Portal hypertension in kala-azar

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SUMMARY The present study records haemodynamic studies in three patients with kala-azar, a parasitic disease. All the three patients had high intrasplenic pressure, mild to moderate elevation of wedged hepatic vein pressure, and increased or normal estimated hepatic blood flow. Liver histology showed marked proliferation and swelling of Kupffer cells in the sinusoids. One patient was studied serially for nine months following treatment which showed persistent elevation of intrasplenic pressure though wedge pressure and liver blood flow touched normal levels. Liver biopsy was essentially normal at this stage. These findings may have some relevance to the role of different parasitic infections in the pathogenesis of a heterogeneous group of non-cirrhotic portal fibroses.

The occurrence of portal hypertension in conditions other than cirrhosis and extrahepatic portal vein obstruction is well documented. These include myeloproliferative disorders (Shaldon and Sherlock, 1962), infiltrative diseases (Rosenbaum, Murphy, and Swisher, 1966), hepatic steatosis (Chiandussi, Greco, Indovina, Cesano, Vaccarino, and Muratori, 1963), infective hepatitis (Preisig, Rankin, Sweeting, and Bradley, 1966), non-cirrhotic portal fibrosis (Datta, 1969), and schistosomiasis (Aufses, Schaffner, Rosenthal, and Herman, 1959). Portal hypertension has been demonstrated in these studies by measurement of intrasplenic pressure. Recently we have studied portal haemodynamics in three patients with kala-azar. Two of these presented with jaundice and ascites as a marked feature and posed initial diagnostic problems.

The present study shows that portal hypertension can occur in kala-azar. Follow-up studies in one patient for nine months revealed the persistence of portal hypertension although clinical, parasitic, and biochemical recovery was complete.

Material and Methods

Standard biochemical methods were employed (King and Wootton, 1956). Haemodynamic studies were undertaken before instituting specific therapy on an afebrile day after ascites had been controlled.

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In one patient (case 2), haemodynamic studies have been repeated at intervals after specific therapy.

The diagnosis of kala-azar was confirmed by demonstration of Leishman Donovan (L.D.) bodies in a bone marrow smear and a splenic aspirate in all the cases and in a liver biopsy in addition in one (case 3).

Hepatic vein catheterization was carried out in fasting patients premedicated with phenobarbitone sodium. Pressures were recorded through an end-hole Cournand catheter no. 7 using an eight-channel electronic recorder and Statham transducer. During the study right atrial, wedge, and free hepatic vein pressures were recorded. Hepatic blood flow was estimated according to the method of Caesar, Shaldon, Chiandussi, Guevara, and Sherlock (1961) using a constant infusion of indocyanine green. Measurements of intrasplenic pressure and splenoportography were carried out while doing splenic aspiration. All the pressures were recorded with a zero point 5 cm below the sternal angle with the patient lying in the supine position. A liver biopsy with Menghini's aspiration needle was obtained before the initiation of specific therapy. It could be repeated after specific therapy in one patient only (case 2).

Case Reports

CASE 1

M.S., a 25-year-old male, was admitted on 7 February 1968, complaining of a mass in the left hypochondrium, weakness, and irregular fever for six months. The mass was gradually increasing in size. Fever was

	Normal	Case 1	Case 2	Case 3
<i>Pressures in mm of Hg</i>				
Right atrial	2.8 ± 1.1	2	4.9	5.1
Wedge hepatic venous pressure	5.4 ± 1.8	12	19	17
Free hepatic venous pressure	3.1 ± 1.6	5	5	5
Corrected sinusoidal pressure	2.3 ± 1.1	7	14	12
Intrasplenic pressure	3-10	22	16	17
<i>Other parameters</i>				
Estimated hepatic blood flow (ml/min)	1351 ± 148	2570	1960	1090
Estimated hepatic blood flow (ml/min/m ²)	890 ± 100	1580	1560	680
Hepatic vascular resistance (dynes/cm ⁻⁵)	116 ± 30	120	414	880

Table *Haemodynamic studies before treatment*¹Mean ± SD of 13 control subjects

episodic, unaccompanied by chill or rigor. During the afebrile periods he was able to work. During the last two months of his illness he developed jaundice. On examination, he was moderately built, pale, icteric, and looked chronically ill. The skin showed scattered erythematous multiple nodular eruptions. The liver was enlarged by 7 cm, the spleen by 23 cm, and ascites was present.

Investigations revealed haemoglobin 8.0 g% total leucocyte count 3 200/c mm, and the erythro-

cyte sedimentation rate of 66 mm in the first hour. Stool and urine examination revealed no abnormality. Liver function tests showed total bilirubin of 5.4 mg % (conjugated 3.2 mg), total protein 8.56 g % (albumin 0.85 g and globulin 7.71 g with a marked increase in gamma globulin), the prothrombin time index was 61 %, and glutamic pyruvic transaminase (SGPT) 18 IU. A clinical diagnosis of chronic active hepatitis was made. However, in view of the history of irregular fever, he was also investigated for kala-azar. The aldehyde test was strongly positive and Leishman Donovan bodies were demonstrated in bone marrow and splenic smears. Because of the presentation of kala-azar with jaundice and marked ascites, the patient was investigated for portal hypertension. Radiological examination did not reveal oesophageal or gastric varices nor were any collaterals found on a splenovenogram. A haemodynamic study revealed raised intrasplenic and wedged hepatic vein pressures together with an increased estimated hepatic blood flow (Table I).

Liver biopsy showed focal areas of chronic granulomatous involvement of the hepatic parenchyma with mononuclear lymphocytes and plasma cells and marked hyperplasia and swelling of Kupffer cells in the sinusoids (Figs. 1 and 2). Evidence of hepatic fibrosis was lacking.

The patient was then treated with urea-stibamine (total 3 g) after which the fever subsided, the liver (2 cm) and splenic size (4 cm) regressed, haemoglobin improved to 12.0 g %, serum total bilirubin fell to 1.7 mg %, and other liver function tests showed improvement. A repeat bone marrow biopsy showed that L.D. bodies had disappeared. He was discharged as cured on 24 April 1968.

After three months, when he came for follow up in the outpatient department, he was found to be in good health but the spleen was still enlarged (2-3 cm) and the liver was just palpable. He did not permit repeat investigations.

Fig. 1 Section of the liver biopsy (H & E × 100) showing multiple granuloma in the hepatic parenchyma (case 1).

Fig. 2 High-power view (H & E $\times$ 400) showing aggregate of mononuclear histiocytes, lymphocytes, and stray polymorphs and plasma cells in the degenerated hepatic parenchyma. In the adjoining hepatic sinusoids the Kupffer cells are prominent (case 1).

Fig. 3 Section of the liver biopsy (H & E $\times$ 400) showing diffuse dilatation of hepatic sinusoids with hypertrophic prominent Kupffer cells. This feature was marked in all the three patients (case 2).

CASE 2

K.B., a 28-year-old male, was admitted for the first time on 11 November 1969 with weakness, abdominal discomfort, and low-grade fever for six months. The illness had started with a low-grade, irregular fever which was periodic. Physical examination revealed anaemia, hepatomegaly of 2 cm, and splenomegaly of 4 cm with detectable ascites. Investigations showed haemoglobin 8.0 g %, total leucocyte count 4 000/cmm with slight lymphocytosis. Total protein was 6.6 g % (albumin 2.3 g and globulin 4.3 g) and the prothrombin time index 100 %. The bone marrow was found to be hypocellular with relative erythroid hyperplasia with megaloblastic change. A liver biopsy showed Kupffer cell hyperplasia with dilated sinusoids (Fig. 3). A diagnosis of megaloblastic anaemia was made and he was treated with vitamin B₁₂ and folic acid. He showed considerable general improvement following therapy but fever and splenic

enlargement continued. He was discharged and advised to come for follow up after six weeks.

Two months later he reported again with progressive ascites and continued low-grade, irregular fever. Examination now revealed mild pedal oedema, marked ascites, jaundice, and an increase of hepatomegaly to 5 cm and splenomegaly to 13 cm. A clinical diagnosis of portal hypertension due to cirrhosis was entertained.

Investigations showed that haemoglobin was 9.0 g %, the total leucocyte count 3,500/c mm, and the erythrocyte sedimentation rate 64 mm in the first hour. Blood urea was 28 mg %. Stools and urine showed no abnormality. Liver function tests revealed serum total bilirubin to be 2.5 mg % (conjugated 1.5), albumin 2.3 %, globulin 4.6 g %, SGPT 16 IU/litre, the prothrombin time index 59 %, alkaline phosphatase 14 KA units, and bromsulphthalein (BSP) retention (45 min) 36 %. In view of the history of

irregular fever an aldehyde test was done which was strongly positive. Bone marrow and splenic smears showed L.D. bodies.

A barium meal showed coarsening of gastric mucosa and a splenovenogram a portal collateral (Fig. 4). A haemodynamic study showed high

Fig. 4 Splenic venogram of case 2 before therapy showing patent splenic (SV) and portal veins (PV). Note the prominent coronary vein (CV)

intrasplenic and wedged hepatic vein pressures, increased estimated hepatic blood flow, and moderate elevation of hepatic vascular resistance (see Table).

Histology of the liver showed marked Kupffer cell hyperplasia again, together with condensation of reticulin.

He was treated with two courses of sodium stibogluconate (total 5 g each) at an interval of one month. About two months later the spleen had

Fig. 5 Sequential alteration in intrasplenic pressure (ISP), wedged hepatic venous pressure (WHVP), estimated hepatic blood flow (EHBF), and hepatic vascular resistance (HVR) in case 2 (K.B.)

regressed to 5 cm and the liver to 1 cm with clinical improvement. The haemoglobin rose to 12 g%, serum bilirubin fell to 0.5 mg%, albumin rose to 3.3 g%, globulin fell to 3.2 g%, and BSP retention fell to 3%. Bone marrow and splenic smears showed no L.D. bodies. A repeat haemodynamic study showed persistence of high intrasplenic and wedged hepatic vein pressures (Fig. 5). Collaterals were seen to persist in the second splenovenogram.

About six months after treatment, when the patient continued to be asymptomatic, studies were repeated again. The spleen was still 5 cm below the costal margin but the liver was not palpable. Liver function tests were essentially normal. The intrasplenic pressure was still raised but wedged hepatic vein pressure and estimated hepatic blood flow had returned to normal. A splenovenogram visualized filling of the inferior mesenteric vein which was not seen earlier. A repeat liver biopsy was essentially normal. A fourth study nine months after treatment showed the findings to be the same.

CASE 3

M.L., a 42-year-old married man, was admitted on 18 November 1970 with the complaint of irregular fever for two months. The fever, associated with

chills and rigor, was periodic. He had been aware of the existence of a splenic mass for the same time. He was well built, not toxic, and had a splenomegaly of 5 cm, and the liver was not palpable.

Investigations revealed haemoglobin 11.0 g%, total leucocyte count 5 000/cmm (polymorphs 80%, lymphocytes 12%, monocytes 7%, and eosinophils 1%). Liver function tests showed no definite abnormality except lowering of the serum albumin (3 g%). A radiograph of the chest was normal. Blood and urine cultures did not show growth of any organism. The Widal test was negative.

A liver biopsy showed marked Kupffer cell hyperplasia in the sinusoids, sinusoidal dilatation, and L.D. bodies were demonstrated in abundance in these cells (Fig. 6). Bone marrow also showed L.D. bodies.

A barium meal showed no oesophageal or gastric varices. No collateral vessels were demonstrated in a splenoportogram. Haemodynamic studies revealed high intrasplenic and wedged hepatic vein pressure with moderate elevation of hepatic vascular resistance and normal estimated hepatic blood flow (see Table).

Fig. 6 Section of the liver (H & E $\times$ 1 000) showing marked Kupffer cells containing a large number of Leishman Donovan bodies (case 3).

He was treated with sodium stibogluconate (total dose 5 g) and showed clinical and biochemical improvement and was discharged with advice for follow up. The patient was readmitted after two months with a recurrence of fever. Clinical examination showed splenomegaly of 7 cm and hepatomegaly of 3 cm with minimal ascites. The results of repeat investigations were essentially the same, together with marked lowering of the serum albumin level (2.2 g%). Splenic aspirate showed L.D. bodies and intrasplenic pressure was 15 mm of mercury with, on this occasion, a small collateral demonstrated on the splenoportogram. The course of stibogluconate (5 g total) was repeated with clinical and biochemical improvement and parasitic cure.

Discussion

The present study has shown the occurrence of portal hypertension in three patients with kala-azar before specific therapy and its persistence in one patient when serially studied over nine months after clinical and parasitic cure. The results of haemodynamic investigations in the absence of any block in the portal vein on splenovenography suggest that at least two factors could be responsible for the portal hypertension demonstrated before treatment. First there was a considerable increase in liver blood flow in two patients (M.S. and K.B.) and secondly there was mild to moderate elevation of wedged hepatic vein pressure in all the three patients suggesting some increase in postsinusoidal or sinusoidal resistance. This resistance was probably due to marked proliferation and swelling of Kupffer cells in the sinusoids with or without Leishman Donovan bodies within the cells. The other evidence of increased sinusoidal resistance was apparent by the finding of marked dilatation of sinusoids. That sinusoidal infiltration alone in the presence of normal liver blood flow can be associated with portal hypertension was also evident in case 3. However, the contribution made by increased liver blood flow in the pathogenesis of portal hypertension in the other two patients (M.S., K.B.) cannot be ignored. The main cause of increased liver blood flow was most likely due to increased portal inflow because of a massively enlarged spleen in addition to some contribution made by a mild degree of anaemia.

The finding of persistently high intrasplenic pressure with collaterals and persistent splenomegaly in one patient even nine months after treatment leading to parasitic cure was noteworthy. Liver blood flow, wedged hepatic vein pressure, and liver histology had returned to normal. This combination of high intrasplenic pressure with no evidence of block in the main portal vein and normal wedge hepatic vein

pressure as well as normal liver blood flow suggested that some type of increased intrahepatic presinusoidal resistance might have set in, the nature of which remains obscure. The patient at this stage was indistinguishable as to clinical findings and haemodynamic observations from some of the patients grouped under the title of non-cirrhotic portal fibrosis (Indian Council of Medical Research, 1969) and tropical splenomegaly (Williams, Parsonson, Kris, and Hamilton, 1966). The question has been raised as to the role of parasitic infection in the aetiology of 'tropical splenomegaly' (Sherlock, 1970). In the absence of adequate parasitic investigations in the reported patients, coupled with the persistence of some foci of parasitic infection, the issue remains an open one. However, the present finding of persistent portal hypertension after clinical and parasitic cure may have some relevance to the role of different parasitic infections in the aetiology of portal hypertension without cirrhosis seen in different tropical countries. It will be recalled that the association of portal hypertension with other parasitic disorders such as schistosomiasis (Aufses *et al*, 1959) and malaria (Williams *et al*, 1968) is well known.

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