Clinical heterogeneity in hereditary haemorrhagic telangiectasia: are pulmonary arteriovenous malformations more common in families linked to endoglin?

Jonathan N Berg, Alan E Guttmacher, Douglas A Marchuk, Mary E M Porteous

Abstract

Pulmonary arteriovenous malformations (PAVMs) occur in up to 27% of patients with hereditary haemorrhagic telangiectasia (HHT) and are associated with a rate of paradoxical cerebral embolism at presentation of up to 36%. At least two different loci have been shown for HHT. Mutations in endoglin have been found in some families and the locus designated ORW1. In other families this locus has been excluded. In this paper we confirm that in families linked to ORW1 there is a prevalence of PAVMs among affected members of 29-2%, compared to a prevalence of 2-9% in families in which this locus has been excluded ($\chi^2 = 19.2$, p<0.001). This information can be used to decide how to screen HHT patients for PAVMs.

(J Med Genet 1996;33:256-257)

Key words: hereditary haemorrhagic telangiectasia; pulmonary arteriovenous malformation; endoglin.

Hereditary haemorrhagic telangiectasia (HHT), also known as Osler-Rendu-Weber syndrome, is an autosomal dominant vascular dysplasia characterised by mucocutaneous telangiectases (fig 1) and severe recurrent epistaxes. Pulmonary arteriovenous malformations (PAVMs) occur in between 4-8% and 27% of patients. PAVMs may be asymptomatic, but can often cause hypoxaemia and pulmonary haemorrhage. PAVMs also lead to high incidence of cerebral abscesses, and cerebrothromboembolic complications occur in up to 36% of patients at presentation.7 Most authors recommend screening for asymptomatic PAVMs in HHT patients,8,9 with occlusion by embolisation of all lesions with a feeding vessel greater than 3 mm.

Two loci for HHT have been identified. The ORW1 locus, mapping to chromosome 9q34, is endoglin, a TGF-β binding protein expressed on endothelial cells.6,9 Recently, a second locus on 12q has been reported.10-11 Several authors have noted a subjectively higher frequency of PAVMs in families showing linkage to ORW1.9,12,13

In this paper we aim to address the size of this difference, using data from three new families (fig 2) and 16 families previously published.1-7

Diagnosis of HHT in the three new families was made by the presence of two of: recurrent epistaxis, mucocutaneous telangiectasia, and an affected first degree relative. Pulse oximetry was performed according to the method described by Hughes4 to detect PAVMs. Three subjects from family 5 had a chest x ray and lung perfusion scans. Clinical details of the thirteen families assessed by our group were all collected before linkage data were available.

For the newly assessed families, microsatellite markers were run using accepted techniques and analysis of results was performed using MLINK or LINKMAP.

Of the 16 families included, eight families are not linked to endoglin on chromosome 9

![Figure 1 Classical telangiectases on the lips of an HHT patient.](http://jmg.bmj.com/ on October 13, 2017 - Published by group.bmj.com)
and eight families show evidence of linkage. The majority of people in this group (93/120) came from families large enough to achieve a lod score of greater than 3. The data are summarised in the table.

In the families linked to endoglin, 35/120 (29.2%) had pulmonary arteriovenous malformations. In the unlinked families, 2/69 (2.9%) had PAVMs. The difference between these two groups is highly significant ($\chi^2 = 19.2$, 1 df, $p<0.001$).

In the endoglin linked group many of the patients had symptomatic PAVMs. There may be several small asymptomatic PAVMs in the non-endoglin population, even though 36/69 were screened by pulse oximetry. This is an unlikely source of bias as more careful screening of the endoglin population would also be expected to turn up a greater number of asymptomatic PAVMs. All families were assessed “blind” before linkage data were available.

The observed difference in PAVM frequency is a biologically plausible finding. Endoglin may well have a role in the development of pulmonary vasculature which is not shared by the other genes in which mutations can cause HHT.

As all those with HHT are at some risk of having a PAVM, it is important to offer screening to all patients, at least by the method of Hughes using supine and erect pulse oximetry and chest x ray.

With members of endoglin linked families having a 29.2% incidence of PAVMs, it is particularly important to target screening on (1) patients from families with HHT linked to endoglin on 9q34, (2) patients who have a family history of PAVMs. For these patients, we feel that formal arterial oxygen measurement and measurement of right to left pulmonary shunt fraction using the 100% oxygen method may be justified.

Firstly we wish to thank all the patients whose participation made this study possible. We also wish to thank Professor J M B Hughes for assessing members of family 5 for PAVMs and Bernadette Farren for helping to collect samples. Particular thanks are due to Catherine Cookson, who has funded much of this work.

Clinical heterogeneity in hereditary haemorrhagic telangiectasia: are pulmonary arteriovenous malformations more common in families linked to endoglin?
J N Berg, A E Guttmacher, D A Marchuk and M E Porteous

doi: 10.1136/jmg.33.3.256

Updated information and services can be found at:
http://jmg.bmj.com/content/33/3/256

Email alerting service
These include:
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/