The liver in hereditary haemorrhagic teleangiectasia: an inborn error of vascular structure with multiple manifestations: a reappraisal

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'On retourne toujours à son premier amour'

SUMMARY Hereditary haemorrhagic teleangiectasia (Rendu-Osler-Weber disease) is an inborn error of vascular structure with multiple manifestations. Its incidence is about 1-2:100 000 in the European population. The incidence of teleangiectases and/or fistula formation was estimated to be 1 in 10 carriers of the Osler trait. The findings in the family reported herewith suggest a much higher incidence if angiography is more frequently performed. Apart from the skin and mucous membrane, teleangiectases and/or arteriovenous fistulas may be present in the lungs, intestinal tract, spleen, kidney, brain, and bones. The liver apparently is more involved than was originally suspected. The vascular derangement includes teleangiectases, arteriovenous fistulas, and connective tissue formation with fibrosis and atypical cirrhosis. In intestinal bleeding laser coagulation seems to be very efficient. The pathogenesis of teleangiectases is not known but involves several factors such as special formation of venules, capillaries and arterioles, abnormal perivascular connective tissue and endothelial cells.

Historical aspects

Hereditary haemorrhagic teleangiectasia (HHT), a term proposed by Hanes (1909), was first described as hereditary epistaxis by Sutton (1864) and Babington (1865). Later Rendu (1896), Osler (1901), and Weber (1907) added some more characteristic features and separated it as a purely vascular lesion from the many other haemorrhagic disorders. This entity is therefore, sometimes referred to as Sutton-Babington-Rendu-Osler-Weber-disease.

An excellent review of the literature up to 1958 was published by Bean (1958). For a long time HHT was characterised by the triad of epistaxis, multiple teleangiectases of the skin and mucous membrane, and mendelian dominant heredity, but it was gradually recognised that the condition was not confined to the skin and mucosa, and that nearly all organ systems might be involved.

In the last three decades teleangiectases, aneurysms and/or arteriovenous shunts have been found in the lung, in the entire intestinal tract, in the liver, spleen, kidney, genital tract, brain, aorta, bones, conjunctiva, and retina (Lechner, 1968; Trell *et al.*, 1972).

It was to be expected that some of these manifestations would occur together in one patient or in one family.

HHT in four generations (Fig. 1)

At present we have one family under observation in which nearly all manifestations occurred in four generations. The great-grandfather had a recurrent anaemia due to nose-bleeding and died at the age of 62 years. The grandfather had many episodes of nose-bleeding and melaena leading to severe anaemia. At the age of 70 years he had an operation for perforated gastric ulcer. His liver was very much enlarged (16 cm), there was epigastric pulsation and a thrill felt above the right lobe. He refused angiography because of old age and died at home from cardiac failure at the age of 72 years; there was no necropsy.

His four daughters have had nose-bleeding from early childhood, teleangiectases on the lips, and large livers. A bruit can be heard above the liver in two of them (nos. 3 and 5). Two sisters (nos. 4 and 5) have arteriovenous shunts in the liver as demonstrated by angiography (Fig. 2). A peritoneoscopy was done in patient no. 3; the liver showed a nodular surface and teleangiectases. One (no. 5) was operated upon because of biliary colic. The gall-bladder was removed and a small adenoma was found in the gallbladder wall. The liver showed macronodular transformation; histologically marked

Fig. 1 Family tree of four generations with Osler's disease and fistula formation in the lung, liver, and intestinal tract.

Fig. 2 Angiography, multiple aneurysms in the liver of patient no. 4 (Fig. 1).

subcapsular fibrosis and increased portal tract fibrosis was demonstrated. The fourth sister (no. 6) has no symptoms and signs of fistula formation in the viscera, whereas her son was found to have a large arteriovenous pulmonary fistula at the age of 9 years. After surgical correction, dyspnoea, cyanosis

and clubbing of the finger disappeared. He has now neither nose-bleeding nor skin signs. The son (no. 7) of patient no. 3 died last year very suddenly from a severe intestinal haemorrhage at the age of 22 years. He had teleangiectases in the lower oesophagus, the cardia, and the liver. His sister has some teleangiectases on the lips. The daughter (no. 9) of patient no. 4 has splenomegaly; the daughter of the third sister (no. 12) angiomas on the lips and epistaxis.

So far, in only one of the two sisters with proven hepatic arteriovenous shunts are there signs of liver fibrosis.

Clinical features

INVOLVEMENT OF LIVER

The problem of liver involvement has been a matter of controversy ever since Osler wrote that 'angiomas have a curious relationship with affections of the liver'. It was apparent from his remarks that he had in mind the lesions which we call arterial vascular spiders. But gradually it became obvious that his curious relationship also applies to the hereditary type of teleangiectases.

Up to 1958 it was possible to collect 55 cases of hereditary haemorrhagic teleangiectasia from the literature in which hepatic involvement could be suspected. In only 15 cases, however, was the

diagnosis confirmed by either biopsy or necropsy. Angiography was not yet available. Five additional cases were added by the author including two a description of which had been previously published as cirrhosis hepatitis teleangiectatica (Martini, 1955; Martini, 1959). One of the cases would now be classified as belonging to the CRST-syndrome (Calcinosis - Raynaud - scleroderma - teleangiectasia: Reynolds *et al.*, 1971).

Since then a considerable number of additional cases have been reported. These observations are divided into three subgroups according to the type of involvement, as proposed by the author in 1955.

1. HHT with teleangiectases in the liver, with fibrosis and/or cirrhosis (Table)
2. HHT with cirrhosis and no teleangiectases (Beck and Magnenat, 1956; Neimann *et al.*, 1958; Fénelon *et al.*, 1961)
3. HHT with teleangiectases in the liver but without fibrosis or cirrhosis (Childers *et al.*, 1967; Condon *et al.*, 1967; Halpern *et al.*, 1968; Michaeli *et al.*, 1968; Paliard *et al.*, 1970; André *et al.*, 1971; Bacardi *et al.*, 1971; Razi *et al.*, 1971; De Keyser, 1972; Kinkhabwala *et al.*, 1972; Vildé *et al.*, 1972; Novak, 1974).

CLINICAL SYMPTOMS

Most of the observations of group 1 and 2 have several clinical symptoms and signs in common. The most frequent sign is nose-bleeding, which is the earliest sign even without visible teleangiectases. Nearly all patients have skin lesions with teleangiectases on the lips (68%), on the face (60%), on the tongue (54%), and/or finger-tips (30%); they appear at the end of the second and the beginning of the third decade and increase in number and intensity with age. In about 50% pains occur in the right upper abdominal region, often similar to biliary colic, but only rarely with gallstones. Anaemia is frequent. The liver is often enlarged up to 18 cm in the mid-clavicular line. The spleen is enlarged in about 50% of the patients. Some have portal hypertension with several episodes of bleeding, very few portocaval encephalopathy, one even without cirrhosis but with teleangiectases in the liver (Michaeli *et al.*, 1968). In the advanced age group cardiac failure is often mentioned, possibly as a consequence of a high output state due to arteriovenous shunting.

Liver function is well preserved in most of the cases. Increased alkaline phosphatase and slight bilirubinaemia, however, should be mentioned.

AGE AND SEX

The average age was 57 years; 24 women were

affected, and eight men. The preponderance of post-menopausal women is remarkable.

Pathological findings

There are several characteristic features which almost all cases of atypical cirrhosis have in common: cirrhosis is more often of the coarse nodular type, very often with thickening of the capsule and sub-capsular vascularity which, in one case (Boussier *et al.*, 1964), was demonstrated by angiography as a huge mass. The broad areas of fibrosis with irregular septa formation are conspicuous in the micro-sections of the liver in most of the cases. The fibrotic bands usually contain many teleangiectases of varying size. The connective tissue is frequently arranged in an intra-acinar fashion with epithelial sprouts similar to those of gall duct proliferation. In these connective tissue strands are enlarged cavities lined with endothelium frequently filled with blood. In some areas the connective tissue is infiltrated by collections of lymphocytes, histiocytes, and plasma cells. Some of the liver cell plates in the neighbourhood of fibrotic bands are disrupted by fibroblasts with early collagen deposition (Zelman, 1962) (Fig. 3).

Parenchymal lobules of varying size are carved out by the extending fibrosis; these carved-out lobules are reminiscent of pseudo-lobule formation in ordinary cirrhosis of the Laënnec type. Zelman's report of the morphological findings in one of his own observations is nearly identical with that of other authors and our own (Martini, 1959). These observations and those of several recent publications as listed in the Table seem to justify the recognition of a special type of fibrosis or cirrhosis in those cases in which no other causes are responsible—for example, alcohol or viral hepatitis. In two of the published cases alcohol may have influenced the development of cirrhosis.

Involvement of the liver can also occur as a purely vascular derangement without cirrhosis or with only slight fibrosis (group 3). Cavernous haemangiomas, hepatic artery aneurysms, and both hepatoportal and hepato-hepatic arteriovenous fistulas have been demonstrated by angiography and in two cases by beautiful corrosion casts (Trell *et al.*, 1972). These cases are recognised only when the liver is enlarged and when the search for even small vascular skin lesions is intensified, and when the family history is explored for such lesions, epistaxis, and/or other unexplained haemorrhagic manifestations. Every member of a HHT family should be repeatedly investigated, including auscultation of the liver and spleen and other suspect vascularised areas. The more angiography is applied systematically in

Table *Fibrosis and/or atypical cirrhosis with teleangiectases in liver*

Author	Age, sex	Morphological findings	Bruit	Angiography	Other findings
Angervall (1954)	71F	Liver: '... collections of connective tissue rather irregularly spread in parenchyma', regressive hepatic cells in connective tissue collections either separately or in small groups. Bile ducts strikingly wide; bile duct proliferations. Dilated blood vessels, some in angioma grouping	—	+	Fibrosis dyspnoea
Zelman (1962)	56M	Broad areas of fibrosis with teleangiectases. Atypical cirrhosis	—	—	Acute hepatitis
Boussier <i>et al.</i> (1964)	65F	Angioma and cirrhosis; teleangiectases in liver; steatosis	—	+	Alcoholism
André <i>et al.</i> (1971)	72F	Hypervascularization; aneurysm of the splenic artery. Arteriovenous shunts in jejunum	+	+	No portal hypertension. Epistaxis; haematemesis; splenomegaly. Congestive cirrhosis?
Guntz <i>et al.</i> (1971)	43F	Fine nodular cirrhosis with numerous vascular dilatations probably anastomoses between arteries and portal veins; steatosis	—	+	Oesophageal varices. Biliary colics
Trell <i>et al.</i> (1972)	49F	Nodular shape of liver; hepatoportal anastomoses; hepatohepatic anastomoses; hepatic nodules formed by helix-shaped vascular convolutes throughout liver with venous walls; 'fibrous stroma'	—	+	—
Feizi (1972)	82F	Macronodular cirrhosis with septa of varying width; only slight inflammatory infiltration; no piecemeal necrosis. Bile ductulus proliferation, widespread clusters of thin-walled blood vessels	—	+	Raynaud's phenomenon; CRST-syndrome?
Vissuzaine <i>et al.</i> (1974)	42F	Enlarged liver (14 cm). Dense fibrosis with vascular proliferation without cellular infiltration	+	+	Liver abscess. Biliary colics
Reynolds (1974)	39F	Two biopsies within three years, first no fibrosis. Enlarged nodular liver; marked fibrosis. Diffuse hepatic artery-hepatic venous shunting. Ascites. No varices	—	+	Development of fibrosis within three years
Sussman and Sternberg (1975)	69F	Numerous teleangiectases in liver; hepatoma in right lobe; satellite tumor nodules; fibrous septa around teleangiectases surrounding regenerating nodules constituted 'a form of cirrhosis'	+	+	Prachepatic coma. Long-term oestrogen treatment
Daly and Schiller (1976)	56M	Blood vessels on liver capsule	—	—	—
(1976)	73F	Coarse 2-8 cm nodules	—	—	—
(1976)	65M	Fine 1-4 mm nodules	—	—	—
Strohmeyer (1977)	52F	Teleangiectases in liver. Angioma, visualised at peritoneoscopy. Biopsy: Laënnec type of cirrhosis	—	—	Oesophageal varices. Portal hypertension. Biliary colic. No gallstones. Alcoholism

families with HHT, the more vascular malformations will be detected (Halpern, 1968). In this group both cardiac failure and peptic ulcer were frequently mentioned.

INVOLVEMENT OF LUNGS

It was only in 1948 that the close relationship of pulmonary arteriovenous fistula formation with HHT was recognised by Goldman. In the meantime about 15% of all cases with HHT were found to have pulmonary arteriovenous fistulas. These right-

to-left shunts can be suspected by the presence of cyanosis, clubbing of the fingers, and a bruit over the lung. There are, however, cases without any symptoms (Hodgson *et al.*, 1959). The radiological findings are round-shaped opacities, very often connected with greater vessels. Tomography and angiography are indispensable methods and will determine whether there is a fistula between one or more arterial branches with one or more veins. It may show a cavernomatous structure or consist of many smaller angiomatous fistulas.

Fig. 3 Liver cirrhosis in hereditary haemorrhagic teleangiectasia.

INVOLVEMENT OF INTESTINAL TRACT

The most life-threatening haemorrhages originate in the intestinal tract. The incidence of intestinal bleeding among all persons with HHT is about 15%. The lesions can be found in practically every part of the intestinal tract. Anaemia with positive occult blood in the stools, haematemesis, and melaena are the main complications. Endoscopy and angiography are the methods of choice for detecting the lesions (Jacobsen and Krause, 1970).

Treatment

The effect of oestrogen therapy is still debated (Moore *et al.*, 1976), but on the whole the long-term results are disappointing. In many cases operations with removal of the lesion is necessary; recently haemorrhage from intestinal lesions has been stopped by laser coagulation in two patients (Frühmorgen *et al.*, 1976).

Morphology of vascular lesion

The character of the vascular lesion of HHT is far from clear. It apparently involves all parts of the vascular system: the small arteries, capillaries, and venules.

Connolly (1954), under the guidance and with the

Fig. 4 Comparison between the schematically simplified modifications in the angioarchitecture of the examined vascular region (above) and the normal situation (below). Note the thick-walled draining veins supplied with longitudinal muscle bundles, the thin-walled ectasias, the increased ramification of the capillaries in the glomerulum digitale, and the localisation of blood clots. Schematic drawing after the reconstruction of the original lesion. (By kind permission of H. A. Connolly).

expert help of Staubesand, made reconstructions and an exact description of an Osler angioma which was excised from one of our patients whose history was published in 1955. It was compared with the lesions of two other patients of the same series and the findings were very similar (Staubesand, 1955). The method used was that of Staubesand and Andres (1953). It proved very successful in clarifying the structure of vascular arterial spiders (Martini and Staubesand, 1953). This tedious method required evaluation of more than 300 sections. Figure 4 shows the rather complicated structure of this type of angioma.

The real teleangiectases have no muscle elements and are therefore unable to contract. They consist of wide and thin-walled blood spaces which are empty and nowhere collapsed. The wall has only an intima lining. These vessels communicate with each other like a network.

The arterioles show some intima proliferation and, remarkably, some intra-arterial thrombi; they are otherwise quite normal. The most conspicuous findings are in the venules. They have longitudinal muscles and, attached outside, there is a thin, but almost closed, ring of muscle. These veins apparently play the leading part in regulating the circulation in the Osler vessels. Because of the development of strong longitudinal bundles the efferent veins are enabled to contract and lead to stasis in the teleangiectases. This might explain the presence of thrombi. These draining venules are vessels of blocking or throttling character. The duration and grade of their contraction might lead to stasis even back into the feeding artery and could unfavourably influence the conditions under which the walls of the dilated vascular regions function. Increased permeability could thus influence the surrounding connective tissue (Staubesand, 1955).

Electronmicroscopic studies confirmed that most of the affected vessels were small venules. In these venules flattened endothelial cells were junctioned by a defective overlapping of terminal villi of the extended cytoplasm. Affected venules thus showed many endothelial gaps which were 'stopped up' by thrombi: in addition, degeneration of the perivascular connective tissue including elastic fibres has been recognised as an important finding (Jahnke, 1970; Hashimoto and Pritzker, 1972). Thus, it appears that the pathogenesis of hereditary haemorrhagic telangiectasia comprises several factors.

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