Hereditary Haemorrhagic Telangiectasia

Subjects: General Medical Research

Submitted by: Helen Arthur

Definition

Hereditary haemorrhagic telangiectasia (HHT) is an inherited vascular disease characterised by bleeding from small blood vessels in the nose and gastrointestinal tract and by larger arteriovenous malformations in the lungs, liver and neural tissues. Recent advances have been made in gaining a better understanding of the cell defects that cause this disease.

1. Introduction

Hereditary Haemorrhagic Telangiectasia (HHT) is an inherited vascular disorder affecting up to 1 in 5000 people. It is an autosomal dominant disorder and the vast majority of patients (>85%) have inherited one allele encoding nonfunctional endoglin (ENG) or activin receptor-like kinase 1 (ACVRL1, also known as ALK1) allele[1]. A minority of HHT cases are due to mutations in *SMAD4* or *BMP9* (GDF2), but these have somewhat different clinical presentations. SMAD4 patients have a combined Juvenile Polyposis–HHT syndrome, whilst BMP9 patients display a mild HHT-like phenotype[2][3]. This review will focus on the two major patient groups, HHT1 and HHT2 that are caused by loss-of-function (LOF) mutations in ENG and ACVRL1, respectively.

HHT1 and HHT2 patients develop very similar clinical symptoms that result from sporadic vascular malformations, with clinical diagnosis based on the “Curacao criteria”. Patients with at least three of the following features are considered to have a definitive diagnosis of HHT: (1) multiple mucocutaneous telangiectases, (2) recurrent nosebleeds, (3) visceral organ arteriovenous malformations (AVMs) and (4) a first degree relative with HHT. Where possible, this diagnosis is confirmed by genetic testing. Telangiectases are small arteriovenous connections found on the skin and mucosal surfaces and are prone to bleeding in the nose and gastrointestinal (GI) tract. In fact, epistaxis from nasal telangiectases is the most highly penetrant phenotype, present in almost all young adults with HHT, and anaemia may be sufficiently severe to necessitate regular iron or blood transfusions. Larger AVMs may be present in the lung, liver and neural tissues. HHT1 and HHT2 patients differ in the incidence of affected tissues, with AVMs in the lung and brain more common in HHT1, whilst a spectrum of hepatic vascular malformations including AVMs are more common in HHT2[4][5]. The reasons for these differences are not yet known.

2. Aetiology of HHT Disease

Although there is a growing consensus that HHT is caused by reduced BMP9/10 signalling in ECs, it is not yet clear why the vascular lesions are localised to specific organs and tissues. Nasal telangiectases and nosebleeds seem to be the most highly penetrant feature affecting over 90% of young HHT adults. Dermal and GI telangiectases accrue later in adult life, whilst pulmonary and cerebral AVMs may be present from birth, usually reaching their final size by adult life[6][7]. The first point to emphasise here is that the majority of the vascular architecture in HHT1/2 patients appears to be normal, supporting the conclusion that one wild type allele (for *ENG* or *ACVRL1*) is sufficient for development, maintenance and function of the vast majority of the vasculature. Therefore, to explain the focal nature of vascular lesions, a local second genetic hit has been postulated, and recent evidence has indeed confirmed biallelic loss of *ENG* or *ACVRL1* gene function in dermal telangiectases from HHT1 and HHT2 patients[8]. This mechanism is yet to be confirmed in larger AVMs from HHT patients when such tissue becomes available. However, this finding is entirely consistent with evidence from preclinical models that reproducibly develop AVMs when functional *Eng* or *Acvrl1* genes are deleted from ECs, but rarely when mice are heterozygous carriers of *Eng* or *Acvrl1* LOF mutations[9]. This second genetic hit event to generate *ENG* or *ACVRL1* null ECs will likely be a stochastic event that is entirely consistent with HHT

vascular lesions that accrue with age such as dermal telangiectases.

If biallelic loss of ENG or ACVRL1 drives the formation of sporadic vascular lesions in HHT, this only partly explains the phenotypic complexity of this disease. An explanation is also required as to the tissue location preference for AVMs and telangiectases. Considering the nasal telangiectases first, these lesions are the most highly penetrant defect in HHT1 and HHT2, and the nasal mucosal tissue is also an area of acute inflammation during frequent respiratory infections such as the common cold. Local inflammation would provide two additional stimuli that may be relevant to initiate telangiectasis formation. Firstly, inflammation triggers removal of the endothelial glycocalyx, and is associated with local release of inflammatory cytokines such as tumour necrosis factor-α (TNFα). This cytokine triggers events leading to cleavage of the extracellular domain of ENG protein, which is released as a soluble form into the circulation[10]. As HHT1 patients have baseline levels of 50% of the normal levels of ENG protein[11], then protein cleavage during inflammation may cause this to drop below the levels required to maintain the normal vascular architecture. It is interesting to note in this context that genetic variants of ADAM17, which encodes a major regulator of TNFα activity, are associated with pulmonary disease severity in HHT1[12]. Secondly, inflammation resulting from infection or tissue injury generates a proangiogenic stimulus that has been shown in preclinical models to be required for AVM formation[9][13]. Organs that are frequently affected in HHT are all exposed to environmental and/or inflammatory insults. This is most obvious for the lung, skin, oronasal and GI tract. However, the liver is also exposed to blood draining from the gut which is rich in antigenic material including microbial debris. As a result, local inflammation is a normal part of liver homeostasis[14]. In addition, although cerebral tissue would normally be protected from environmental insults, there is an increased risk of embolic stroke and cerebral abscess caused by microthrombi passing through lung AVMs, even when these are small and clinically silent[6][7]. It therefore logically follows that there is an increased risk of proinflammatory microthrombi reaching the brain that may be insufficient to cause clinical stroke or abscess, but still provide sufficient pathophysiological proinflammatory trigger for vessel remodelling to form brain AVMs (BAVMs). Therefore, it may be no coincidence that lung and brain AVMs are both present in HHT1 patients more frequently than HHT2 patients. Furthermore, the variability of clinical symptoms even within the same HHT family carrying the same mutation (in ENG or ACVRL1) can be explained by this complex pathogenesis that depends on the timing of the second hit—a stochastic mutation event and/or exposure to an inflammatory or other environmental stimulus that promotes angiogenesis. Indeed, developmental angiogenesis may help drive the formation of congenital AVMs in the presence of biallelic ENG or ACVRL1 LOF mutations. Ultimately, however, the precise reasons for the specific tissue distribution of vascular lesions in HHT remain to be uncovered in detail in future work.

Once an abnormal arteriovenous shunt is formed it becomes extremely challenging to reverse due to the increased blood flow. Added to this is evidence that loss of ACVRL1 signalling alters the endothelial response to shear stress [15][16]. Analysis of zebrafish embryos harbouring a LOF mutation in acvrl1 showed increased EC numbers in cerebral arteries that further increased in response to blood flow to generate stabilised AVMs[16]. This increase in EC number to generate an AVM is not due to increased proliferation, but rather to reduced migration of ECs against blood flow leading to an accumulation of ECs that would normally have migrated towards the heart[17]. This reduced migration defect has also been confirmed in a mouse model of HHT1[18]. In this way, due to a failure of normal EC migration against blood flow, congenital AVMs may further enlarge during developmental angiogenesis. Furthermore, additional local secondary events likely come into play as blood shunting via an AVM and bypassing a local capillary bed cannot efficiently exchange oxygen leading to local tissue hypoxia. Low oxygen leads to a local increased expression of many genes, including VEGF, which potentially drives a positive feedback scenario in HHT causing further angiogenic stimulation and AVM expansion.

Another important contributory element to AVM formation is the disruption of crosstalk between ECs and pericytes. Following loss of ENG, there is reduced pericyte–EC contact that may affect vasoregulation and vessel stability in HHT. Evidence from mouse models of HHT shows reduced vascular smooth muscle coverage and reduced pericyte–endothelial integration leading to vessel instability[19][20]. Reduced

pericyte number and coverage have also been reported in sporadic brain AVMs (BAVMs)[21], and may also be the case in BAVMs in HHT patients.

To summarise, in addition to genetic loss of ENG or ACVRL1, developmental angiogenesis, blood flow and local environmental triggers driving neovessel formation, such as hypoxia and inflammation, are critical players driving the formation of AVMs in HHT.

4. Overlapping Endothelial Cell Abnormalities in HHT and Spontaneous BAVMs

Although up to 5% HHT patients develop BAVMs, the majority of BAVMs in patients presenting at neurology clinics are spontaneous. There is an inherent high risk of haemorrhage from a BAVM which accounts for the majority of haemorrhagic strokes in young adults. This risk has driven major efforts to better understand BAVM pathobiology, and in light of recent progress in this area it is important to consider whether there are overlaps between the downstream molecular changes that give rise to spontaneous and HHT BAVMs. Recent seminal work has revealed that somatic activating mutations in KRAS are associated with the majority of spontaneous BAVMs[22]. These constitutively active (CA) KRAS mutations are present in ECs of spontaneous BAVMs in a mosaic fashion. This parallels evidence from a mouse model of HHT1, where mosaicism for Eng mutations in ECs is sufficient to generate AVMs[18]. Thus, only a proportion of ECs need to harbour a new mutant allele to develop AVMs in both HHT and in spontaneous BAVMs. In HHT, the new mutation is a loss of the second functional ENG or ACVRL1 allele, whereas in spontaneous brain AVMs it is gain of a CA-KRAS mutation. It is striking that ECs with gain of KRAS activity or LOF ENG mutations both show elevated phospho-ERK activity, suggesting that this may be a common pathway associated with AVM formation[23][24]. Furthermore, as inhibiting MEK signalling can reverse established AVMs due to activated KRAS in the zebrafish model[23], this finding may be relevant to HHT (as discussed below). However, it is not yet clear whether the proproliferative role of the activated RAS/RAF/MEK/ERK pathway makes a direct contribution to AVMs[23]. Similarly, it is not known to what extent loss of the antiproliferative role of BMP9 signalling in the absence of ENG or ACVRL1 proteins drives the increased EC proliferation seen in telangiectases from HHT2 patients and in AVMs in preclinical models of HHT[25][26][27][28][29]. Nevertheless, the similarities in cellular responses in AVMs in HHT and spontaneous BAVMs suggest that scientific progress in these two fields may be mutually informative[30].

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Keywords

BMP9/10;ENG;ACVRL1;VEGF;angiogenesis;arteriovenous malformation

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