Title

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Journal

ERJ Open Research, 9(3)

ISSN

2312-0541

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Publication Date

2023-05-01

DOI

10.1183/23120541.00751-2022

Peer reviewed

An analysis of sex differences in pulmonary arteriovenous malformation presentation, complications and management in a large, multinational registry of patients with hereditary haemorrhagic telangiectasia

Received: 28 Dec 2022
Accepted: 22 March 2023

To the Editor:

Among individuals with hereditary haemorrhagic telangiectasia (HHT), an estimated 40–50% have pulmonary arteriovenous malformations (PAVMs) (anomalous direct communications between pulmonary arteries and veins without an intervening capillary network) visible on computed tomography (CT) [1, 2]. Hypoxaemia, haemorrhage and paradoxical embolisation are some of the potentially serious complications associated with untreated PAVMs [2, 3]. There is, in general, a paucity of published sex-based data on HHT, including on PAVMs [4]. In one analysis of ∼1300 individuals with HHT cared for at a single centre in the Netherlands, PAVM frequency was observed to be ∼15% higher among females than males with HHT-1 (caused by mutation in the endoglin gene) but not with HHT-2 (caused by mutation in the activin A receptor type-like kinase 1 (*ACVRL1*) gene) [4]. Diffuse PAVMs, which are associated with even higher morbidity and mortality than nondiffuse PAVMs, have also been reported to occur more frequently among females than males with HHT in two small case series [5, 6]. However, rate of brain abscess complication related to PAVMs was observed to be ∼3.5-fold greater in males than females after adjustment in a study involving 57 individuals with HHT in the UK [7]. If there are indeed significant sex-based differences in the presentation and complications of PAVMs, tailoring of PAVM diagnostic and management approaches by sex may be indicated. International HHT guidelines currently make no distinction in PAVM diagnostic and management recommendations between females and males [8, 9]. Using a large, multicentre, multinational HHT database, our purpose was to evaluate for possible biological sex-based differences in PAVM presentation, complications and management among individuals with HHT.

We analysed data from the Brain Vascular Malformation Consortium (BVMC) HHT Project database [10], which contained demographic and clinical data between 2010 and 2019 on individuals with established HHT from 14 HHT Centres for Excellence around the world, including in the USA, Canada and the Netherlands. To be included in the database, individuals had to have a confirmed HHT diagnosis, either genetically or clinically (based on three or more Curaçao criteria [11]). Individual-level information included in the database came from comprehensive history, physical examination and laboratory and imaging investigations undertaken at the HHT Centres for Excellence as part of standard HHT clinical care, as per international HHT guidelines [8, 9]. As part of standard HHT clinical care [8, 9], if an individual screened positive for a possible PAVM (such as on agitated saline contrast echocardiography), then further diagnostic imaging (*i.e.* thoracic CT) and treatment (*i.e.* pulmonary angiography with embolisation) were undertaken, where appropriate. The database included information on: presence of significant-sized PAVM (*i.e.* visible on thoracic CT); select PAVM physical characteristics, including number of PAVMs, diameter of the largest feeding artery and presence of diffuse PAVMs; whether a significant-sized PAVM had been identified through routine screening (*i.e.* an agitated saline contrast echocardiography being undertaken, being positive, which then led to further investigation); pre-treatment PAVM-related haemorrhagic and neurovascular complications; receipt of embolotherapy; and possible new development of significant-sized PAVM after initial screening.

Shareable abstract (@ERSpublications)
This large, multinational, sex-based analysis among individuals with HHT showed that pulmonary AVM frequency, physical characteristics, presentation, complications and management do not generally significantly differ between males and females https://bit.ly/3TNLA6v

Cite this article as: Tuff-Gordon E, Faughnan ME, Kim H, *et al*. An analysis of sex differences in pulmonary arteriovenous malformation presentation, complications and management in a large, multinational registry of patients with hereditary haemorrhagic telangiectasia. *ERJ Open Res* 2023; 9: 00751-2022 [DOI: 10.1183/23120541.00751-2022].

Chi-squared test of proportions was used to evaluate for statistically significant differences between males and females, using a $p<0.05$ threshold.

Out of 1664 individuals with HHT in the database, 677 (40.7%) were males and 987 (59.3%) were females, and HHT gene mutation status was as follows: 26.9% endoglin; 19.3% *ACVRL1*; 2.1% *SMAD4*; 2.2% had completely negative genetic testing; and in 49.6%, complete genetic testing was unavailable. Among individuals with significant-sized PAVMs (n=795), the distribution of HHT gene mutation status was: 38.5% endoglin; 6.9% *ACVRL1*; 1.6% *SMAD4*; 2.6% had completely negative genetic testing; and in 50.3%, complete genetic testing was unavailable.

While significant-sized PAVMs were observed more frequently in females (n=491, 49.8%) than males (n=303, 44.8%), the difference between sexes was not statistically significant (p=0.13). Presence of diffuse PAVMs was also not significantly different between females and males (5.9% *versus* 4.0%, respectively; p=0.23) (table 1). There were no significant differences between sexes in the proportion of individuals with multiple PAVMs or with PAVMs with feeding arteries ⩾3 mm. PAVMs tended to be diagnosed more frequently through routine screening (67% *versus* 63.5%, p=0.32) and at a younger age (30.0% *versus* 25.1%, p=0.12) among males *versus* females but differences were again nonsignificant. There was no significant difference in frequency of overall PAVM complication (including both haemorrhage and neurovascular) between sexes but stroke/transient ischaemic attack tended to occur in females more commonly (9.2% *versus* 6.3%, p=0.15) and cerebral abscess in males more commonly (4.3% *versus* 2.2%, p=0.10). There was no significant difference in the proportion receiving embolotherapy between sexes. After initial screening, there was no significant difference between sexes with respect to new development of significant-sized PAVM.

We separately examined complications by sex among individuals with selected PAVM subtypes: those with diffuse PAVMs (n=41); those with PAVMs with feeding arteries ⩾3 mm (n=339); and those with more than one PAVM (n=295). There were no significant differences in the frequencies of overall complication between sexes among the three selected PAVM subtypes. Among individuals with more than one PAVM, haemorrhage (5.4% (n=6) *versus* 0.5% (n=1), p=0.008) and abscess (7.2% (n=8) *versus* 2.2% (n=4), p=0.03) complications were significantly more frequent among males than females. No other complication subtypes were significantly different between sexes by selected PAVM subtypes.

In contrast to the limited previously published literature that found some sex-based differences [4–7], our study, which used the largest and most population-diverse HHT sample to date, demonstrated generally no significant differences in PAVM frequency, physical characteristics, presentation, complications and management between males and females. It is possible that previously published sex-based differences [4–7] were related to small and/or selected study samples used. While haemorrhage and abscess complications occurred with notably significantly greater frequency among males in the subgroup individuals with more than one PAVM, these results should be interpreted with caution, since they were based on very small numbers; given our overall pattern of results, further study with larger sample sizes is needed for confirmation.

TABLE 1 Frequencies of pulmonary arteriovenous malformation (PAVM) presentation, complication and management characteristics among males and females with significant-sized PAVMs

Characteristic	Males (n=303)	Females (n=491)	p-value
Has diffuse PAVMs	4.0	5.9	0.23
PAVM feeding artery diameter ⩾3 mm	43.9	42.0	0.59
>1 PAVM	36.6	37.5	0.81
PAVM diagnosis occurred at age <30 years	30.0	25.1	0.12
Any pre-treatment PAVM complication	11.6	12.8	0.59
Pre-treatment haemorrhage complication	3.0	2.0	0.40
Pre-treatment stroke/TIA complication	6.3	9.2	0.15
Pre-treatment abscess complication	4.3	2.2	0.10
PAVM treated with embolotherapy	71.3	72.3	0.76
PAVM identified on routine screening	67.0	63.5	0.32
New PAVM developed after initial screening	16.8	14.1	0.29

Data are presented as %. TIA: transient ischaemic attack.

Our analysis has several limitations. Although we used the largest size sample to date to investigate possible sex-based differences in PAVMs, it is possible that had our study included even larger numbers, some nonsignificant trends may have achieved statistical significance. Although the BVMC HHT Project database is multinational, it is known that White subjects account for >90% of participants [1] and this lack of ethnic diversity may have influenced our findings. Our analysis was not adjusted for potential confounders but a multivariable-adjusted analysis was intentionally not undertaken since there were generally no significant sex-based associations identified at the univariate level. The BVMC HHT Project did not collect data on all PAVM physical characteristics of potential interest (*e.g.* number of feeding arteries, size of the aneurysmal component and degree of shunting). Our study demonstrated that ∼30% of both males and females with HHT with PAVMs did not receive embolotherapy. The BVMC HHT Project database did not capture information on reasons why PAVMs went untreated, but PAVMs too small in size to treat, technical challenges with embolotherapy and patient preference are likely factors.

Among individuals with HHT, PAVM frequency, physical characteristics, presentation, complications and management do not generally significantly differ between sexes. Our findings support that a similar diagnostic and management approach can be applied to males and females with HHT with respect to PAVMs.

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Provenance: Submitted article, peer reviewed.

Members of the Brain Vascular Malformation HHT Investigator Group: Murali Chakinala, Marianne S. Clancy, Marie E. Faughnan, James R. Gossage, Steven W. Hetts, Vivek Iyer, Raj S. Kasthuri, Helen Kim, Timo Krings, Michael T. Lawton, Doris Lin, Hans-Jurgen Mager, Douglas A. Marchuk, Justin P. McWilliams, Jamie McDonald, Ludmila Pawlikowska, Jeffrey Pollak, Felix Ratjen, Karen Swanson, Dilini Vethanayagam, Shantel Weinsheimer, Andrew J. White and Pearce Wilcox.

Support statement: N.T. Vozoris received no funding for this study. The Brain Vascular Malformation Consortium (BVMC) is part of the Rare Diseases Clinical Research Network (RDCRN), which is funded by the National Institutes of Health (NIH) and led by the National Center for Advancing Translational Sciences (NCATS) through its Office of Rare Diseases Research (ORDR). BVMC is funded under grant number U54NS065705 as a collaboration between NCATS and the National Institute of Neurological Disorders and Stroke (NINDS). All RDCRN consortia are supported by the network's Data Management and Coordinating Center (DMCC) (U2CTR002818). Funding support for the DMCC is provided by NCATS and NINDS. Funding information for this article has been deposited with the Crossref Funder Registry.

Conflicts of interest: All authors declare no conflicts of interest.

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