew by subependymal laminar infiltration’ to ‘while metastatic

lesions first seed to the ventricular side of the ependyma and then grow by subependymal laminar infiltration.'

Conclusion:

29. The Conclusion needs to be re-written in a more concise and clear manner. I suggest systematically going through the clinical and MRI differences between 'true' and 'false BFGs.' Grouping all of the characteristics of 'true BFGs' into a single sentence makes it confusing and difficult to follow/interpret.

30. Instead of 'regardless of metastasis of other locations' please use 'regardless of metastasis to other locations.'

31. Instead of 'concurred pineal region tumor' please use 'concurrent pineal region tumor.'

References:

32. References are adequate.

Figures:

33. Figures (images) are generally adequate. However, images magnified/zoomed to better depict the region of the tumor may be helpful.

34. Legend for Figure 2 reads 'One Patient' – please correct to 'One patient.'

Comments to the Author:

In this study authors investigated the correlation between ECG-gated CTA images and intraoperative images in terms of pulsation (wall motion) of unruptured intracranial aneurysms by visual assessment. Out of 43 available aneurysms, 9 (4 with pulsation and 5 without) were treated surgically in their institute which gave the authors the chance to make an intraoperative image to compare with ECG-gated CTA images. Their results show that aneurysms with dark-reddish colour (thin wall) in the intraoperative image correspond to the pulsatile ones in the CTA images and the aneurysms with regular wall (thick wall) correspond to the non-pulsatile ones. Therefore they concluded that 4D CTA is a suitable technique for studying dynamic and structural features of the aneurysm wall.

Major strengths:
• The research topic is of importance in the field and several studies has been performed on techniques to study aneurysms dynamics and investigate parameters related to its rupture risk.
Major weaknesses:
• The research question and hypothesis are not clearly stated or addressed in the conclusion.
• The novelty of the study is not evident or stated in the manuscript.
• The study has not been compared to similar studies on the same topic.
• No statistical/numerical analysis is provided.

Comments:
• Abstract: It is not clear what the research question is and how it have been addressed by the study. Considering the title and abstract, it is not clear if you are investigating the capabilities of 4D -CTA or the aneurysm wall thickness as a rupture risk factor.
• Abstract: In the method section there is no information about the intraoperative imaging.
• Abstract: In the result section, again there is no information regarding the intraoperative images.
• Introduction: Literature review is limited. More studies needs to be added and discussed, e.g. the ones added as reference at the end of the comments.
• Introduction: Nothing has been mentioned about the current study and its novelty in comparison to similar studies.
• Introduction: It does not guide the reader through the paper. No explanation is provided regarding the paper sections and content.
• Methods: What was the patients' selection criteria?
• Methods: What was the quantitative measure for detecting aneurysm wall motion? (how many mm displacement in aneurysmal wall in different frames was considered a change?)
• Methods: Did you consider noise in your measurements? Since the aneurysm wall displacements are in the order of mm, making sure that we are measuring data and not noise, is essential.
• Methods: It is not clear which intraoperative images have been made for the purpose of comparison to 4D-CTA and how they have been made.
• Methods: No information has been included regarding the criteria of comparison between 4D-CTA and intraoperative images.
• Results: No statistical analysis or quantitative results have been provided.
• Results: Effectively only 9 aneurysms have been included in this study, since the authors did

not have access to the ones treated on other hospitals. This number is very limited for such a study.
• Results: The reason for presenting the representative clinical cases is not clear.
• Discussion: Most of the information presented in the discussion part belongs to introduction part. Therefore discussing the limitations of the method and suggestions for future work are missing.
• Conclusion: Again it is not clear if the goal was to investigate the performance of 4D-CTA or aneurysm wall thickness as a measure for rupture risk.
• The novelty of this study and its contribution to the field is not clear. Similar studies have been performed regarding aneurysm wall motion and its relation to rupture risk, as well as presenting 4D-CTA as a suitable modality for such studies [1]. For example, in [2], it has been shown that walls of ruptured aneurysms were less rigid than unruptured ones but there was no correlation between aneurysm wall thickness and its rupture. It was also concluded that other biomechanical properties/conditions of the aneurysm may contribute to the rupture as well. Or in [3], the relation between aneurysm wall thinning and its pulsation using ECG-gated CTA and intraoperative investigations has been discussed. Further in [4], it has been shown that aneurysm wall is heterogeneous with variable thickness which can play a role in its rupture risk. Therefore the authors need to look deeper into literature and emphasis the knowledge that their study adds to the field.
• Overall, the English language used in this manuscript is not fluent and often has grammatical mistakes. There are instances where the language is not scientific as well, e.g. First paragraph of the introduction.
• Abbreviations are not consistent and/or not expanded at first instance.
• Figures: They are not clear. The amount of changes that has been pointed out in the figures, look more like noise that anything else. Therefore defining quantitative measures and criteria are necessary.
References:
[1]. Firouzian A, Manniesing R, Metz CT, et al. Quantification of intracranial aneurysm morphodynamics from ECG-gated CT angiography, Acad Radiol. 2013; 20(1):52-8.
[2]. Costalat V, Sanches M, Ambard D, et al. Biomechanical wall properties of human intracranial aneurysms resected following surgical clipping, J Biomech 2011; 44(15):2685-91.
[3]. Hayakawa M1, Katada K, Anno H, Imizu S, et al. CT angiography with electrocardiography gated reconstruction for visualising pulsation of intracranial aneurysms: identification of aneurysmal protuberance presumably associated with wall thinning, AJNR 2005; 26(6): 1366-9.
[4]. Kadasi LM, Dent WC, Malek AM, Cerebral aneurysm wall thickness analysis using intraoperative microscopy: effect of size and gender on thin translucent regions , J Neurointerv Surg. 2013 ;5(3):201-6.

Confidential Comments to the Senior Editor:

Dear Editor,

Thank you very much for the opportunity to review the manuscript titled: "BLINDED"

Overall, the article was original in the sense it used a simple scoring technique developed by the authors to based on a gadolinium intensity scoring system grading degree of enhancement of leading edge in adrenoleukodystrophy and how well scoring prior to treatment with hematopoietic stem cell transplant predicts neurologic outcome following transplant. ALD is rare but the authors had a very robust number of patients which was a strength. Their data showed statistical significance between GIS score prior to transplant and clinical outcome following transplant when compared to CHIT levels and NFS. I thought the abstract and introduction were fairly well structured with a solid purpose and good background information with well defined hypothesis. I was however, a bit confused by certain points in the methods and results section which I would like clarification for as I will ask below (eg.Why no correlation between Loes score and GIS system developed by authors, how were discrepancy between readers resolved). It was also unclear sometimes how they stratified "high risk" patients. Was it based on Loes score, NFS, CHIT levels? This was also unclear in the discussion.

There are some shortcomings but I feel this article is suitable for publication after revision.

Thank you.

Comments to the Author:

Dear authors,

Thank you for your efforts in writing your manuscript titled, "BLINDED".

It was very interesting in the sense that it uses a simple and reproducible scoring system for grading enhancement in ALD and how this score can predict clinical outcome following HSCT. While the actual number of patients is not large, given the rarity of ALD, this number is robust. Also, the correlation between csf CHIT value with GIS score was interesting and implies higher GIS score correlates well with higher CHIT values implying worse clinical outcome. There are some issues/questions that require clarification:

Introduction:
1. you stated pretransplant Loes score does not predict neurologic outcome. What data/literature supports this definitively? According to some literature, Loes does correlate well; Outcomes following allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. Blood 2011;118:1971–78

2.please give citation for following sentence: ...use of HSCT, a procedure that carries significant risk of injury and mortality.

3.You compare the GIS score with clinical outcomes while correlating with csf CHIT. Why didnt you also compare the GIS with the Loes score? I think this comparison would be interesting.

Methods:
1.You state patients were excluded for analysis if they were homozygous null CHIT. Please briefly explain in paper difference between homozygous and heterozygous CHIT.

2.I am a bit confused....you state higher risk ALD patients were included for retrospective analysis. Low risk patients were not included at all? Why not?

3.Any thoughts on how the transplant protocol could affect the results?

4.What time frame (years) was the patient collected date in?

5.For GIS scoring done by the 3 neuroradiologists, how many discrepancies were there and were they resolved by consensus?

6. Did low risk on the Loes score correlate with low risk based on GIS?

7.Please give MR sequence and type of contrast used.

Results:
1.Again, how well does Loes score correlate with GIS score?

2.Was "higher risk cALD" based on Loes score or GIS? You have a number of 25 but your high GIS group has n=34??

3. You state: "As absolute pre-HSCT Loes score within
the higher-risk cALD group has not alone proved prognostic, additional predictive
biomarkers for this challenging patient sub-set are sought". The wording of this statement implies that pre HSCT Loes score is not helpful and other biomarkers would be more useful. I think rewording of this statement is needed as one could potentially use different scores and biomarkers to prospectively ascertain clinical outcome following transplant in patients.

Discussion:
1.You may also want to cite a paper that studied the use of DTI to predict clinical outcome in ALD patients following transplant; Childhood Cerebral X-Linked Adrenoleukodystrophy: Diffusion Tensor Imaging Measurements for Prediction of Clinical Outcome after Hematopoietic Stem Cell Transplantation
Am. J. Neuroradiol. 2013 34: 641-649

Figures:

1.Fig.4 appears to have an error. I assume the "GIS=0/2" on the x-axis should be 2/3.