Reviewer’s report

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

Version: 2 Date: 28 Jul 2020

Reviewer's report:

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. I only have some minor comments.

Minor comments:
Abstract, Case presentation, line 24: 'The heterozogous…' is suggested this is changed to 'A heterozygous ENG variant, c.3G>A (p.Met1lle), 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.'

Abstract, Conclusion, line 29: A 'may' or a similar caution should be included in the sentence 'Our findings…' such as 'Our finding may expand …'

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 …'

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'.

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

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

Case presentation, 2nd paragraph, line 22: '…EKG was ..' changed to '…ECG showed …'
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.'

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……'.

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).

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].'

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

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

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…'.

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

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Yes

Are the methods sufficiently described to allow the study to be repeated?

Yes

Is the use of statistics and treatment of uncertainties appropriate?

Yes

Is the presentation of the work clear?

Yes

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Yes