Reviewer's report

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

Version: 1 Date: 05 Jun 2020

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This is a well written presentation of Hereditary Hemorrhagic Telangiectasia (HHT) in two siblings with CNS manifestations of the disease. This risk of severe manifestation of HHT is important to be aware of and in this sense the 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 mutation in ENG is a known HHT related variant and the CNS complication is likewise well known. It is, however, relative rare with cortical development malformations, though prevalence is probably not completely known since most HHT patients only have MRI of cerebrum performed if they have symptoms. The effect of the ENG variant is well studied and nicely presented in the figure.

Minor comments:

Abstract - case presentation:
1st line: 'Here we describe the case of ..' can be changed to 'Here we describe a'
24th line: The sentence 'We did detect the novel heterozygous ENG...' can be changed to 'A heterozygous ENG variant, c.3G>A (p.Met1Ile) was detected in the patient.'

Background:
2nd paragraph, line 29: 'six loci have been so far..' can be changed to "six loci have so far been..'
3rd paragraph, line 42: 'in' instead of 'across'?
3rd paragraph, line 43: 'confirmed' instead of 'supported'.
3rd paragraph, line 44: '...by the identification of the ENG..' should be changed to "..by identification of a previously reported ENG c.3G>A substitution. In Human Gene Mutation Database (HGMD®) it is reported as disease causing (Alaa El Din (2015) PLoS One, PMID: 26176610, PM Tørring (2014) Clin Genet, PMID: 24001356, in supplementary files).

Case presentation:
2nd paragraph, line 60: '..polymicrogyria and recurrent..' can be changed to '...polymicrogyria and had recurrent.'
6th paragraph, page 4,line 29: 'A clinical diagnosis..' suggest rephrased to 'The mother of the patient had clinical HHT with XX and displayed pulmonary AVM but no cAVM'
Clinical diagnose of HHT should follow the Curacao criteria, which consist of spontaneous and recurrent epistaxis, telangiectasia at characteristic sites, visceral AVMs and a first-degree relative with HHT. Fulfilling at least three criteria makes a definite diagnosis of HHT.
7th paragraph, page 4, line 33: Add the age of the brother.
8th paragraph, page 4: This paragraph can more or less be omitted with reference to the published cases (see also https://arup.utah.edu/database/ENG/ENG_display.php) and Fig. 2. Some of the information might be available in text to the figure.
9th paragraph, page 4: Though the methods need not be presented in details in a case report, it should be indicated why and how quantitative RT-PCT was done (commercially available kit?). It might just be in the figure text.

Discussion and Conclusions:
2nd paragraph, line 9: The sentence RT-PCR…’ I think speculations on effect should be avoided/deleted. Instead it should be discussed that we regard the variant as 'first hit' and leading to - at least - functional haploinsufficiency, but RT-PCT analysis showed normal transcript level supporting the NetStart suggested misstart as a likely explanation.
3rd paragraph, line 29: '..Patient...' should be changed to '…patient..' 
4th paragraph, line 38: 'Index patient suffered from polymicrogyria: interestingly only ENG mutations (HHT1) have been associated with this peculiar radiologic evidence'. No clinical signs were mentioned so, change to 'Our index patient had polymicrogyria: interestingly only ENG variants (HHT1) have been associated with this radiologic findings'.
4th paragraph, line 47: 'Authors...' changed to 'The authors..'
4th paragraph, line 58: 'This conclusion fits with our patient where cAVMs are in close…' changed to ' This conclusion fits with the finding in our patient where cAVMs are seen in close…'
5th paragraph, page 6, line 12: It could also be unrelated to the ENG variant and HHT. This should probably be mentioned.
Last paragraph: As they usually have other signs of HHT it could be added ’ especially when the patient report recurrent epistaxis.

Figure legend:
Fig 2a Instead of HHT (yellow symbol) indicate symptoms that led to the clinical diagnose (confirmed by the finding of the ENG variant)
If possible the electrograms should be enlarged in the figure.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?

If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

Quality of written English

Please indicate the quality of language in the manuscript:

Acceptable

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