Peer Review File

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Reviewer A: In the manuscript by Liu et al., the authors perform a retrospective review of 5 cases of persistent fifth aortic arch (PFAA) and report the clinical manifestations and diagnostic imaging of PFAA. Briefly, two cases were diagnosed by computed tomography angiography (CTA) along with echocardiography and other 3 cases were diagnosed by only echocardiography. Two cases showed interruption of the 4th aortic arch with coarctation of PFAA and cardiac surgery was performed for one of these 2 cases. The other 3 cases showed no coarctation of PFAA and cardiac surgery was performed for one of these cases. While PFAA is a rare congenital anomaly of aortic arch development and it is important to evaluate the accuracy of echocardiography and CTA for the diagnosis of PFAA. Overall, the findings are not particularly surprising but are supportive of literature. I have some comment which are detailed below:

Comment 1. While the main conclusion of this manuscript shows that use of both echocardiography and CTA can improve the accurate diagnosis of PFAA leading to suitable treatment strategies, it is widely established that CTA and cardiac magnetic resonance imaging along with echocardiography can be used to evaluate aortic arch anatomy. Yang et al. reported the accuracy of echocardiography for the diagnosis of PFAA with comparison to CTA (PMID: 32118745). This manuscript has less valuable information compared to the paper by Yang et al. If the authors focus on the diagnostic tools for PFAA in the manuscript, the details of the effectiveness of CTA and difficulty of echocardiography for the diagnosis of PFAA in case 1 and 2 should be included. The authors may want to compare the results of echocardiography, CTA and surgical findings.

Reply 1. Thanks a lot for your valuable comments. We have also read Yang's paper already, which benefit us a lot. While we were modifying our manuscript for the second time last year, I found out that paper was published at the same time. In addition, in our manuscript, our intention was to improve the understanding of the 5th aortic arch after we regretfully missed to identify the first two patients. We thought the reason was because we mainly focused on the stenosis of the aortic isthmus, and also limited understanding about this disease. In reality, the echocardiography is a very useful tool to identify this malformation, so when we paid much attention to this point and enhanced our thought, we managed to identify another 3 cases in a not long time. We realized that with the support of whole scanning suprasternal view we are able to improve the incidence rate. Secondly, we

learned a lot during the journey of documenting this paper, we reviewed the history, classification, and embryonic development of the aortic arch. Plus, Gupta pointed out another different opinion about the 5th aortic arch through an animal method. Thus, the naming might be improperly collateral channels not PFAA, but no matter how it was called, it should be examined successfully and received the proper treatments.
Changes in the text: Discussion line 149-158

Comment 2. What is the indication of cardiac surgery for Case 2 at the age of 8 months old? Do the authors think that the symptoms of cough and fever in Case 2 were associated with heart failure? Case 2 did not have severe coarctation and cardiac dysfunction. Also, atrial septal defect (ASD) usually does not cause heart failure for infants. Therefore, the detailed clinical manifestations, concrete characteristics of the cardiac phenotype and the indication of surgical intervention should be mentioned.
Reply 2. we agreed the reviewer's comments and modified our text as advised in Results. The forward flow is faster in the descending aorta measured by echocardiography, and the inside diameter is thinner by CTA. Moreover, the blood pressure between the upper and lower limbs of this patient differed and there exists a bigger atrial septal defect with an enlarged right heart. So we thought this patient is better to have surgery.
Changes in the text: Results line 102-113.

Comment 3. Why was echocardiography performed for Case 3-5? Case 3-5 were asymptomatic and visited for a routine health examination. The necessity of performing echocardiography for these cases should be included.
Reply 3. Three patients (Cases1-3) had obviously heart murmur, and two of them combined with coughing, fever, breathing difficulty and differences in blood pressure between the upper and lower extremities. The other two patients (Cases 4,5) had no initial symptoms, one was for a routine health examination, another one was from screening for congenital heart disease. You know, the medical system in China had some differences with other countries. So, some parents in a larger city want to do a further health examination for their baby before buying some insurance, and some babies in a small remoted village maybe have a chance to screen the congenital heart disease for free.
Changes in the text: We accepted the reviewer's comments and modified our text as advised in Results, Line 77-91.

Comment 4. Accurate and detailed diagnosis of PFAA by echocardiography and CTA is clinically important to decide appropriate surgical intervention. Anatomical reconstruction using native tissue including PFAA is required for cases during infancy to allow for growth of vessels in contrast to adult cases. Information about the surgical strategy, evaluation of PFAA at the time of surgery and follow-up (re-stenosis of PFAA or aneurysm) should be included if available.
Reply 4. We accepted the reviewer's comments and modified our text as advised in discussion. Echocardiography can provide the earliest discovery of the 5th aortic arch and other lesions. When the patient had a stenotic PFAA, further CTA examination was suggested to get the detailed information about the aortic arch for preparing surgery. In case the patient demonstrated a normal PFAA without any other severe congenital heart disease, then the patient only need a follow-up assessment but not surgery or CTA examination
Changes in the text: Line 163-176.

Reviewer B: The authors present a series of five infants with type I (Freedom's classification) persistent fifth aortic arch (PFAA). They report on associated cardiac anomalies, different hemodynamic consequences of PFAA and therapeutic approaches (observation vs. surgical therapy).

Major comment
Comment 1. Limited data are available PFAA patients. Most publications describe case reports, few articles series of a small number of cases. Accuracy of various diagnostic approaches (Echo vs. CT) has been previously described. Although a series of five infants of PFAA, especially a homogenous cohort of five infants with type I PFAA, is of value, the information reported by the authors are very limited. More detailed descriptions of the clinical course of the patients would be of value, including details on surgical procedures in the two infants who received cardiac surgery, postoperative course and follow-up results (postoperative development of blood pressure gradient, LVEF,..). Details on follow up examinations for the infants who did not receive surgery would also be of interest. The variability in clinical expression and course / development among children with type I PFAA should be more clearly elaborated.
Reply 1. We accected the reviewer's coments and modified our text as advised in Discussion
Changes in the text: Discussion line 115-176

Minor comments

Comment 2. The authors state twice in the Methods section that informed consent was waived. Once is enough.
Reply 2. we have modified our text as advised in Methods
Changes in the text: Methods line 74-75.

Comment 3. Figure 2A does not provide any additional information and could be deleted. Figure 2F requires a better description of what is seen in the Figure. I recommend to keep only Fig 2B-2E for this case (four instead of six pictures).
Reply 3. We have modified our figures as advised.

Comment 4. Table 3: I recommend to replace "complications" by "associated anomalies".
Reply 4. We have modified our table as advised

Comment 5. Please further specify why / how infant #4 and #5 were diagnosed with PFAA, as they had no symptoms and no heart murmur.
Reply 5. We accepted the reviewer's comments and modified our text as advised in Results. Cases 4 and case 5 had no initial symptoms, one was for a routine health examination, another one was from screening for congenital heart disease.
Changes in the text: Line 81-83

Comment 6. Please state that this study is of descriptive nature, in abstract and manuscript text
Reply 6. we have modified our text as advised in Discussion
Changes in the text: Abstract and Discussion

Comment 7. The authors should get advice by an English medical language expert for further language improvements.
Reply 7. We have modified our text as advised

Reviewer C: The authors present a single-center experience of five cases of persistent fifth aortic arch (PFAA), aged between 3 and 48 months. PFAA is rare and I applaud the authors for their contribution to the literature. I have some comments to improve their manuscript:

<u>Major Comments</u>
Comment 1. Line 52, "extremely rare": can the authors shed some light on the incidence of PFAA as well as etiological considerations (e.g., genetics, geographical

differences, etc.)?

Reply 1. People rarely know PFAA, so the clinical incidence is unclear. Gerlis supported the existence of a pair of fifth arch arteries in human embryos at a prevalence of 0.3% from post-mortem specimen examinations in the Discussion.

Changes in the text: Discussion line 115-116

Comment 2. Line 79 and 91: the authors mention “Freedman classification” but describe the Freedom classification in Table 1 (as well as the accompanying Freedom et al. reference). This should be corrected. Additionally, the authors should briefly describe here the Freedom classification for readers and not wait until the discussion (where the classification is currently described).

Reply 2. Thank you for your suggestion, and we add the mainly type of classification in the results.

Changes in the text:results line 87-90

Comment 3. Lines 121 and 183: the authors mention that PFAA remains “debated” and “controversial” but do not delve into what the controversy is. Can the authors elaborate the other (contrarian) view to this to illustrate the controversy? Do the authors refer to this with the Gupta’s classification? If so, this should be clarified and the validity of both classifications should be discussed.

Reply 3. we discussed the controversy and provided our understanding about the definition of the PFAA. Van Praagh defined the first human PFAA characterized by a double-lumen aortic arch. Then the PFAA was classified into 4 types based on anatomical and physiological characteristics by Freedom. Gupta raised a new concept about the PFAA, which was an extra-pericardial vessel arising from the ascending aorta proximal to the brachiocephalic artery’s origin, and terminating either on the dorsal aorta or on the pulmonary arteries via the patent ductus arteriosus. Based on Gupta’s definition, the existing of PFAA should be combined with a large PDA, but in our study, only one had a narrow ductus arteriosus. That was the different point of the definition of PFAA among Freedom and Gupta.

Changes in the text: discussion line 120-136,

Comment 4. The authors state the importance of timely diagnosis to plan treatment and surgical care. Can the authors further describe the management (both surgical and non-surgical) of PFAA?

Reply 4. Thanks for this valuable suggestion, as advised, we added some further explanation.

Changes in the text: Line 162 to 170

Minor Comments

Comment 1. Line 68: the sentence is missing a period at the end of the sentence.

Reply 1. we have modified our text as advised.

Comment 2. Lines 94 and 96: “visited” instead of “were visited”.

Reply 2. we have modified our text as advised.