Author’s response to reviews

Title: Progressive stenosis and radiological findings of vasculitis over the entire internal carotid artery in moyamoya vasculopathy associated with Graves’ disease: A case report and review of the literature

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Author’s response to reviews:

We would like to thank the reviewers and the editor for the valuable and constructive comments on our initial manuscript. We appreciate this opportunity to revise our manuscript based on the reviewers’ recommendations. Changes to the text are highlighted in yellow. Our point-by-point responses to the reviewer comments follow.

First, we added information and a figure in Figure 4D about the recent cerebral angiograms, which showed improved blood flow of the left ACA, MCA and ICA, as well as mild improvement of stenosis of the terminal portion of the left ICA. Its comments are located in Pages 9, lines 141-143 in manuscript and in Page 27, lines 432-433.

Second, we added the result of genetic analysis of RNF213. It was wild type, suggesting that this case is not Moyamoya disease associated with c.14576 G>A variant (rs112735431) in the RNF 213 gene. The comments are located in Pages 9, lines 143-146 in manuscript and in Page 13, lines 203-204.
Dr Ioanna Koutroulou (Reviewer 1) comments

This case report seems to be very interesting, since it describes a rare condition of Graves' disease combined with moyamoya vasculopathy.

We appreciate your favorable comments.

Major points:

1. The phrase "increased signal intensity", which is used frequently in the manuscript, will probably lead to false interpretations, so it should be replaced with another more comprehensible expression like "improved flow".

We are thankful for this suggestion. We replaced them with "improved flow" as the reviewer recommended. They are located in Page 4, lines 62, Page 9, lines 138, Page 12, lines 187-188, in Page 13, lines 201, Page 15, lines 239, and lines 241, in Page 17, lines 263, and Page 26, lines 402 and lines 409. We replaced it with "increased blood flow" in Page 28, line 433.

2. In the "Case Presentation" section, the term "watershed subcortical" should be avoided, because these infarcts are also cortical and not clearly watershed. A more general term should be used.

We appreciate this suggestion. We changed the term "watershed subcortical" to “cortical and subcortical infarcts in the left MCA territory” as the reviewer 2 recommended, in Page 6, lines 95-6.

3. In the "Case Presentation" section, the stroke is referred, as of unknown etiology, but there are no references, regarding the diagnostic procedure, which concluded to this diagnose.

Thank you for this beneficial suggestion. We added and modified information regarding unknown etiology of stroke to clarify the procedures by which we concluded this diagnosis in Page 7, lines 111- Page 8, lines 115. We added the sentence there, “MRA excludes over 50% stenosis of intracranial and extracranial cerebral arteries and we could not find any major risks of cardioembolic source of embolism, through electrocardiography, echocardiography, and cardiac rhythm monitoring for over 24 hours, so heparin, then warfarin (4 mg/day) were administrated as treatments for stroke as unknown etiology.”

4. In the "Case Presentation" section, a 3D computed tomographic angiography is referred, but there is no corresponding image. Display an image or delete this examination from the manuscript.

We are sorry for this confusing expression. We have deleted this information about a 3D computed tomographic angiography, which was located in Page 7, line 98.
5. In the "Case Presentation" section, it is referred "clopidogrel and aspirin from loading doses". This phrase makes no sense, so please rephrase.

We are thankful for this suggestion. We have added information about this phrase in Page 8, lines 121-122. We changed the phrase to “clopidogrel (300 mg on day 1, and 75 mg/day from day 2), and aspirin (300 mg on day 1, and 100 mg/day from day 2)".

6. In the "Case Presentation" section, it is referred "but the vessel wall remained enhanced on CE 3D-T1WI" and there is no corresponding image. Please specify.

We are thankful for this suggestion. We specified this sentence as follow; “the vessel wall of the left ICA from the proximal to the distal portion still remained enhanced on CE 3D-T1WI in the same way as the previous one.” in Page 9 lines 139-141. It is almost the same image as the previous one (Figure 5). If we add the image as a new figure, it may be redundant. So, we did not put corresponding images as a figure. However, if the reviewer strongly thinks that there should be the corresponding images, we can prepare the images.

7. In the "Thyrotoxicity and cerebrovascular disease in the first episodes" section, there should be a statistical analysis.

Thank you for this beneficial suggestion. We consulted with a statistician in my hospital about statistical analysis. It seems difficult to conduct statistical analysis, if we want to know whether there is an association between ischemic stroke and thyrotoxicity or not. This is because we need data about the patients with moyamoya vessels who do not develop ischemic stroke in thyrotoxicity, in order to conduct chi-square test. Moreover, we reviewed reports with follow-up for over 4 months, so it could have bias of data collection.

8. In the "Treatment" section, a patient with thyroidectomy is mentioned twice and there is no report of the patients with no treatment. It would be also very interesting to make a comment, about the prevalence of women among these patients.

We appreciate this suggestion. We replaced the original sentence with “Two patients (10%) were treated with only thyroidectomy, 2 patients (10%) with PSL and radioactive iodine therapy (RIT), and 1 patient (5%) with PSL and thyroidectomy.” in Page 11, lines 176-178, and added sentence "There was no report of patients with no treatment” in Page 12, lines 180, and “the majority of the patients were female.” in Page 11, lines 166.

9. In line 191, the meaning of the phrase "common underlying immune mechanisms" is not clear. Please specify or delete this phrase.

We are thankful for this suggestion. We also consider that the sentence which includes "common underlying immune mechanisms" is confusing. So, we removed the sentence itself, which was located in Page 13 line 221.
10. In lines 222-225, the phrase "Increased signal…disease" is not understandable. Please rephrase.

We appreciate this suggestion. We replaced the sentence with “Improved flow of the left ICA and MCA on MRA was observed after administration of PSL and MTX, and in the euthyroid state. On the other hand, such a favorable result, the improved flow, can not occur in Moyamoya disease, in which MCA disappear as the next stage in the Suzuki stage [29].” In Page 15, lines 239- Page 16, lines 2243.

Figure:

1. In Figure 1, the upper panel should preferably be a separate figure from the MRA images. The reference values should also be mentioned in the vertical columns.

We are thankful for this suggestion. We separate the figure of MRA images from Figure 1 as the reviewer recommended. We leave the reference values in the vertical columns as it was. We changed the figures as follows:

Figure 1 upper panel in the previous manuscript: Figure 3 in the current manuscript
Figure 1 brain MRA in the previous manuscript: Figure 1 in the current manuscript
Figure 1 cervical MRA in the previous manuscript: Figure 2 in the current manuscript
The previous Figure2 in the previous manuscript: Figure 4 in the current manuscript
The previous Figure3 in the previous manuscript: Figure 5 in the current manuscript

2. In Figure 1, the MRA panels should be aligned.

We appreciate this suggestion. We aligned the MRA panels.

3. In Figure 1, it is better "an euthyroid"

We are thankful for this suggestion. We changed the expression to "an euthyroid" in Figure 3 in the current manuscript.

4. In Figure 1, (A) there should be only a comment on the image.

We are thankful for this suggestion. We removed the comment “Cerebral infarction can occur during thyrotoxicity without obvious stenosis of ICAs on MRA.”. We add the sentence “MRA did not show obvious stenosis of ICAs” in Page 25, lines 427.

5. In Figure 1, (F,G) these panels should be commented on separately in the legend.
We appreciate this suggestion. We commented on Figure 1 (F), (G) (Figure 2 (A), (B) in the current manuscript) separately in the legend as follows in Page 26, lines 404-407: Figure 2 (A): Cervical MRA showed very mild or no obvious stenosis in the first episode. Figure 2 (B): Cervical MRA showed progressed stenosis of the left ICA at proximal portion and CBN was observed in the second episode for the first time.

6. In Figure 1, (H) the phrase "increased signal… in Moyamoya disease" should be deleted.

We are thankful for this suggestion. We also consider it confusing, so we deleted the phrase, which was located in Page 26, lines 410.

7. In Figure 2, (A) it is better "of the terminal portion of the left ICA"

We appreciate this suggestion. We replaced the expression with "of the terminal portion of the left ICA" in Page 27, line 418.

8. In Figure 2, (C) it is better "12 months after the second" and "vessels might have been developed"

We are thankful for this suggestion. We changed the expression to "12 months after the second" and "vessels might have been developed" in Figure 4 in the current manuscript, Page 27, line 422 and line 423.

9. In Figure 3, there should be a reorganization of the panels (without and with CE side by side) and a revised legend because the meaning is obscure.

Thank you for this beneficial suggestion. We reorganized the panels without and with CE side by side. Moreover, we revised the legend in order to make the meaning of each figure clear as follows in Figure 5 in the current manuscript in Page 28, lines 437-443; Six months after recurrence, 3D-T1WI (A) and CE 3D-T1WI (B) of the ICAs were performed (Upper 2 figures: axial images of the distal portion; Lower 2 figures: coronal images of the proximal portion in Figure A, B). (A): 3D-T1WI showed smooth, concentric wall thickening over the entire left ICA (arrow). (B): CE 3D-T1WI showed diffuse contrast enhancement on vessel walls (dashed arrow in Figure B) over the entire left ICA, suggesting vasculitis radiologically [23, 24].

10. In Supplementary figure 2- title, please rephrase "in the first and the second episode"

We are thankful for this suggestion. We rephrased the expression to "in the first and the second episode" in Page 28, lines 448-Page 29, lines 449.

11. In Supplementary figure 2, (A) there should be an arrow indicating the mild stenosis. The meaning of this sentence is not right, please clarify. Specify also, what these images depict (A-B)

We appreciate this constructive suggestion and apologize for our confusing expressions. We deleted the phrase "Very mild stenosis of the left ICA" because it was not clear, and rephrased
this sentence as follows in Page 29, lines 450-451; The vessel walls might be thicker over the left entire ICA compared to the right, but it was not clear.

12. In Supplementary figure 2, (B) a dissection is presumed due to an aortic dissection, but there is no evidence of this in the manuscript. Please clarify.

We are thankful for this constructive suggestion and apologize for our confusing expressions. We also considered an aortic dissection due to vasculitis was just one of the possibilities and we do not have further evidence for dissection. We deleted the original sentence. Instead, we added the following sentence in the manuscript in Page 8 lines 124-125; “High intensity lesion on T1W1 in the distal portion of the left ICA was observed.” and in Page 13-14, lines 213-217, legend in Page 28, line 453-457; “In the second episode, high intensity lesion on T1W1 (arrow) in the distal portion of the left ICA was observed (Supplementary Fig 2B). Dissection might be considered as the etiology of this lesion, because dissection shows eccentric wall thickening with T1 bright wall components representing intramural hematoma [24]. Moreover, vasculitis can cause aortic dissection, for example, Takayasu arteritis.”.

13. In Supplementary figure 3, the legend refers to "wall thickening with diffuse gadolinium.....", but the actual pictures are from MRA. Please make another relevant comment.

Thank you for this beneficial suggestion. We add the comment about MRA as the reviewer recommended; “We hypothesize that vessel wall thickness by vasculitis contributes to the formation of the CBN and stenosis of the entire left ICA on MRA. This is because they became more evident in the second episode than in the first episode in our case.” in Page 29, lines 461-463.

Minor points:

1. In the "Abstract" section, please rephrase as follows "of progression of the lesions.." and "progression, thyrotoxicity and treatment"

We are thankful for this suggestion. We rephrased the expressions to “the processes of progression of the lesions in the proximal ICA” in Page 3 lines 46 and "progression, thyrotoxicity and treatment", in Page 4, lines 50-51.

2. In the "Background" section, please rephrase as follows "despite the control of GD" and "progression and the lesions"

We appreciate this suggestion. We rephrased the expression to "despite the control of GD” in Page 5, lines 80-81 and "progression and the lesions” in Page 6, lines 84.
3. In the "Case presentation" section, please rephrase as follows "seemed thicker in the left ICA than in the right" and "[anti-thyroid peroxidase…(TRAb, 8.3 IU/ml)]". Also in line 112 "show new infarction"

We are thankful for this suggestion. We replaced the expressions with "seemed thicker in the left ICA than in the right" in Page 7, lines 98-99, "[anti-thyroid peroxidase…(TRAb, 8.3 IU/ml)]" in Page 7, lines 102-103, as well as with "show new infarction" in Page 8, lines 118.

4. In the "Discussion- Patients" section, please rephrase as follows "the 20 patients included, 19 females…"

We appreciate this suggestion. We rephrased the expression to "the 20 patients included, 19 females" in Page 11, lines 165.

5. In the "Discussion- Treatment" section, please rephrase as follows "and 10 of these patients"

We are thankful for this suggestion. We replaced the expression to "and 10 of these patients” in Page 11, lines 175-176

6. In line 205 please rephrase as follows "and may be caused."

We appreciate this suggestion. We rephrased the expression to "and may be caused." in Page 14, lines 222.

7. In line 228, please rephrase as follows "might have worked"

Thank you for this suggestion. We rephrased the expression to "might have worked" in Page 16, lines 246.

8. In line 234, please rephrase as follows "be reasonable choice"

We appreciate this suggestion. We rephrased the expression to "be reasonable choice" in Page 16, lines 252-253.

9. In the "Conclusion" section, please rephrase as follows "we treated the patient as having vasculitis of medium-to-large vessels with IVMP"

Thank you for this suggestion. We rephrased the expression to "we treated the patient as having vasculitis of medium-to-large vessels with IVMP” in Page 17, lines 261-262.

Finally, we are very thankful for the helpful and constructive comments.

Klearchos Psychoyios (Reviewer 2) comments
It is a well written and interesting case report as well as review of the literature regarding a very rare complication of Graves Disease. Consider adding some points to clarify the case presentation.

We appreciate these favorable and constructive comments.

1. Possible systematic manifestations of Graves Disease during the initial diagnosis.

   We appreciate this suggestion. Actually, the patient had few systematic symptoms of Graves Disease, but we also think that we should mention about that. We add the sentence, “Although she felt palpitation and sweating at times, exophthalmic and enlarged thyroid lobes were not observed” in Page 6, lines 93-95.

2. Provide us with information regarding cardiac evaluation during the initial event.

   Thank you for this beneficial suggestion. We added and modified information regarding cardiac evaluation during the initial event by which we concluded this diagnosis in Page 7-8, lines 111-115. We added the sentence there, “MRA excludes over 50% stenosis of intracranial and extracranial cerebral arteries and we could not find any major risks of cardioembolic source of embolism, through electrocardiography, echocardiography, and cardiac rhythm monitoring for over 24 hours, so heparin, then warfarin (4 mg/day) were administrated as treatments for stroke as unknown etiology.”.

3. On line 93 (p.6) I believe that it is more accurate to write «cortical and subcortical infarcts in the left middle cerebral artery territory.

   We appreciate this suggestion. We changed the term "watershed subcortical" to “cortical and subcortical infarcts in the left MCA territory” as the reviewer 1 also recommended, in Page 6, lines 95-96.

4. On line 430 (p.28) I believe «aortic dissection due to vasculitis» is not correct. In order to imply a possible dissection of the terminal portion of the left ICA, it should be better to provide Vessel Wall MRI images with Fat Sat Black Blood T1 before and after gadolinium enhancement.

   We are thankful for this constructive suggestion and apologize for our confusing expressions. We also considered an aortic dissection due to vasculitis was one of the possibilities and we do not have further evidences for dissection. We deleted the original sentence. Instead, we added the following sentence in the manuscript and legend; “In the second episode, high intensity lesion on T1W1 in the distal portion of the left ICA (arrow) was observed. Dissection might be considered as the etiology of this lesion, because dissection shows eccentric wall thickening with T1 bright wall components representing intramural hematoma [24]. Moreover, vasculitis can cause aortic dissection, for example, Takayasu arteritis.” They are located in Page 14, lines 213- 217, and Page 28, lines 453-457.

Finally, we appreciate the helpful and constructive comments.