Author’s response to reviews

Title: Hereditary Hemorrhagic Telangiectasia associated with Cortical Development Malformation due to a start loss mutation in ENG

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Author’s response to reviews:

Reviewer reports

Reviewer 1
Overall: Abstract, Background and Discussion/Conclusion sections could still benefit from rewrite to clarify and focus on main points authors wish to make in reporting these cases. Is it that HHT should be considered in patients who present with acute ischemic events, because of its association with pulmonary AVMs/shunts? That type II cortical dysplasia is being reported in an HHT patient for the first time? Two first degree relatives with both HHT and cerebral cortical dysplasia? All of the above?
We thank Reviewer 1 for his/her comments aiming to improve our manuscript. Main novel finding in our report is the detection of cortical development malformations in two first degree relatives with HHT, one of them displaying previously unreported type II cortical dysplasia. In our opinion, it is also important to consider HHT in young patients presenting with acute cerebral ischemic events of unknown origin.

Comment 1
Abstract:
Suggest revising Conclusion. It does not reflect discussions/conclusions at the end of the paper that novel finding is type II cortical dysplasia; or what is emphasized in the actual case reports.

ANSWER
We revised the conclusion statement in the abstract.

Comment 2
Line 11 - substitute "their" with "cAVMs". As written implies that all AVMs cause intracranial hemorrhage.

ANSWER
We changed as requested.

Comment 3
Line 17- Why only giving pAVM rate, not cAVM rate here?

ANSWER
We included the rate of pulmonary and cerebral AVMs in the revised version of the manuscript.

Comment 4
Line 24 - Remove "usually". (The Curacao Criteria specify that the tells must occur at these locations to "count" as diagnostic criteria)

ANSWER
We changed as requested.

Comment 5
Line 29 - Rewrite this sentence. As written suggests that diagnosis can be made based on 2 criteria, which is not the case. For purposes of this paper, probably sufficient to just say that Clinical Diagnosis is made when patient meets 3 diagnostic criteria.

ANSWER
We modified the sentence, as requested.

Comment 6
Line 33 - Remove "might"

ANSWER
We modified the paragraph.

Comment 7
Line 40- suggest replacing "has been postulated" with "is accepted"

ANSWER
We changed as requested.

Comment 8
Line 53 - suggest omitting last sentence of this paragraph. This is the case for all those affected with HHT. Not relevant to state here.

ANSWER
We modified as requested.

Comment 9
Line 58- Background requires at least a few sentence summary of the Klostranec paper - one of two key previously published papers that "inform" what follows.

ANSWER
As suggested, we moved part of the Discussion in the Introduction section, setting the stage for the Case Presentation.

Comment 10
Case report:
Line 2 - substitute "which" with "whom"

ANSWER
We modified as requested.

Comment 11
Line 18 - Was subject know to have polymicrogyria prior to this E.D. visit? The timeline and details of his case report are still confusing.

ANSWER
Before his admission to the Emergency Department, the index patient had displayed focal epilepsy secondary to polymicrogyria.

Comment 12
Line 44/45 - Suggest omit this sentence. It's arguable that heparin not indicated in this situation when R>L shunt secondary to multiple pAVMs was the assumed cause of the TIA.

ANSWER
We understand the criticism raised by Reviewer 1. However, we think that this sentence should be maintained in the revised version of the manuscript considering that secondary prevention treatment of ischemic stroke caused by paradoxical embolism is still debated and anticoagulation may represent an option in this case. Here we hypothesized that our patient had an ischemic stroke due to paradoxical embolism that occurs when thrombotic emboli of venous origin occlude arteries after bypassing the filtering system of the pulmonary capillaries. Considering this possible pathogenesis, we considered anticoagulation as the most appropriate treatment.

Comment 13
Line 49 - This report case begs more details of # of PAVMs seen i.e. what was range of feeding artery size, what was size of "biggest" one fixed, and of those not treated. Were those treated considered too small to treat? If not, why not treated? This is particularly important given current conclusion.

ANSWER
We thank the reviewer for this comment which gives us the opportunity to provide additional details about pulmonary AVMs found in our patient. These details are now included in the Case Description. The radiologist confirms that all pulmonary AVMs, regardless their dimension, were treated.

Comment 14
Line 60 - Be consistent with abbreviations, or lack there of. (cA VM and pulmonary A VM are in this sentence)

ANSWER
Taking into consideration the comments from Reviewer 1 and 3, we use “Cerebral AVMs”, “Pulmonary AVMs” (and so on…) throughout the manuscript.

Comment 15
Page 4/Line 4 Either "Coding regions" or "Exons" would be correct terminology

ANSWER
We changed as requested.

Comment 16
Line 40 - suggest this sentence read "Reported clinical findings included epistaxis, tel, GI bleeding, hepatic and pulmonary AVMs. AND suggest omitting last sentence in this paragraph. The lack of reported of cAVM (reported about 10% of all individuals with HHT even when screened asymptotically) in 6 case is not noteworthy. The inclusion of the sentence here suggests it is.

ANSWER
We modified as requested.

Comment 17
Line 47 suggest "present with", or preferably "Cerebral AVMs are detected in about 10% of HHT patients". (The latter doesn't suggest that 10% present symptomatically- which is significantly less than 10%)

ANSWER
We modified the sentence as suggested.

Comment 18
Line 58 Remove "seem". This is very well established, from many reports.

ANSWER
We modified as requested.

Comment 19
Page 6/Line 1-30 - Such moving most this summary of Klostranec paper to Background. With key points from it specifically relevant to discussion of your own case should be mentioned in this Discussion/Summary section.

ANSWER
We modified the Discussion as requested.

Reviewer 3
As mentioned in the first review of the manuscript it presents two siblings with Hereditary Hemorrhagic Telangiectasia (HHT) and CNS manifestations. This risk of severe manifestation of HHT is important to be aware of and in this sense this case report is an interesting educational case on HHT-related acute cerebral ischemic events - especially in young patients with frequent epistaxis. In addition it sheds some light on the HHT related cerebral malformations in relation to CAVMs. The added new information is, however, somewhat limited.
The manuscript has clearly been improved by the revision. The authors have changed the manuscript according to all the reviewers' comments.

ANSWER
We thank the reviewer for the positive comments.

Comment 1
Abstract, Case presentation, line 24: 'The heterozogous…' is suggested this is changed to 'A heterozygous ENG variant, c.3G>A (p.Met11le), was detected in the patient. It was also found in the mother of the patient and in his younger brother who displayed cortical dysplasia type 2.'

ANSWER
We modified the sentence as suggested.

Comment 2
Abstract, Conclusion, line 29: A 'may' or a similar caution should be included in the sentence 'Our findings…' such as 'Our finding may expand …'
ANSWER
We changed as requested.

Comment 3
Page 3, Background, first paragraph: Concerning abbreviation and AVMs. As arteriovenous malformations are abbreviated AVMs already in the abstract I suggest that pulmonal, cerebral etc. are written out throughout the manuscript. This is almost the case with few exceptions. This means that the last sentence in the 1st paragraph should be 'Pulmonal AVMs …'

ANSWER
Taking into consideration the comments from Reviewer 1 and 3, we use “Cerebral AVMs”, “Pulmonary AVMs” (and so on…) throughout the manuscript.

Comment 4
Page 3, Background, 3rd paragraph, line 33: Suggest that you change the first line to 'In most HHT patient germline mutations in ENG (HHT1: OMIM 187300), encoding the TGF-β transmembrane receptor endoglin or ACVRL1 (HHT2: OMIM 600376) which codes for the activin receptor-like kinase-1, is found [4]. In addition a phenotype of HHT and Juvenile Polyposis syndrome (JP-HHT) combined is caused by mutations in SMAD4'.

ANSWER
We modified the sentence, as suggested.

Comment 5
Page 3, Background, 4th paragraph, line 53: ‘…cDM display first HHT…' suggested changed to '…cDM display their first HHT…'

ANSWER
Taking into consideration the comment of Reviewer 1 (Comment 8), we removed this sentence.

Comment 6
Page 3, Background, 5th paragraph, line 58: '..cAVMS…' suggest changed to'…cerebral AVMs..' according to previous comment.

ANSWER
We modified as requested.

Comment 7
Case presentation, 2nd paragraph, line 22: &apos;…EKG was ..&apos; changed to &apos;…ECG showed …&apos;

ANSWER
We changed as requested.

Comment 8
Case presentation, 2nd paragraph, line 27: ‘…cerebral arteriovenous malformations (cAVMS)’ changed to ‘…cerebral AVMs’.

In addition I suggest that the information is compressed to fewer paragraphs as follows: 'Brain MRI (Fig. 1A, 1B) confirmed left multifocal polymicrogyria and disclosed a right frontal acute stroke and multiple infratentorial and supratentorial AVMs. Spinal AVMs were absent but spinal MRI disclosed a focal cavity of the (cervical) ependymal canal. Transcranial ultrasound Doppler (UD) disclosed a right to left shunt with shower pattern. Carotid UD, cardiac echocardiography and blood tests including thrombophilia screening were normal. The transthoracic contrast-enhanced echocardiography revealed, however, an extra cardiac shunt. Chest CT was performed with evidence of multiple pulmonary AVMs as the obvious source of paradoxical embolism (Fig. 1C). Given the risk of a recurrent event, the patient was started on a full dose of low-molecular-weight heparin and underwent successfully endovascular embolization of the biggest AVMs. Anticoagulation was replaced by aspirin 100 mg daily six months later.'

ANSWER
We thank Reviewer 3 for his/her help to summarize key points in the presentation of our case. We modified Case Presentation accordingly.

Comment 9
Discussion, 1st paragraph, line 28: 'According NetStart [10] the mutation might cause the…' should be changed to 'According to NetStart [10] the mutation might cause a……'.

ANSWER
We changed as requested.

Comment 10
Discussion, 3rd paragraph, line 47: ‘…cAVMs..’ should be changed to ‘…cerebral AVMs…’ (see above).
In addition reference 8 could also be mentioned (prevalence of PAVM was 52.3% in patients with an ENG mutation and 12.9% in the ACVRL1 mutation carriers).

ANSWER
We changed as suggested.

Comment 11
Discussion, 5th paragraph, page 6, line 11: The sentence 'Our…'could be changed to 'The findings in our index patient add support for an association of polymicrogyria to variants in ENG [7]'.

ANSWER
We modified the sentence as suggested.

Comment 12
Discussion, 6th paragraph, page 6, line 40: ‘…in HHT.' suggest changed to '…in a HHT patient'.

ANSWER
We changed as suggested.

Comment 13
Discussion, 6th paragraph, page 6, line 42: '…unrelated with ENG mutation of HHT.' Suggest changed to '…unrelated to ENG mutation and HHT.'

ANSWER
We changed as suggested.

Comment 14
Discussion, 7th paragraph, page 6, line 47: 'Overall, our findings expand' should instead be 'Overall our findings may expand…'
Second sentence 'Although…' Is suggest this is changed to 'Although HHT is relatively rare and literature data on risk of ischemic events due to pulmonary AVMs in HHT patients is still somewhat limited, we…' .

ANSWER
We modified the sentence as suggested.

Comment 15
Abbreviations: CAVMS and PAVM can be deleted from the list. Maybe MRI and ECG should be added or written out in the manuscript.

ANSWER
We changed as requested

Reviewer 4
This reviewer congratulates the authors since they have reformatted and changed the manuscript according to all the reviewers' suggestions. They have worked out the case report and the result is excellent. The manuscript may be published as it is now.

ANSWER
We thank the reviewer for the positive comments.