= Hereditary hemorrhagic telangiectasia =

Hereditary hemorrhagic telangiectasia (HHT) , also known as Osler ? Weber ? Rendu disease and Osler ? Weber ? Rendu syndrome , is an autosomal dominant genetic disorder that leads to abnormal blood vessel formation in the skin , mucous membranes , and often in organs such as the lungs , liver , and brain .

It may lead to nosebleeds , acute and chronic digestive tract bleeding , and various problems due to the involvement of other organs . Treatment focuses on reducing bleeding from blood vessel lesions , and sometimes surgery or other targeted interventions to remove arteriovenous malformations in organs . Chronic bleeding often requires iron supplements and sometimes blood transfusions . HHT is transmitted in an autosomal dominant fashion , and occurs in one in 5 @,@ 000 people .

The disease carries the names of Sir William Osler , Henri Jules Louis Marie Rendu , and Frederick Parkes Weber , who described it in the late 19th and early 20th centuries .

= = Signs and symptoms = =

= = = Telangiectasias = = =

Telangiectasia (small vascular malformations) may occur in the skin and mucosal linings of the nose and gastrointestinal tract . The most common problem is nosebleeds (epistaxis) , which happen frequently from childhood and affect about 90 ? 95 % of people with HHT . Lesions on the skin and in the mouth bleed less often but may be considered cosmetically displeasing ; they affect about 80 % . The skin lesions characteristically occur on the lips , the nose and the fingers , and on the skin of the face in sun @-@ exposed areas . They appear suddenly , with the number increasing over time .

About 20 % are affected by symptomatic digestive tract lesions , although a higher percentage have lesions that do not cause symptoms . These lesions may bleed intermittently , which is rarely significant enough to be noticed (in the form of bloody vomiting or black stool) , but can eventually lead to depletion of iron in the body , resulting in iron @-@ deficiency anemia .

= = = Arteriovenous malformation = = =

Arteriovenous malformation (AVM , larger vascular malformations) occur in larger organs , predominantly the lungs (50 %) , liver (30 ? 70 %) and the brain (10 %) , with a very small proportion (< 1 %) having AVMs in the spinal cord .

Vascular malformations in the lungs may cause a number of problems . The lungs normally " filter out " bacteria and blood clots from the bloodstream ; AVMs bypass the capillary network of the lungs and allow these to migrate to the brain , where bacteria may cause a brain abscess and blood clots may lead to stroke . HHT is the most common cause of lung AVMs : out of all people found to have lung AVMs , 70 ? 80 % are due to HHT . Bleeding from lung AVMs is relatively unusual , but may cause hemoptysis (coughing up blood) or hemothorax (blood accumulating in the chest cavity) . Large vascular malformations in the lung allow oxygen @-@ depleted blood from the right ventricle to bypass the alveoli , meaning that this blood does not have an opportunity to absorb fresh oxygen . This may lead to breathlessness . Large AVMs may lead to platypnea , difficulty in breathing that is more marked when sitting up compared to lying down ; this probably reflects changes in blood flow associated with positioning . Very large AVMs cause a marked inability to absorb oxygen , which may be noted by cyanosis (bluish discoloration of the lips and skin) , clubbing of the fingernails (often encountered in chronically low oxygen levels) , and a humming noise over the affected part of the lung detectable by stethoscope .

The symptoms produced by AVMs in the liver depend on the type of abnormal connection that they form between blood vessels . If the connection is between arteries and veins , a large amount of blood bypasses the body 's organs , for which the heart compensates by increasing the cardiac

output . Eventually congestive cardiac failure develops (" high @-@ output cardiac failure ") , with breathlessness and leg swelling among other problems . If the AVM creates a connection between the portal vein and the blood vessels of the liver , the result may be portal hypertension (increased portal vein pressure) , in which collateral blood vessels form in the esophagus (esophageal varices) , which may bleed violently ; furthermore , the increased pressure may give rise to fluid accumulation in the abdominal cavity (ascites) . If the flow in the AVM is in the other direction , portal venous blood flows directly into the veins rather than running through the liver ; this may lead to hepatic encephalopathy (confusion due to portal waste products irritating the brain) . Rarely , the bile ducts are deprived of blood , leading to severe cholangitis (inflammation of the bile ducts) . Liver AVMs are detectable in over 70 % of people with HHT , but only 10 % experience problems as a result .

In the brain , AVMs occasionally exert pressure , leading to headaches . They may also increase the risk of seizures , as would any abnormal tissue in the brain . Finally , hemorrhage from an AVM may lead to intracerebral hemorrhage (bleeding into the brain) , which causes any of the symptoms of stroke such as weakness in part of the body or difficulty speaking . If the bleeding occurs into the subarachnoid space (subarachnoid hemorrhage) , there is usually a severe , sudden headache and decreased level of consciousness and often weakness in part of the body .

= = = Other problems = = =

A very small proportion (those affected by SMAD4 (MADH4) mutations , see below) have multiple benign polyps in the large intestine , which may bleed or transform into colorectal cancer . A similarly small proportion experiences pulmonary hypertension , a state in which the pressure in the lung arteries is increased , exerting pressure on the right side of the heart and causing peripheral edema (swelling of the legs) , fainting and attacks of chest pain . It has been observed that the risk of thrombosis (particularly venous thrombosis , in the form of deep vein thrombosis or pulmonary embolism) may be increased . There is a suspicion that those with HHT may have a mild immunodeficiency and are therefore at a slightly increased risk from infections .

= = Genetics = =

HHT is a genetic disorder by definition . It is inherited in an autosomal dominant manner , which means that an affected person carries one abnormal gene with a 50 % chance of passing this gene to offspring . Those with HHT symptoms that have no relatives with the disease may have a new mutation . It seems that carrying two abnormal copies of the gene is not compatible with life , and hence no homozygotes have been described .

Five genetic types of HHT are recognized . Of these , three have been linked to particular genes , while the two remaining have currently only been associated with a particular locus . More than 80 % of all cases of HHT are due to mutations in either ENG or ACVRL1 . A total of over 600 different mutations is known . There is likely to be a predominance of either type in particular populations , but the data are conflicting . MADH4 mutations , which cause colonic polyposis in addition to HHT , comprise about 2 % of disease @-@ causing mutations . Apart from MADH4 , it is not clear whether mutations in ENG and ACVRL1 lead to particular symptoms , although some reports suggest that ENG mutations are more likely to cause lung problems while ACVRL1 mutations may cause more liver problems , and pulmonary hypertension may be a particular problem in people with ACVRL1 mutations . People with exactly the same mutations may have different nature and severity of symptoms , suggesting that additional genes or other risk factors may determine the rate at which lesions develop ; these have not yet been identified .

= = Pathophysiology = =

Telangiectasias and arteriovenous malformations in HHT are thought to arise because of changes in angiogenesis , the development of blood vessels out of existing ones . The development of a new

blood vessel requires the activation and migration of various types of cells , chiefly endothelium , smooth muscle and pericytes . The exact mechanism by which the HHT mutations influence this process is not yet clear , and it is likely that they disrupt a balance between pro- and antiangiogenic signals in blood vessels . The wall of telangiectasias is unusually friable , which explains the tendency of these lesions to bleed .

All genes known so far to be linked to HHT code for proteins in the TGF @-@ ? signaling pathway . This is a group of proteins that participates in signal transduction of hormones of the transforming growth factor beta superfamily (the transforming growth factor beta , bone morphogenetic protein and growth differentiation factor classes) , specifically BMP9 / GDF2 and BMP10 . The hormones do not enter the cell but link to receptors on the cell membrane ; these then activate other proteins , eventually influencing cellular behavior in a number of ways such as cellular survival , proliferation (increasing in number) and differentiation (becoming more specialized) . For the hormone signal to be adequately transduced , a combination of proteins is needed : two each of two types of serine / threonine @-@ specific kinase type membrane receptors and endoglin . When bound to the hormone , the type II receptor proteins phosphorylate (transfer phosphate) onto type I receptor proteins (of which Alk @-@ 1 is one) , which in turn phosphorylate a complex of SMAD proteins (chiefly SMAD1 , SMAD5 and SMAD8) . These bind to SMAD4 and migrate to the cell nucleus where they act as transcription factors and participate in the transcription of particular genes . In addition to the SMAD pathway , the membrane receptors also act on the MAPK pathway , which has additional actions on the behavior of cells . Both Alk @-@ 1 and endoglin are expressed predominantly in endothelium , perhaps explaining why HHT @-@ causing mutations in these proteins lead predominantly to blood vessel problems . Both ENG and ACVRL1 mutations lead predominantly to underproduction of the related proteins , rather than misfunctioning of the proteins .

= = Diagnosis = =

Diagnostic tests may be conducted for various reasons . Firstly , some tests are needed to confirm or refute the diagnosis . Secondly , some are needed to identify any potential complications .

= = = Telangiectasias = = =

The skin and oral cavity telangiectasias are visually identifiable on physical examination , and similarly the lesions in the nose may be seen on endoscopy of the nasopharynx or on laryngoscopy . The severity of nosebleeds may be quantified objectively using a grid @-@ like questionnaire in which the number of nosebleed episodes and their duration is recorded .

Digestive tract telangiectasias may be identified on esophagogastroduodenoscopy (endoscopy of the esophagus , stomach and first part of the small intestine) . This procedure will typically only be undertaken if there is anemia that is more marked than expected by the severity of nosebleeds , or if there is evidence of severe bleeding (vomiting blood , black stools) . If the number of lesions seen on endoscopy is unexpectedly low , the remainder of the small intestine may be examined with capsule endoscopy , in which the patient swallows a capsule @-@ shaped device containing a miniature camera which transmits images of the digestive tract to a portable digital recorder .

= = = Arteriovenous malformations = = =

Identification of AVMs requires detailed medical imaging of the organs most commonly affected by these lesions . Not all AVMs cause symptoms or are at risk of doing so , and hence there is a degree of variation between specialists as to whether such investigations would be performed , and by which modality ; often , decisions on this issue are reached together with the patient .

Lung AVMs may be suspected because of the abnormal appearance of the lungs on a chest X @-@ ray , or hypoxia (low oxygen levels) on pulse oximetry or arterial blood gas determination . Bubble contrast echocardiography (bubble echo) may be used as a screening tool to identify

abnormal connections between the lung arteries and veins . This involves the injection of agitated saline into a vein , followed by ultrasound @-@ based imaging of the heart . Normally , the lungs remove small air bubbles from the circulation , and they are therefore only seen in the right atrium and the right ventricle . If an AVM is present , bubbles appear in the left atrium and left ventricle , usually 3 ? 10 cardiac cycles after the right side ; this is slower than in heart defects , in which there are direct connections between the right and left side of the heart . A larger number of bubbles is more likely to indicate the presence of an AVM . Bubble echo is not a perfect screening tool as it can miss smaller AVMs and does not identify the site of AVMs . Often contrast @-@ enhanced computed tomography (CT angiography) is used to identify lung lesions ; this modality has a sensitivity of over 90 % . It may be possible to omit contrast administration on modern CT scanners . Echocardiography is also used if there is a suspicion of pulmonary hypertension or high @-@ output cardiac failure due to large liver lesions , sometimes followed by cardiac catheterization to measure the pressures inside the various chambers of the heart .

Liver AVMs may be suspected because of abnormal liver function tests in the blood , because the symptoms of heart failure develop , or because of jaundice or other symptoms of liver dysfunction . The most reliable initial screening test is Doppler ultrasonography of the liver ; this has a very high sensitivity for identifying vascular lesions in the liver . If necessary , contrast @-@ enhanced CT may be used to further characterize AVMs . It is extremely common to find incidental nodules on liver scans , most commonly due to focal nodular hyperplasia (FNH) , as these are a hundredfold times more common in HHT compared to the general population . FNH is regarded as harmless . Generally , tumor markers and additional imaging modalities are used to differentiate between FNH and malignant tumors of the liver . Liver biopsy is discouraged in people with HHT as the risk of hemorrhage from liver AVMs may be significant . Liver scans may be useful if someone is suspected of HHT , but does not meet the criteria (see below) unless liver lesions can be demonstrated .

Brain AVMs may be detected on computed tomography angiography (CTA or CT angio) or magnetic resonance angiography (MRA) ; CTA is better in showing the vessels themselves , and MRA provides more detail about the relationship between an AVM and surrounding brain tissue . In general , MRI is recommended . Various types of vascular malformations may be encountered : AVMs , micro @-@ AVMs , telangiectasias and arteriovenous fistulas . If surgery , embolization , or other treatment is contemplated (see below) , cerebral angiography may be required to get sufficient detail of the vessels . This procedure carries a small risk of stroke (0 @.@ 5 %) and is therefore limited to specific circumstances . Recent professional guidelines recommend that all children with suspected or definite HHT undergo a brain MRI early in life to identify AVMs that can cause major complications . Others suggest that screening for cerebral AVMs is probably unnecessary in those who are not experiencing any neurological symptoms , because most lesions discovered on screening scans would not require treatment , creating undesirable conundrums .

= = = Genetic testing = = =

Genetic tests are available for the ENG , ACVRL1 and MADH4 mutations . Testing is not always needed for diagnosis , because the symptoms are sufficient to distinguish the disease from other diagnoses . There are situations in which testing can be particularly useful . Firstly , children and young adults with a parent with definite HHT may have limited symptoms , yet be at risk from some of the complications mentioned above ; if the mutation is known in the affected parent , absence of this mutation in the child would prevent the need for screening tests . Furthermore , genetic testing may confirm the diagnosis in those with limited symptoms who otherwise would have been labeled " possible HHT " (see below) .

Genetic diagnosis in HHT is difficult , as mutations occur in numerous different locations in the linked genes , without particular mutations being highly frequent (as opposed to , for instance , the ?F508 mutation in cystic fibrosis) . Sequence analysis of the involved genes is therefore the most useful approach (sensitivity 75 %) , followed by additional testing to detect large deletions and duplications (additional 10 %) . Not all mutations in these genes have been linked with disease .

Mutations in the MADH4 gene is usually associated with juvenile polyposis , and detection of such a

mutation would indicate a need to screen the patient and affected relatives for polyps and tumors of the large intestine .

= = = Criteria = = =

The diagnosis can be made depending on the presence of four criteria , known as the " Curaçao criteria " . If three or four are met , a patient has " definite HHT " , while two gives " possible HHT " :

Spontaneous recurrent epistaxis
Multiple telangiectasias in typical locations (see above)
Proven visceral AVM (lung , liver , brain , spine)
First @-@ degree family member with HHT

Despite the designation " possible " , someone with a visceral AVM and a family history but no nosebleeds or telangiectasias is still extremely likely to have HHT , because these AVMs are very uncommon in the general population . At the same time , the same cannot be said of nosebleeds and sparse telangiectasias , both of which occur in people without HHT , in the absence of AVMs . Someone 's diagnostic status may change in the course of life , as young children may not yet exhibit all the symptoms ; at age 16 , thirteen percent are still indeterminate , while at age 60 the vast majority (99 %) have a definite diagnostic classification . The children of established HHT patients may therefore be labeled as " possible HHT " , as 50 % may turn out to have HHT in the course of their life .

= = Treatment = =

Treatment of HHT is symptomatic (it deals with the symptoms rather than the disease itself) , as there is no therapy that stops the development of telangiectasias and AVMs directly . Furthermore , some treatments are applied to prevent the development of common complications . Chronic nosebleeds and digestive tract bleeding can both lead to anemia ; if the bleeding itself cannot be completely stopped , the anemia requires treatment with iron supplements . Those who cannot tolerate iron tablets or solutions may require administration of intravenous iron sucrose , and blood transfusion if the anemia is causing severe symptoms that warrant rapid improvement of the blood count .

Most treatments used in HHT have been described in adults , and the experience in treating children is more limited . Women with HHT who get pregnant are at an increased risk of complications , and are observed closely , although the absolute risk is still low (1 %) .

= = = Nosebleeds = = =

An acute nosebleed may be managed with a variety of measures , such as packing of the nasal cavity with absorbent swabs or gels . Removal of the packs after the bleeding may lead to reopening of the fragile vessels , and therefore lubricated or atraumatic packing is recommended . Some patients may wish to learn packing themselves to deal with nosebleeds without having to resort to medical help .

Frequent nosebleeds can be prevented in part by keeping the nostrils moist , and by applying saline solution , estrogen @-@ containing creams or tranexamic acid ; these have few side effects and may have a small degree of benefit . A number of additional modalities has been used to prevent recurrent bleeding if simple measures are unsuccessful . Medical therapies include oral tranexamic acid and estrogen ; the evidence for these is relatively limited , and estrogen is poorly tolerated by men and possibly carries risks of cancer and heart disease in women past the menopause . Nasal coagulation and cauterization may reduce the bleeding from telangiectasias , and is recommended before surgery is considered ; often , several sessions are needed . It may be possible to embolize vascular lesions through interventional radiology ; this requires passing a catheter through a large artery and locating the maxillary artery under X @-@ ray guidance , followed by the injection into the vessel of particles that occlude the blood vessels . The benefit from the procedure tends to be short

@-@ lived , and it may be most appropriate in episodes of severe bleeding .
If other interventions have failed , several operations have been reported to provide benefit . One is septal dermoplasty or Saunders ' procedure , in which skin is transplanted into the nostrils , and the other is Young 's procedure , in which the nostrils are sealed off completely .

= = = Skin and digestive tract = = =

The skin lesions of HHT can be disfiguring , and may respond to treatment with long @-@ pulsed Nd : YAG laser . Skin lesions in the fingertips may sometimes bleed and cause pain . Skin grafting is occasionally needed to treat this problem .
With regards to digestive tract lesions , mild bleeding and mild resultant anemia is treated with iron supplementation , and no specific treatment is administered . There is limited data on hormone treatment and tranexamic acid to reduce bleeding and anemia . Severe anemia or episodes of severe bleeding are treated with endoscopic argon plasma coagulation (APC) or laser treatment of any lesions identified ; this may reduce the need for supportive treatment . The expected benefits are not such that repeated attempts at treating lesions are advocated . Sudden , very severe bleeding is unusual ? if encountered , alternative causes (such as a peptic ulcer) need to be considered ? but embolization may be used in such instances .

= = = Lung AVMs = = =

Lung lesions , once identified , are usually treated to prevent episodes of bleeding and more importantly embolism to the brain . This is particularly done in lesions with a feeding blood vessel of 3 mm or larger , as these are the most likely to cause long @-@ term complications unless treated . The most effective current therapy is embolization with detachable metal coils . The procedure involves puncture of a large vein (usually under a general anesthetic) , followed by advancing of a catheter through the right ventricle and into the pulmonary artery , after which radiocontrast is injected to visualize the AVMs (pulmonary angiography) . Once the lesion has been identified , coils are deployed that obstruct the blood flow and allow the lesion to regress . In experienced hands , the procedure tends to be very effective and with limited side effects , but lesions may recur and further attempts may be required . CTA scans are repeated to monitor for recurrence . Surgical excision has now essentially been abandoned due to the success of embolotherapy .
Those with either definite pulmonary AVMs or an abnormal contrast echocardiogram with no clearly visible lesions are deemed to be at risk from brain emboli . They are therefore counselled to avoid scuba diving , during which small air bubbles may form in the bloodsteam that may migrate to the brain and cause stroke . Similarly , antimicrobial prophylaxis is advised during procedures in which bacteria may enter the bloodstream , such as dental work , and avoidance of air bubbles during intravenous therapy .

= = = Liver AVMs = = =

Given that liver AVMs generally cause high @-@ output cardiac failure , the emphasis is on treating this with diuretics to reduce the circulating blood volume , restriction of salt and fluid intake , and antiarrhythmic agents in case of irregular heart beat . This may be sufficient in treating the symptoms of swelling and breathlessness . If this treatment is not effective or leads to side effects or complications , the only remaining option is liver transplantation . This is reserved for those with severe symptoms , as it carries a mortality of about 10 % , but leads to good results if successful . The exact point at which liver transplantion is to be offered is not yet completely established . Embolization treatment has been attempted , but leads to severe complications in a proportion of patients and is discouraged .
Other liver @-@ related complications (portal hypertension , esophageal varices , ascites , hepatic encephalopathy) are treated with the same modalities as used in cirrhosis , although the use of transjugular intrahepatic portosystemic shunt treatment is discouraged due to the lack of

documented benefit .

= = = Brain AVMs = = =

The decision to treat brain arteriovenous malformations depends on the symptoms that they cause (such as seizures or headaches) . The bleeding risk is predicted by previous episodes of hemorrhage , and whether on the CTA or MRA scan the AVM appears to be deep seated or have deep venous drainage . Size of the AVM and the presence of aneurysms appears to matter less . In HHT , some lesions (high @-@ flow arteriovenous fistulae) tend to cause more problems , and treatment is warranted . Other AVMs may regress over time without intervention . Various modalities are available , depending on the location of the AVM and its size : surgery , radiation @-@ based treatment and embolization . Sometimes , multiple modalities are used on the same lesion .

Surgery (by craniotomy , open brain surgery) may be offered based on the risks of treatment as determined by the Spetzler ? Martin scale (grade I @-@ V) ; this score is higher in larger lesions that are close to important brain structures and have deep venous drainage . High grade lesions (IV and V) have an unacceptably high risk and surgery is not typically offered in those cases . Radiosurgery (using targeted radiation therapy such as by a gamma knife) may be used if the lesion is small but close to vital structures . Finally , embolization may be used on small lesions that have only a single feeding vessel .

= = = Experimental treatments = = =

Several anti @-@ angiogenesis drugs approved for other conditions , such as cancer , have been investigated in small clinical trials . The anti @-@ VEGF antibody bevacizumab , for instance , has been used off @-@ label in several studies . In the largest study conducted so far , bevacizumab infusion was associated with a decrease in cardiac output and reduced duration and number of episodes of epistaxis in treated HHT patients . Thalidomide , another anti @-@ angiogenesis drug , was also reported to have beneficial effects in HHT patients . Thalidomide treatment was found to induce vessel maturation in an experimental mouse model of HHT and to reduce the severity and frequency of nosebleeds in the majority of a small group of HHT patients . The blood hemoglobin levels of these treated patients rose as a result of reduced hemorrhage and enhanced blood vessel stabilization .

= = Epidemiology = =

Population studies from numerous areas in the world have shown that HHT occurs at roughly the same rate in almost all populations : somewhere around 1 in 5000 . In some areas , it is much more common ; for instance , in the French region of Haut Jura the rate is 1 : 2351 - twice as common as in other populations . This has been attributed to a founder effect , in which a population descending from a small number of ancestors has a high rate of a particular genetic trait because one of these ancestors harbored this trait . In Haut Jura , this has been shown to be the result of a particular ACVRL1 mutation (named c.1112dupG or c.1112 _ 1113insG) . The highest rate of HHT is 1 : 1331 , reported in Bonaire and Curaçao , two islands in the Caribbean belonging to the Netherlands Antilles .

Most people with HHT have a normal lifespan . The skin lesions and nosebleeds tend to develop during childhood . AVMs are probably present from birth , but don 't necessarily cause any symptoms . Frequent nosebleeds are the most common symptom and can significantly affect quality of life .

= = History = =

Several 19th century English physicians , starting with Henry Gawen Sutton (1836 ? 1891) and followed by Benjamin Guy Babington (1794 ? 1866) and John Wickham Legg (1843 ? 1921) ,

described the most common features of HHT , particularly the recurrent nosebleeds and the hereditary nature of the disease . The French physician Henri Jules Louis Marie Rendu (1844 ? 1902) observed the skin and mucosal lesions , and distinguished the condition from hemophilia . The Canadian @-@ born Sir William Osler (1849 ? 1919) , then at Johns Hopkins Hospital and later at Oxford University , made further contributions with a 1901 report in which he described characteristic lesions in the digestive tract . The English physician Frederick Parkes Weber (1863 ? 1962) reported further on the condition in 1907 with a series of cases . The term " hereditary hemorrhagic telangiectasia " was first used by the American physician Frederic M. Hanes (1883 ? 1946) in a 1909 article on the condition .

The diagnosis of HHT remained a clinical one until the genetic defects that cause HHT were identified by a research group at Duke University Medical Center , in 1994 and 1996 respectively . In 2000 , the international scientific advisory committee of HHT Foundation International published the now widely used Curaçao criteria . In 2006 , a group of international experts met in Canada and formulated an evidence @-@ based guideline , sponsored by the HHT Foundation International .