Hepato-lienal fibrosis without cirrhosis: non-cirrhotic intrahepatic portal hypertension

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In 1933, John McMichael was awarded a gold medal by the University of Edinburgh for his M.D. thesis. This was entitled 'The pathology of hepatolienal fibrosis' and was published in an abridged form in 1934 in the *Journal of Pathology and Bacteriology*. It was a masterly account of the pathological changes associated with portal hypertension. Pathological changes in spleen and portal vasculature were identical whether or not cirrhosis was present. McMichael was particularly interested in the non-cirrhotic cases. In all of them a mild 'hepatitis' usually portal zone lesions, could be demonstrated. He speculated that it might be due to vasodilatation of the hepatic arteries or to spasm of the portal venules in the liver. These observations were at least 30 years ahead of their time. The newer techniques of intrasplenic and wedged hepatic venous pressure measurement, hepatic blood flow and splenic venography have only served to confirm McMichael's original observations (Fig. 1).

FIG. 1. Factors concerned in 'primary' portal hypertension.

The author would like to express her gratitude to J.McM. for launching her into the labyrinth of the portal venous system and for guiding her into its intricacies.

Portal zone lesions

In this group the portal hypertension is clearly pre-sinusoidal. The intrasplenic pressure is raised and the wedged hepatic venous pressure is normal; hepatic blood flow is also normal and the portal vein patent by venography.

In schistosomiasis the portal hypertension results from the ova causing a reaction in the minute portal venous radicles.

Congenital hepatic fibrosis consists histologically of broad, densely collagenous fibrous bands surrounding otherwise normal hepatic lobules (Kerr *et al.*, 1961). The bands contain large numbers of small, microscopic well-formed bile ducts, some of which may contain bile. Portal hypertension is common. Occasionally, this may be due to defects in the main portal vein. More often it is due to hypoplasia or fibrous compression of portal zone radicles in the fibrous bands surrounding the lobules. The portal hypertension is usually pre-sinusoidal. This is supported by the finding in one patient of a raised intrasplenic pressure with a normal wedged-hepatic-vein-pressure (Kerr *et al.*, 1961).

The portal hypertension sometimes complicating the myeloproliferative diseases may be the result of infiltration of the portal zones with primitive haematopoietic tissue. Portal hypertension has been reported with myelosclerosis and myeloid leukaemia. Patients with Hodgkin's disease or myelosclerosis may even bleed from radiologically-demonstrable oesophageal varices. Wedged-hepatic-vein-pressure is normal while intrasplenic pressure is increased (Shaldon & Sherlock, 1962). Observations of hepatic blood-flow have given divergent results. In one series hepatic blood-flow was normal (Shaldon & Sherlock, 1962). In another hepatic blood-flow was considerably increased in all four patients (Rosenbaum, Murphy & Swisher, 1966). These authors postulate that, in addition to portal zone obstruction, increased splenic blood-flow might be contributory. The pathological process in the liver might also reduce hepatic vascular distensibility so that the marked increase in blood-flow through the liver could not be fully accommodated without the development of portal hypertension.

In virus hepatitis, haemodynamic studies have shown that the intrasplenic pressure is raised while the wedged hepatic venous pressure is normal and suggested that the portal hypertension might be related to the portal zone lesion (Preisig *et al.*, 1966).

The portal hypertension developing in alcoholics with acute fatty infiltration of the liver may also be sinusoidal in type (Leevy *et al.*, 1958).

The role of increased splenic blood-flow

The possibility that portal hypertension might exist without mechanical obstruction to the portal venous system had been suggested by McMichael (1934). It had been related to increased flow through a large spleen (Tisdale, Klatskin & Glenn, 1959). Increases in hepatic blood-flow have been seen in Italian and French patients showing these features although, even in these instances, pre-sinusoidal resistance was found to be greatly increased (Patrassi, del Palu & Ruol, 1961; Benhamou *et al.*, 1963). This indicates some obstruction to portal flow. Similar instances have been reported from Uganda (Leather, 1961; Williams *et al.*, 1966). In part, the portal hypertension in these patients with 'idiopathic tropical splenomegaly' could be explained by the increased hepatic blood-flow consequent upon an increased splenic flow. In some there was also an increased pre-sinusoidal resistance which was difficult to explain and did not seem to correlate with hepatic histology. On splenic venography, however, secondary and subsequent branches of the portal vein within the liver seemed to be narrowed. Similar findings have been reported from Calcutta in patients with tropical splenomegaly (Boyer *et al.*, 1967).

In all patients with 'primary essential' portal hypertension there seems to be, in addition to the factor of increased hepatic blood-flow, some increase in intrahepatic resistance. This may well be an occlusive process in the intrahepatic portal venous system which may complicate all forms of portal hypertension. Further study of the liver biopsies from the Calcutta cases (Boyer *et al.*, 1967) and from those of Tisdale *et al.* (1959) have revealed sclerosis and sometimes obliteration of the intrahepatic portal vascular bed. In the portal hypertension associated with gross splenomegaly in the Sudan moderate or heavy sinusoidal lymphocytic infiltration has been seen which again might cause increase in intrahepatic resistance (Mustafa, 1965). This has been related to chronic malaria. Changes in the intrahepatic vascular bed have also been reported from the United States in patients with extrahepatic portal obstruction (Mikkelsen *et al.*,

1965). Hepatic biopsies showed subtle changes with distortion of the lobular architecture and sometimes thickening of the portal vein radicles. Phlebosclerosis of the extrahepatic portal vein was also seen. Thrombosis and intimal thickening in the whole portal system has also been reported from Hong Kong, not only in patients with massive splenomegaly but also in those with cirrhosis (Hou & McFadzean, 1965). McMichael (1931) made similar observations.

The mechanism of the portal-venous sclerotic change is uncertain. In some patients with massive splenomegaly it may be primary. In others it may be secondary to such conditions as myeloid metaplasia or chronic malaria. In those with splenomegaly it may be a response to the increased blood flow and would, of course, explain an increased pre-sinusoidal resistance. In other forms of portal hypertension it may be a response to the rise in pressure (Pei-Lin, 1940). A primary phlebosclerosis is also possible (Mikkelsen *et al.*, 1965).

The relation of this concept of increased splenic flow with secondary intrahepatic and extrahepatic portal venous sclerosis to the Banti syndrome remains uncertain. This may well be the sequence that Banti described originally. This first stage of splenomegaly gave rise to the second of portal hypertension. It is difficult, however, to know how Banti's *cirrhosis* could develop. In the light of present knowledge it is probably better not to use the term 'Banti syndrome' but rather to describe each patient in terms of both splanchnic haemodynamic findings and hepatic and portal venous morphology.

Post-sinusoidal non-cirrhotic portal hypertension

Two conditions can be considered in this group: partial nodular hyperplasia and the Budd-Chiari syndrome.

Partial nodular hyperplasia (Sherlock *et al.*, 1966)

The liver is not enlarged but up to two-thirds of the perihilar region is replaced by nodules. The periphery of the liver is normal or atrophic. The portal hypertension is presumably due to obstruction to hepatic blood-flow by the nodules. It is probably post-sinusoidal in type. This was confirmed by detailed circulatory studies in one patient (Sherlock *et al.*, 1966). Liver-cell function remains fairly good and duration of life is considerably longer than in cirrhosis. Diagnosis is difficult: it may be suggested by findings on wedge liver biopsy but confirmation must await autopsy. A normal needle-biopsy of the liver does not exclude the condition. The aetiology has not been established. It is a rare disease.

The Budd-Chiari syndrome

Occlusion of the hepatic veins is a rare condition usually caused by tumour or thrombus arising either locally or by extension from the inferior vena cava. The role of congenital lesions is disputed. The aetiology remains unknown in over two-thirds of patients.

Intrahepatic venous occlusion can follow the ingestion of certain alkaloids, particularly senecio (veno-occlusive disease). These are taken in herbal medicines, particularly in the West Indies, India and the Middle East. Plant toxins are probably important causes of hepatic injury.

Phlebitis of the centrizonal hepatic veins can also follow radiation applied to the liver and also the use of cytotoxic drugs such as urethane.

The condition should be suspected if a patient with a tendency to thrombosis or with malignant disease in or near the liver develops tender hepatomegaly with gross ascites.

Special radiological investigations (Clain *et al.*, 1967) are essential to confirm the diagnosis. Hepatic venography may fail or show narrow occluded hepatic veins. Adjacent veins show a tortuous, lace-like spider-web pattern. These probably represent abnormal venous collaterals. The catheter cannot be advanced the usual distance along the hepatic vein and wedging occurs 2–12 cm from the diaphragm. The features of a normal wedged venogram are absent. Inferior vena-cavography establishes the patency of the inferior vena cava. The hepatic segment of the vein may show side-to-side narrowing due to a large liver. Splenic venography may show a collateral circulation. Selective coeliac arteriography shows a small hepatic artery with branches of fine calibre.

Hepatic scintiscans are abnormal with poor uptake of isotope into the areas drained by the occluded hepatic vein. The caudate lobe may show good uptake.

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References

- BENHAMOU, J.-P., MAILLARD, J.N., RUEFF, B. & MICHON, H. (1963) Les fausses thromboses portales chez le cirrhotique. *Presse med.* **71**, 2358.
- BOYER, J.L., SEN GUPTA, K.P., BISWAS, S.K., PAL, N.C., BASU MALLICK, K.C., IBER, F.L. & BASU, A.K. (1967) Idiopathic portal hypertension. *Ann. intern. Med.* **66**, 41.
- CLAIN, D., FRESTON, J., KREEL, L. & SHERLOCK, S. (1967) Clinical diagnosis of the Budd-Chiari syndrome. A report of six cases. *Amer. J. Med.* **43**, 544.
- HOU, P.C. & MCFADZEAN, A.J.S. (1965) Thrombosis and intimal thickening in the portal system in cirrhosis of the liver. *J. Path. Bact.* **89**, 473.
- KERR, D.N.S., HARRISON, C.V., SHERLOCK, S. & MILNES WALKER, R. (1961) Congenital hepatic fibrosis. *Quart. J. Med.* **30**, 91.
- LEATHER, H.M. (1961) Portal hypertension and gross splenomegaly in Uganda. *Brit. med. J.* **1**, 15.
- LEEVEY, C.M., ZINKE, M., BABER, J. & CHEY, W.Y. (1958) Observations on the influence of medical therapy on portal hypertension in hepatic cirrhosis. *Ann. intern. Med.* **49**, 836.
- McMICHAEL, J. (1931) Local vascular changes in splenic anaemia. *Edinb. med. J.* **38**, 1.
- McMICHAEL, J. (1934) The pathology of hepatolienal fibrosis. *J. Path. Bact.* **39**, 481.
- MIKKELSON, W.P., EDMONDSON, H.A., PETERS, R.L., REDEKER, A.G. & REYNOLDS, T.B. (1965) Extra- and intra-hepatic portal hypertension without cirrhosis (hepatoportal sclerosis). *Ann. Surg.* **162**, 602.
- MUSTAFA, D. (1965) Gross splenomegaly in the Sudan. *J. trop. Med. Hyg.* **68**, 183.
- PATRASSI, G., DEL PALU, C. & RUOL, A. (1961) *La Pletora Portale*, p. 331. Roma.
- PEI-LIN LI (1940) Adaptation in veins to increased intravenous pressure, with special reference to the portal system and inferior vena cava. *J. Path. Bact.* **50**, 121.
- PREISIG, R., WILLIAMS, R., SWEETING, J. & BRADLEY, S.E. (1966) Changes in sulfobromophthalein transport and storage by the liver during viral hepatitis in man. *Amer. J. Med.* **40**, 170.
- ROSENBAUM, D.L., MURPHY, G.W. & SWISHER, S.N. (1966) Hemodynamic studies of the portal circulation in myeloid metaplasia. *Amer. J. Med.* **41**, 360.
- SHALDON, S. & SHERLOCK, S. (1962) Portal hypertension in the myeloproliferative syndrome and the reticuloses. *Amer. J. Med.* **32**, 758.
- SHERLOCK, S., FELDMAN, C.A., MORAN, B. & SCHEUER, P.J. (1966) Partial nodular transformation of the liver with portal hypertension. *Amer. J. Med.* **40**, 195.
- TISDALE, W.A., KLATSKIN, G. & GLENN, W.W.L. (1959) Portal hypertension and bleeding esophageal varices. *New Engl. J. Med.* **261**, 209.
- WILLIAMS, R., PARSONSON, A., SOMERS, K. & HAMILTON, P.J.S. (1966) Portal hypertension in tropical splenomegaly. *Lancet*, **i**, 329.

The management of the coronary crisis

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Until recently the death rate of patients admitted to hospital following an acute myocardial infarction was as high as 30%. The cause of death is not always clearly understood and in order to increase our knowledge and reduce the appalling mortality in this condition Sir John

McMichael in 1962 suggested making a detailed study of the haemodynamic and other changes taking place in such patients. Little work had previously been done in this direction as it had been considered that the patients were too ill to study in detail; in many cases treatment