Author’s response to reviews

Title: Why Does my Patient's Basilar Artery Continue to Grow? A Four-Year Case Study of a Patient with Symptoms of Vertebrobasilar Dolichoectasia

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Author’s response to reviews:

Dear Dr Jorge Manuel Serrador

Thank you for your letter and for the reviewers’ comments concerning our entitled “Why Does my Patient's Basilar Artery Continue to Grow? A Four-Year Case Study of a Patient with Symptoms of Vertebrobasilar Dolichoectasia” (NURL-D-18-00001). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made corresponding correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and response to the reviewers’ comments are as following:

Comments:

Victor Brutto (Reviewer 1)

Background:
- Authors state the prevalence of vertebrobasilar dolichoectasia is rare. I encourage to report the specific prevalence of such vascular anomaly in the general population as well as patients with stroke.

Response: As suggested by the reviewer, we now provide prevalence estimates for the general population in addition to those provides for stroke patients.

- Meta analysis done by Wolter et al (2013) assessed the clinical outcomes of VBD based on 12 articles for a total of 375 patients (no 958 papers as stated in the manuscript, those were the citations reviewed)

Response: We apologize for our error and have corrected the figure to 375 patients.

Case:

- Along 4 years of recurrent hospital admissions, authors mentioned interval enlargement of the basilar artery. I suggest to present the arterial dimensions (diameter and length) across time and different imaging modalities. The degree of arterial dilation (>10mm vs "giant" >25 mm) has been associated with increased risk of complications.

Response: We totally agree with the reviewer’s kind suggestion. We now present BA diameter and length data for the January 2015 and December 2016 TOF-MRA studies. This information is also provided in a new figure (Fig. 5) in the revised manuscript.

- Physical findings reported by authors are unspecific and poorly described (i.e. moderate hemisensory loss -> sensory modalities involved?, face was affected?). Instead of reporting the modified Rankin score, I would suggest to provide a summarized and focused neurological examination specifying old neurological sequel from new deficits across each of the presentations.

Response: We have added detailed neurological findings and focused on changes in old neurological sequel and new deficits across the examination time points.
- Authors stated the mechanism of infarction is artery-to-artery embolism as well as hypoperfusion. Progressive enlargement of the basilar artery may also obliterate the origin the penetrating vessels as seen on one of the paramedian pontine lesion which reach the ventral surface of the pons. This mechanism should be added on the discussion.

Response: We appreciate the reviewer’s good advice and have added discussion of the pathogenic mechanism of infarction in VBD.

- After recurrent ischemic events what was the plan for secondary prevention? Antiplatelets or anticoagulation were offered? Were surgical or endovascular interventions considered? There is no evidence guided approach for secondary prevention and this should be addressed in the discussion.

Response: We now address the present VBD treatment dilemma based on germane papers in the literature (Wolters et al. 2013, Del Brutto et al. 2017).

- Authors conclude there was spontaneous dissection of the basilar artery based on MRI vessel wall imaging however it is not clear if this is a true dissection or vessel wall hematoma?. Vessel wall hematoma is a crucial step on pathological progression of dolichoectasia as stated on the review of Nakatomi H, Segawa H, Kurata A, et al. Clinicopathological study of intracranial fusiform and dolichoectatic aneurysms : insight on the mechanism of growth. Stroke 2000;31(4):896-900.

Response: We were very interested in and too great care to review the important article mentioned. We believe our consideration of the work improved our insights into the pathological progression of dolichoectasia. We pursued serious inquiry with two experienced radiologists once again regarding our MRI vessel wall imaging, and considered that the present images probably measured up to intramural hemorrhage. Therefore, in agreement with Nakatomi’s opinion, we revised some words in the present manuscript and now cite this important literature as a reference in our paper.

- Finally, patient expired for a complicated pneumonia. Was this secondary to recurrent aspiration due to lower cranial nerves deficits?
Response: Indeed, the pneumonia was secondary to recurrent aspiration due to lower cranial nerve deficits associated with posterior circulation recurrent strokes. This information was added.

Discussion:

- Basilar ectasia is defined by a diameter > 4.5mm at the mid-pons level (Smoker et al 1986) not by increase in 2mm. Progressive dilation does not define this arteriopathy.

Response: I apologize for the incorrect statement, which has since been corrected.

- Follow up imaging might identify patients with increase risk of complications but certainly does not improve outcome by itself as stated in the manuscript.

Response: As we contemplated this case repeatedly, we came to regret that we did not pursue a surgical strategy before the development of obstructive hydrocephalus. The patient’s prognosis might have been improved by an earlier surgical intervention (Pico et al. 2015). In particular, the vessel-wall hematoma was a crucial step in the patient’s pathological progression of dolichoectasia. In the future, knowledge of this possible mechanism of progression and of corresponding MRI characteristics will be considered as we make decisions regarding the timing of surgical intervention.

- I agree that factors associated with progression of the arteriopathy are not clear, but is infection and inflammation associated with enlargement (?). There are few reported cases that associate infections (i.e. HIV, VZV, syphilis) as well as inflammatory disorders (SLE, neoplasia) as the etiology of dolichoectasia but it is unclear to me that there is an association with enlargement progression. Author could explain their statement.

Response: We appreciate the reviewer’s insightful opinions. After reviewing the literature(Gutierrez et al. 2016, Pico et al. 2015, Toyoshima et al. 2012), we developed some explanation of the complicated associations among infection, inflammation, and artery enlargement in the revised manuscript.
Vicente Vanaclocha (Reviewer 2):

The article should be re-written to give it a better format. Cases like this are rare and the information available limited, so it is interesting to get more information. Most people only have the chance to treat only a very limited bunch of cases. Next time we would recommend to get a postmorten if at all possible.

Response: We appreciate the reviewer’s kind and constructive suggestions. We have revised the manuscript to include additional information of interest and improve its formatting. If possible, in the future, we will try to obtain postmortem examination reporting to enhance our knowledge of this complicated disease process.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper.

We appreciate for you and the reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Yours Sincerely

Dao Pei Zhang