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**Grand Round**

# Hereditary haemorrhagic telangiectasia
## *From coils to genes*

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**Summary**

A 36 year old man with hereditary haemorrhagic telangiectasia (HHT) causing pulmonary and cerebral arteriovenous malformations (AVM) was successfully treated with pulmonary steel coil embolisation. Patients with pulmonary AVM are at risk of cerebrovascular accidents or cerebral abscesses if left untreated. This patient suffered such a complication before his pulmonary AVM was discovered and treated. Most pulmonary AVM are associated with HHT and relatives of people with AVM or HHT should be offered screening. By means of a family screening programme, 9 affected relatives of this case have been detected. From 3 large affected families a gene for HHT has been mapped to the long arm of chromosome 9. The implications for diagnósis and therapy are discussed.

**Case History**

A 36 year old man suddenly developed headache and right arm weakness. CT scan of the brain revealed that this was due to a cerebral haemorrhage and magnetic resonance imaging revealed two small cerebral arteriovenous malformations (AVM), one of which had bled. He made a full spontaneous recovery and the cerebral AVM were treated elsewhere with stereotactically-guided radiotherapy; a technique referred to as the 'gamma knife' (Coffey et al, 1995). He has had no neurological problems since. At that time his chest radiograph was found to be abnormal. He was referred to the Hammersmith Hospital for further investigations, this being a national referral centre for pulmonary AVM.

He was a healthy man, working as a chef and as a soldier in the Territorial Army. His only symptom was epistaxis, occurring 2 to 5 times a week. His brother, sister and father were similarly affected by nosebleeds and his father had died from a cerebral abscess.

Examination was normal except for widespread telangiectasia on his skin and mucous membranes (see Figure 1), suggesting the clinical diagnosis of hereditary haemorrhagic telangiectasia (HHT). There was no residual neurological deficit, no cyanosis and no pulmonary murmur.

Chest x-ray showed a round 5 cm opacity in the lower lobe of the right lung and CT scan of the chest revealed the characteristic feeding and draining vessels of a pulmonary AVM. Radionucleide perfusion scan showed that 8 % of his cardiac output was bypassing the pulmonary capillaries by flowing through the lesion. These investigations confirmed the presence of an asymptomatic pulmonary AVM which put him at significant risk of cerebrovascular accidents or brain abscesses caused by paradoxical emboli.

After careful discussion he elected to have the pulmonary AVM embolised. A 'pig-tail' catheter was passed through the femoral vein, right atrium, pulmonary artery and under direct fluoroscopic vision into the pulmonary AVM. A metallic coil was passed through the catheter into the AVM which was seen to be occluded as a result (Figure 2). This embolisation of the single pulmonary AVM was uncomplicated.

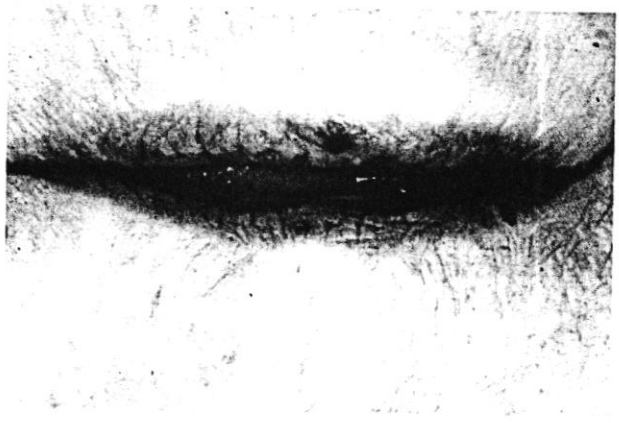

*Figure 1*
Telangiectasia visible on the lips of a woman with HHT.

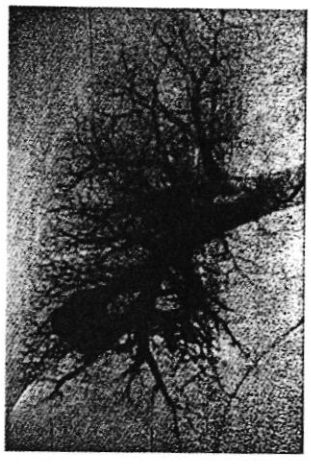

*Figure 2(a)*

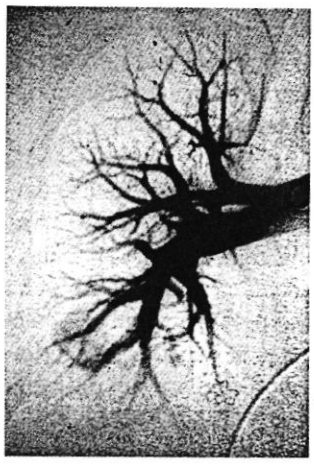

*Figure 2(b)*

Figure 2: Pulmonary angiogram of the patient described in the text. (a) Diagnostic angiogram with 'pig-tail' catheter in the right pulmonary artery showing the AVM (b) Post-embolisation study showing occlusion of feeding artery and pulmonary AVM.

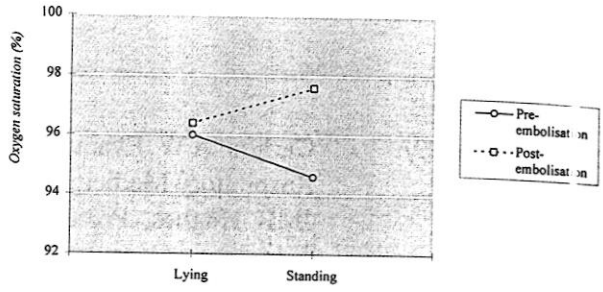


*Figure 3(a)*

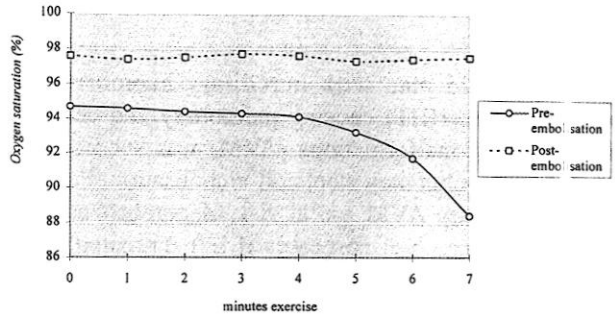


*Figure 3(b)*

Figure 3: Transcutaneous measurement of blood oxygen saturation (multiple readings over 30 minutes) of the patient described in the text before (solid line) and after (broken line) embolisation therapy. (a) Whilst lying and standing. (b) During exercise (6 minutes exercise was equivalent to 180 Watts)

The response to this therapy was confirmed by pulse oximetry, a simple and non-invasive way of measuring the percentage oxygenation of the blood with a sensor on the finger or ear. Figure 3a shows average oxygen saturation of the blood whilst lying and standing (multiple readings over 30 minutes). Before embolisation there was a fall in oxygenation on standing. This occurs because AVM are concentrated in the lower parts of the lung which are better perfused when standing. After embolisation there was improved baseline oxygenation and no fall in oxygenation on standing. Similarly, Figure 3b shows that before therapy exercise induced significant oxygen desaturation which completely resolved after embolisation.

Perfusion scanning post-embolisation also showed resolution of the intra-pulmonary shunt. The patient has been completely well since embolisation, except for persistent nosebleeds.

**Comment**

Pulmonary AVM may be thought of as 'giant telangiectasia' connecting the pulmonary arterioles to venules, bypassing the pulmonary capillary bed. This causes decreased oxygenation of the blood, particularly on exertion, when transit time for blood passing through the lungs in decreased. Pulmonary haemorrhage may occur, especially in pregnancy, and may be life threatening. However, the most important effect of pulmonary AVM is the risk of paradoxical embolism (Haitjema et al, 1996). The pulmonary capillary bed not only oxygenates the blood, but also filters it, removing micro-thrombi from the circulation. Pulmonary AVM bypass this capillary filter, allowing micro-thrombi to pass direct from the systemic venous circulation to the systemic arteries, including the carotid arteries. As a result 33 - 72 % of people with pulmonary AVM at some time suffer either transient ischaemic attacks or cerebral infarction (Romain et al, 1978; White et al, 1988). Similarly, infected micro-emboli, often arising in the mouth (Russi et al, 1996), may bypass the pulmonary capillary filter causing a life-time risk of cerebral abscess of five to nine per cent (Romain et al, 1978; White et al, 1988). The patient R W was unusual in this respect because his stroke was caused by bleeding from a separate cerebral AVM; paradoxical embolism via a pulmonary AVM is a commoner cause of stroke in patients with pulmonary AVM or HHT.

**Diagnosis**

Pulmonary AVM are therefore medically important, but how may they be detected? The combination of finger clubbing, cyanosis and a pulmonary bruit may suggest the clinical diagnosis in severe cases. Postural oxygen desaturation (orthostatic hypoxaemia) is characteristic of pulmonary AVM and it is a useful screening test. Oxygen desaturation on exercise testing is more sensitive but less specific. Chest x-rays do not identify small AVM, even if they are multiple. Pulmonary angiography provides definitive diagnosis but is invasive and causes some morbidity. This hospital has developed the use of radionucleide perfusion scanning to detect and quantify the right to left shunt due to pulmonary AVM (Whyte et al, 1992). Radio-labelled micro-spheres of albumin are injected and become trapped in the lung because the micro-spheres are larger than the pulmonary capillaries. Figure 4a shows a radionucleide perfusion lung scan of a patient with a pulmonary AVM: most of the radioactive micro-spheres have lodged in the lungs but the pulmonary AVM has allowed some of the injected dose to escape through the dilated AVM blood vessels to reach the systemic circulation, including the kidneys. The fraction of kidney radioactivity reflects the magnitude of the right to left shunt through the AVM. The scan in Figure 4b is from the same patient after embolisation of the AVM. This normal scan shows radioactivity emitted only from the lungs.

**Treatment**

The diagnosis of pulmonary AVM is important because effective treatment is available. Antibiotic prophylaxis should always be given to cover dental procedures to decrease the risk of cerebral abscess. Surgical excision of the pulmonary lesion was the traditional treatment but involved the risks of thoracotomy, sacrifice of surrounding normal lung tissue and surgery cannot treat multiple diffuse AVM. In contrast, transcutaneous embolisation is safe and effective and has made surgical excision virtually redundant.

The Hammersmith experience over the last 8 years has involved 59 patients, 81 % of whom have HHT. Sixty-one per cent have had their AVM completely ablated and all but 7 have had significant benefit with minimal morbidity and no mortality.

**Hereditary haemorrhage telangiectasia**

37 - 88 % of patients with pulmonary AVM have HHT (Osler-Weber-Rendu syndrome) (White et al, 1988; Dines et al, 1974; Guttmacher et al, 1995), and up to 2,000 people are affected in Great Britain. The inheritance is autosomal dominant with variable penetrance so an affected person passes the disease on to, on average, half of his or her children. The pathology involves dilatation of capillaries and venules which is thought to result from a defect in vascular basement membrane proteins. Almost all patients have frequent nosebleeds and approximately 75 % of adults have telangiectasia in the skin and mucous membranes.

AVM also occur in the bowel (10 - 40 %), lungs (14 - 30 %) and brain (5 - 11 %) (Haitjema et al, 1996; Guttmacher et al, 1995). At present the diagnosis is made clinically if there are telangiectasia or AVM in two sites together with a family history suggestive of HHT. However, the lesions develop progressively through life and often the diagnosis is not made until complications have occurred, as was the case in this patient.

**Genetics**

Identifying the gene associated with HHT would aid diagnosis and facilitate understanding of the disease pathogenesis. Furthermore, gene therapy may one day

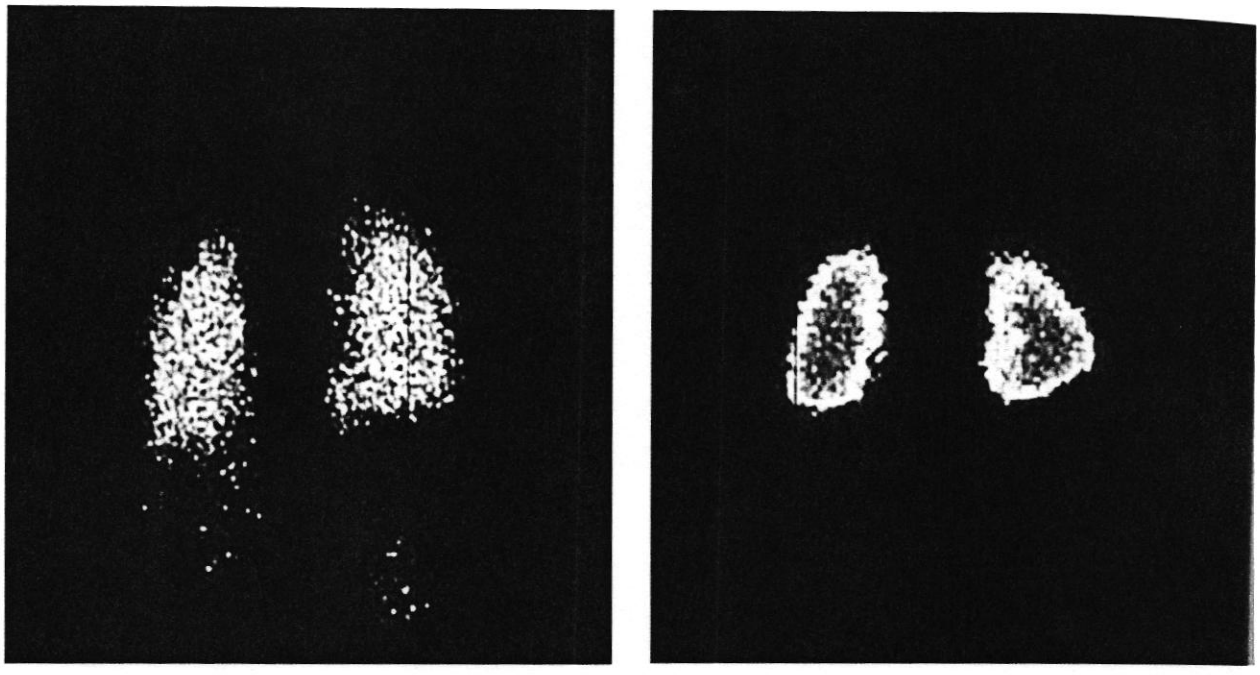

*Figure 4(a)* *Figure 4(b)*

Figure 4: Radionucleide perfusion scanning with intravenously injected technetium-99m radio-labelled micro-spheres, 7-25 μm in diameter. (a) Scan from a patient with a pulmonary AVM which has allowed some of the injected microspheres to bypass the pulmonary capillaries and reach the systemic circulation, causing radiation to be emitted from the kidneys. (b) Normal scan from the same patient after embolisation of the pulmonary AVM: micro-spheres are trapped in the lung capillaries, with no radiation emitted from the region of the kidneys.

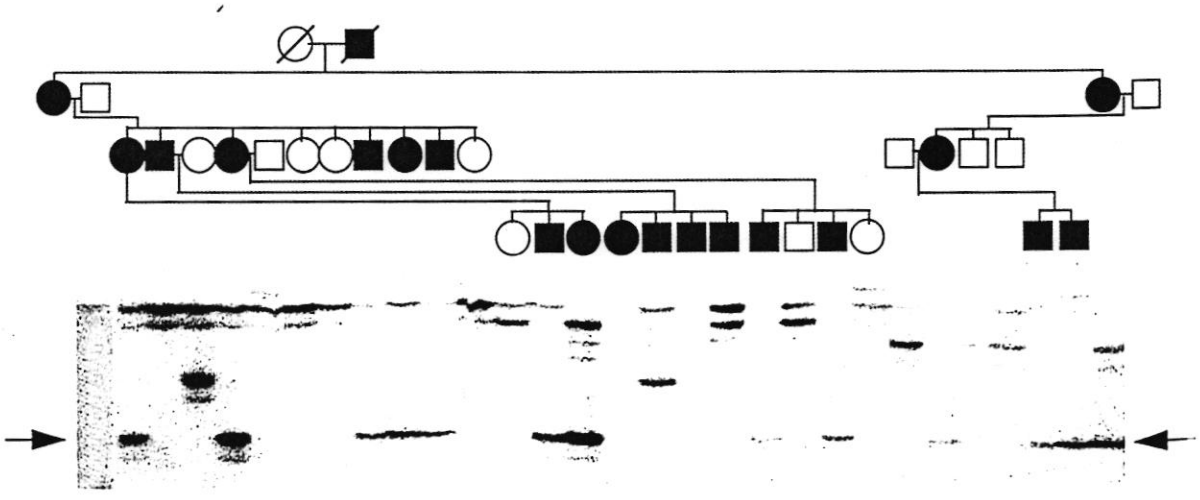

*Figure 5*

Figure 5: Linkage analysis for a family with HHT. Top: family tree. Bottom: electrophoretic gel showing linkage of the D9S65 marker to symptomatic disease (see text).

become possible. The location of such a gene may be established by linkage analysis studies. Linkage analysis involved tracking the inheritance of polymorphic tandem repeats through the generations in affected families. These are unique sequences of repetitive DNA which have been mapped to known points on chromosomes. If a tandem repeat is inherited in the same pattern as the disease, then the tandem repeat must be close to the causative gene. It takes 300 tandem repeats to map the human genome so it makes sense to start with a tandem repeat marker close to a likely area for the HHT gene.

Telangiectasia occur in other diseases including xeroderma pigmentosum, the gene for which has been mapped to the long arm of chromosome 9 and the initial search for the HHT gene was made in this area.

Figure 5 shows how the gene for HHT, and hence the disease, was passed through the generations of an affected family. Below the family tree is an electrophoretic gel in which the different tandem repeats associated with the marker D9S65, which lies on the long arm of chromosome 9, are characterised for all the members of this affected family.

Each person has 2 bands corresponding to their 2 alleles, the faint bands being artefacts. The lower-most band (arrowed) occurs in 13 / 18 of the relatives shown in the figure who had proven or suspected HHT, but not in any unaffected people. The likelihood of the inheritance pattern in this family happening by chance is less than 1 in 10,000 and suggests that the HHT gene is close to the tandem repeat D9S65. Similar analysis for nearby markers established the gene's position in a region which is about 2,000,000 base pairs or 25 genes long. This has been confirmed in 2 other families but one further family with HHT shows no linkage with this region on chromosome 9, suggesting that at least one other disease locus is yet to be identified (Shovlin et al, 1994). Identification of the gene responsible for HHT will assist with diagnosis and assessment of prognosis, with prospects eventually for gene therapy.

**Discussion**

JMBH: I would like to take this opportunity to thank the families of this patient and other patients for their considerable help in tracing both healthy and affected family members, some living in other countries. Many of these people have provided blood samples and their co-operation has made this research possible.

JS: Xeroderma pigmentosum is associated with telangiectasia, but these are thought to result from defective DNA repair - a quite different mechanism from that operating in HHT. Would the gene for HHT really, therefore, be expected to be in the same region as the gene for xeroderma pigmentosum?

JMBH: Although the similarity between these two causes of telangiectasia is rather tenuous and the genes are probably functionally unrelated, this link made the long arm of chromosome 9 a reasonable place to search for the gene before randomly selected areas. I agree that the early success in this region was partly fortuitous.

CD: Now that a gene has been mapped to this region of chromosome 9, what is the priority for your continuing research?

JMBH: This does appear to be the only gene for HHT and detailed mapping of this and other regions is in progress to allow cloning of the genes responsible for this condition. Once the genes are cloned then molecular diagnosis should be feasible and research can progress more rapidly towards understanding the pathogenesis of HHT, with the aim of developing more effective therapies, possibly even gene therapy.

*Footnote*

A gene on chromosome 9 linked to some cases of HHT has been identified as Endoglin (McAllister et al, 1994), which encodes an integral membrane glycoprotein on endothelial cells.

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