Progress report

Hepatosplenic schistosomiasis: a clinical review

Hepatosplenic schistosomiasis refers to the major complication of chronic infection with *Schistosoma mansoni*, *S japonicum* and *S mekongi*, schistosomal portal hypertension. Hepatosplenic schistosomiasis is usually, but not invariably, associated with enlargement of the liver and spleen, and reversible hepatosplenomegaly may occur in early infections not complicated by the development of portal hypertension. This paper broadly examines current knowledge concerning hepatosplenic schistosomiasis, emphasising clinical aspects. It draws on the author’s experience in East Africa,1 and is concerned mainly with schistosomiasis mansoni. Infection with *S japonicum* and *S mekongi*, both restricted to parts of the Far East, are not specifically discussed. Clinical aspects of hepatosplenic schistosomiasis cannot be considered distinct from the epidemiology, pathology and pathogenesis of the condition, and these are briefly reviewed.

Epidemiology

It has been estimated that over 200 million people worldwide harbour some form of schistosomal infection.2 Probably 100 million individuals suffer from schistosomiasis mansoni or japonica, of whom several million must have hepatosplenic disease. Warren suggests that 60% of Africans live in areas where transmission of schistosomiasis is possible, and that 40% of such people are infected.

The two major schistosome species affecting man in Africa are *S haematobium* and *S mansoni*. Chronic infection with *S haematobium* results in a variety of genitourinary problems, but there is no evidence that it causes liver disease.3 Infection with *S intercalatum* occurs particularly in Central and West Africa.4 This species of schistosome is of relatively high infectivity but low pathogenicity, although heavy infections have been associated with severe intestinal involvement and hepatosplenomegaly. *S haematobium* and *S intercalatum* are not further considered.

Hepatosplenic schistosomiasis in Africa results from infection with *S mansoni*. According to a recent review,2 transmission of *S mansoni* does not occur in Tunisia, Algeria, Morocco, Mauritania, Guinea-Bissau, Niger, the Congo Republic (Brazzaville), Somalia, and Mauritius. It is prevalent throughout much of the rest of Africa, although its distribution varies greatly within different regions, countries and even small districts. Such variations have a major impact on local patterns of disease, and problems of clinical diagnosis and management must be related to some understanding of medical geography. In unselected patients seen in Nairobi, hepatosplenic schistosomiasis was the cause of portal hypertension in one third of 85 patients with documented oesophageal varices.1
Schistosomiasis mansoni is also endemic in certain parts of South America, especially Brazil, and in a few islands of the Caribbean.²

Pathology

The original description of clay pipestem fibrosis by Symmers⁵ is still considered accurate, but the term cirrhosis is no longer used as nodular regeneration and diffuse distortion of hepatic lobular architecture are not features of hepatosplenic schistosomiasis. The liver is enlarged, although it may be of normal size or even small, and the surface in severe cases is irregular and bosselated. Sometimes the left lobe is disproportionately enlarged. Round or stellate white lesions are seen on the cut surface, the clay pipestem lesions described by Symmers, which result from massive portal fibrosis.⁵

On light microscopy, ova are seen in the portal and periportal regions, initially surrounded by eosinophilic granulomata. The portal tracts show varying amounts of fibrosis and generally contain an inflammatory infiltrate which often includes eosinophils. Schistosomal pigment may be present, resembling malarial haemozoin. The presence of pigment in the liver biopsy of an individual expected to have attained relative immunity to malaria should always raise the possibility of S mansoni infection. The liver parenchyma is normal and lobular architecture is essentially maintained.

A variety of subtle changes are frequently seen in tropical liver biopsies which in temperate areas would be considered abnormal. These include portal inflammation, mild stellate fibrosis emanating from the portal tracts, Kupffer cell hyperplasia and variation in the size and number of nuclei in parenchymal cells (‘parenchymal cell unrest’).⁶ These non-specific changes frequently accompany the pathological appearances of hepatosplenic schistosomiasis described above.

A study of vinylite casts of the intrahepatic vessels of cadavers with hepatosplenic schistosomiasis showed extensive destruction and distortion of small portal branches.⁷ Such lesions were especially marked in the periphery of the liver, and corresponding histological sections often showed occluded or apparently absent portal vein radicles. Arterial branches were increased in size and number, explaining the normal hepatic blood flow maintained in the majority of patients with hepatosplenic schistosomiasis.

The pathology of hepatosplenic schistosomiasis has been well reviewed by Cheever and Andrade,⁸ Warren,⁹ McCully et al,¹⁰ Edington and Gilles,¹¹ and Edington.¹²

Pathogenesis and relation to intensity of infection

There is agreement that obstruction to portal blood flow probably occurs at the level of smaller portal tracts, and that the macroscopic clay pipestem lesions are not themselves the cause of portal hypertension.⁷ ¹³ ¹⁴

Controversy surrounds the role of granulomata in causing chronic portal fibrosis. Warren¹⁵ firmly associates granulomatous reaction to eggs with the development of fibrosis and subsequent portal hypertension. Evidence against this are the observations that broad fibrosis may be seen distant from any granuloma,¹⁶ that in the absence of Symmer’s fibrosis ova do not always accumulate in portal areas even in heavily infected cases,³ and that
in experimentally infected chimpanzees fibrosis preceded egg deposition in the portal tracts. A further interesting observation is that excess collagen may be deposited independent of any granuloma in the space of Disse, producing fibrosis at the level of the sinusoids.

Genetic factors probably predispose certain individuals to developing hepatosplenic schistosomiasis. In Brazil, hepatosplenic schistosomiasis was found more frequently in whites than in blacks with similar levels of infection, and was also shown to be more common in patients of blood group A. A report from Egypt associated histocompatibility antigens (HLA) A1 and B5 with a greater likelihood of developing hepatosplenic schistosomiasis.

Intensity of infection appears to be the main variable determining the development of hepatosplenic schistosomiasis. Pathological studies in Brazil and Egypt showed that hepatosplenic schistosomiasis was present in patients with the heaviest worm loads. Epidemiological surveys in Brazil and St Lucia support this relationship between intensity of infection and clinical manifestations. In Kenya, in an essentially non-malarious village in Machakos District, prevalence and intensity of infection were high and intensity correlated with hepato- and splenomegaly. In a similar study on the malarious shores of Lake Victoria, however, where rates and levels of schistosomal infection were lower, an inverse relationship existed between infection intensity and splenomegaly. In another malarious area, the West Nile region of Uganda, prevalence and intensity of infection were high, and splenomegaly was common but not related to egg output. It was suggested in these latter studies that simultaneous stable malaria, itself associated with a high frequency of splenomegaly, might mask hepatosplenic schistosomiasis or depress the host response to schistosomal infection. The weakness of such epidemiological studies is that they assume that hepatosplenomegaly is schistosomal in origin, when in fact hepatosplenic schistosomiasis can only be diagnosed with certainty after detailed investigation.

It seems reasonable to conclude that frequency and severity of disease correlate with prevalence and intensity of infection, but all such generalisations apply to groups rather than to individuals, and other factors may play a significant role.

Clinical features

Hepatosplenic schistosomiasis affects both sexes and all age groups, including children. Patients are often young and usually look well, most frequently seeking medical attention for discomfort from splenomegaly or after an episode of upper gastrointestinal bleeding. Previous symptoms of intestinal schistosomiasis are often lacking, and in Nairobi less than one third of patients with histologically diagnosed hepatosplenic schistosomiasis gave a previous history of dysentery.

Splenomegaly in schistosomiasis is congestive in nature, a consequence of portal hypertension, but also results from reticulo-endothelial hyperplasia. Not every patient with schistosomal splenomegaly has established portal hypertension, and enlargement of the spleen is a well recognised feature of acute schistosomiasis ('Katayama fever'). In Nairobi, oesophageal varices could be demonstrated in 12 of 22 patients presenting with
chronic splenomegaly in whom liver biopsy showed significant schistosomal involvement and no other pathology. These two groups of patients with schistosomal splenomegaly did not differ in any other obvious way. The rest of this discussion concerns patients with established schistosomal portal hypertension.

In uncomplicated cases of hepatosplenic schistosomiasis features of liver cell failure are rare, so that stigmata of chronic liver disease usually associated with cirrhosis are lacking. Gynaecomastia, spider naevi, and palmar erythema (difficult, anyway, to see on black skin), jaundice, altered hair distribution, neuropsychiatric manifestations and a bleeding diathesis are not seen except in terminal disease.

The spleen may be visibly enlarged and sometimes fills much of the abdomen. It may result in ‘hypersplenism’ with pancytopenia detectable on a peripheral blood smear, but this is rarely of clinical significance. Anaemia is unusual but may result from occult gastrointestinal blood loss. The shortened red cell survival associated with splenomegaly is generally of minor importance. The spleen is firm and smooth to palpation, and when it is very large more than one notch may be evident. The liver is also usually enlarged, although not to the same degree as the spleen, and is abnormally firm.

Portal hypertension in hepatosplenic schistosomiasis is presinusoidal in type, so that splenic pulp and portal vein pressures are raised while wedged hepatic vein pressure is normal. Because liver function is well maintained, gastrointestinal bleeding is well tolerated in hepatosplenic schistosomiasis provided adequate resuscitative measures are instituted, unlike in cirrhosis where liver failure is often precipitated. The main danger of variceal haemorrhage in hepatosplenic schistosomiasis is exsanguination, a real possibility when medical facilities are limited and access to hospital is difficult.

It remains uncertain what exactly causes oesophageal varices to bleed. Portal hypertension is considered present when the portal vein pressure is raised to 5 mmHg above inferior vena caval pressure, when the intrasplicenic pressure is above 15 mmHg or when the portal vein pressure measured directly at surgery is above 30 cmH₂O. While portal hypertension is a prerequisite for the development of a collateral circulation, in cirrhosis risk of bleeding cannot be directly correlated with exact portal vein pressure, although haemorrhage is unlikely in cases where the portal vein pressure is less than 10 mmHg above inferior venal caval pressure. Large varices appear more likely to bleed than small ones, although above a critical diameter there is no relationship between bleeding risk and the size of oesophageal varices. Whether such observations apply also to hepatosplenic schistosomiasis has not been studied.

In Nairobi, 52% of patients with hepatosplenic schistosomiasis gave a previous history of haematemesis or melaena. As with other forms of presinusoidal portal hypertension, ascites is most often absent although its formation may be precipitated by gastrointestinal bleeding. Ascites was seen in about one-third of our patients with hepatosplenic schistosomiasis.

**Diagnosis**

Diagnosis requires understanding of the various causes of the related but
distinct clinical problems of chronic undiagnosed splenomegaly and portal hypertension in the tropics. The differential diagnosis of chronic splenomegaly in Africa is wide.\textsuperscript{34} Individual cases may result from causes common in industrialised, temperate areas, but the majority are related to the tropical environment. Tropical splenomegaly syndrome ('hyper-reactive malarial splenomegaly'),\textsuperscript{1,35} schistosomiasis, visceral leishmaniasis and, more rarely, trypanosomiasis, are important causes resulting from parasitic infections. Other conditions such as tuberculosis, brucellosis, and certain haemoglobinopathies are seen world wide but occur more frequently in tropical Africa. Non-schistosomal forms of portal hypertension such as cirrhosis and portal vein occlusion are also common, and idiopathic portal hypertension is probably more frequent than in the developed world.\textsuperscript{1}

Firm diagnosis requires proof of schistosomal infection, demonstration of portal hypertension and determination of its cause. Infection may be diagnosed parasitologically or immunologically. Faecal examination is best carried out using a concentration method such as the Kato technique,\textsuperscript{36} although in heavy infections ova may be readily detected in a single wet smear. In light infections examination of snips of rectal mucosa taken with a curette through a proctoscope is more sensitive.\textsuperscript{36} Material thus obtained is compressed between two glass slides and examined immediately under the low power lens of a light microscope. Quantification of egg excretion is of interest but not clinically important in individual cases. Paradoxically, patients with advanced hepatosplenic schistosomiasis may have low faecal egg counts, the result of previous treatment, senescence of worms, and, perhaps, shunting of ova to the lungs via the collateral circulation.

Serodiagnostic techniques in schistosomiasis have been reviewed by Smithers and Doenhoff.\textsuperscript{37} The enzyme linked immunosorbent assay (ELISA) has been the most successful immunodiagnostic technique for \textit{S mansoni} infection. While cheap, easy to do and highly sensitive,\textsuperscript{38} it lacks specificity.\textsuperscript{39} Cross reaction with \textit{S haematobium} infection occurs. In addition, in schistosomiasis, infection does not necessarily signify pathology, and serology is incapable of distinguishing between simple infections and hepatosplenic disease. In a study of splenomegaly and portal hypertension in Kenya, De Cock\textsuperscript{1} concluded that a negative ELISA reliably excluded hepatosplenic schistosomiasis but that a positive result in an endemic area gave no applicable diagnostic information. Serodiagnosis may become more specific in the future with the development of more highly purified antigens.\textsuperscript{40}

In patients with splenomegaly, diagnosis of portal hypertension can be made by the radiological or endoscopic demonstration of oesophageal varices. Barium swallow examinations are easy to carry out and interpret but less sensitive than upper gastrointestinal endoscopy. This latter investigation may sound unrealistically sophisticated in developing countries but is in fact easily applicable. In Kenya, Thomas \textit{et al}\textsuperscript{41} showed that endoscopy was cheaper and more reliable than barium studies for the diagnosis of oesophageal varices. Other African centres have published their experience with endoscopy\textsuperscript{42} and the technique, within the competence of any specialist physician after suitable training, could have significant impact. The initial cost of the instruments and their maintenance pose difficulty.
Measurement of portal vein pressure is of little clinical value. Demonstration that the portal vein is patent is required before the therapeutic creation of a portacaval shunt, and excludes portal vein occlusion as the cause of oesophageal varices. Splenoportovenography is a simple technique but may be complicated by haemorrhage. Superior mesenteric angiography with study of the venous phase is safer but requires angiographic facilities restricted to major referral centres. Ultrasound is a non-invasive technique that has recently been used to assess portal hypertension in hepatosplenic schistosomiasis. The investigation of portal hypertension is covered in standard texts.

Liver biopsy continues to play a central role in diagnosis. In endemic areas, the finding of ova in stool does not prove that portal hypertension is schistosomal in origin. Even liver biopsy may be misleading, because granulomata and haemozoin pigment may be frequent findings in apparently healthy individuals. Dusek et al have discussed difficulties of histological diagnosis of hepatosplenic schistosomiasis based on needle biopsy of the liver. Certain diagnosis of hepatosplenic schistosomiasis, rather than of simple infection, depends on observation of significant portal fibrosis.

**TREATMENT**

Treatment is aimed at eradicating schistosomal infection and dealing with the complications of portal hypertension. It is unlikely that established fibrosis can regress to any significant degree, but treatment of infection is important to prevent progression. As splenomegaly is not purely congestive, specific chemotherapy sometimes causes reduction in splenic enlargement.

**SPECIFIC CHEMOTHERAPY**

This has been reviewed recently by De Cock. The most familiar drugs are praziquantel, oxamniquine, hycanthone and niridazole.

Praziquantel is effective against all major schistosome species and is well tolerated in advanced disease. Two oral doses of 25–30 mg/kg at an interval of four hours are usually adequate treatment for *S mansoni* infection. Praziquantel damages the schistosome integument and interferes with inorganic ion transport and glucose metabolism. Side effects are rare and not serious. They include skin rash, fever, pruritus, abdominal discomfort, nausea, headache, and dizziness. This drug is currently the treatment of choice for all forms of schistosomiasis.

Oxamniquine is also well tolerated in advanced hepatosplenic schistosomiasis. The usual dose is 20 mg/kg/day orally for three consecutive days. The drug is effective only against *S mansoni*. Drowsiness, dizziness and headache are the major adverse effects, and orange discolouration of the urine sometimes occurs. Its mode of action is unknown. Currently, the use of oxamniquine and praziquantel may be severely limited in the developing world by their expense.

Hycanthone should be avoided in hepatosplenic schistosomiasis or other forms of liver disease because of occasional cases of fulminant hepatic failure. Reports of mutagenicity also cause concern. Nevertheless, in simple infections the drug continues to be used with the approval of expert consultative groups. Problems should be exceptional with a reduced
dosage of 1.5 mg/kg body weight, given once only by intramuscular injection.

Niridazole should no longer be used in view of its high frequency of side effects. Neuropsychiatric disturbances may occur when the unmetabolised drug reaches the brain, as in the presence of portasystemic collaterals.

MANAGEMENT OF PORTAL HYPERTENSION

Two related problems require consideration, the management of acute variceal haemorrhage and long term measures to prevent recurrent bleeding. Variceal haemorrhage has been the subject of a recent international symposium.\(^4^6\) The continued discussion about modalities of treatment that have been in use for many years emphasises the therapeutic uncertainties that surround this field.

Patients should be managed at as intense a level of care as possible. Early efforts are directed at assessment of the patient, estimation of blood volume depletion and resuscitation. If possible, emergency endoscopy should be done to determine that bleeding is variceal in origin. Blood is transfused as required to maintain cardiac output and a stable haematocrit. Vasopressin infusion acts to constrict splanchnic arterioles thus reducing portal blood flow. Its long acting analogue, glypressin, may be more effective.\(^4^7\) The simultaneous administration of nitroglycerin has recently been shown to enhance the effects of vasopressin and to reduce is side effects.\(^4^8\) Oesophageal balloon tamponade using the Sengstaken-Blakemore tube or the Linton-Nachlas tube may give useful temporary control of bleeding. This dramatic medical emergency can stretch the resources and skills of even the best equipped institutions, and may overwhelm available facilities in many endemic areas.

Long term intervention to prevent further haemorrhage may be surgical, endoscopic, or pharmacological. Portal decompression by the surgical creation of a portacaval shunt is effective in preventing further bleeding, but is complicated by a high rate of hepatic encephalopathy.\(^4^9\) This is disappointing as well as somewhat difficult to explain in view of the well maintained liver function in most cases of hepatosplenic schistosomiasis. It presumably results from reduction in hepatic blood flow with deprivation of hepatotrophic factors contained in portal blood. Exhaustive review of the different procedures possible is beyond the scope of this paper, but Raia and colleagues\(^5^0\) \(^5^1\) have suggested that the distal splenorenal shunt, in which hepatic blood flow is better maintained, results in a lower rate of encephalopathy. This procedure also lessens the risk of egg embolisation to the lungs associated with the traditional portacaval shunt. Long term results in cirrhosis have generally failed to show marked benefit from choosing the distal splenorenal rather than the traditional portacaval shunt. For the time being, therefore, it seems premature to unhesitatingly recommend this more difficult operation.

Splenectomy alone does not affect portal hypertension, and even when combined with gastro-oesophageal devascularisation is associated with a high rate of rebleeding. Oesophageal transection using a stapling gun\(^5^2\) is a temporising measure which is often followed by further bleeding when varices redevelop. It is, however, a simpler operation than a shunt and may be life saving when medical treatment is failing in acute haemorrhage.

Endoscopic sclerotherapy is becoming the favoured treatment for
oesophageal varices. Although technically difficult when bleeding is active, sclerotherapy can stop acute haemorrhage and lower the incidence of rebleeding, and in the long term it reduces bleeding risk and may improve survival. Most workers use a flexible endoscope, although many technical details remain controversial, such as the frequency of injections, the choice and volume of sclerosant and whether injections should be intra- or paravariceal. Any trained endoscopist should be able to learn the technique, and little equipment is needed over and above the endoscope, the light source and the needle for injection. Encouraging results have been published of two Egyptian controlled trials of sclerotherapy,\textsuperscript{57 58} in which a large number of patients with hepatosplenic schistosomiasis were included, and one uncontrolled study.\textsuperscript{59} There is no role for prophylactic surgery in the management of portal hypertension, but whether prophylactic sclerotherapy should ever be considered deserves further study.\textsuperscript{60}

Great interest was stimulated by work from France\textsuperscript{61} showing that beta adrenergic blockade reduced portal pressure and the frequency of variceal haemorrhage. The remarkable results with propranolol achieved by Lebrec and colleagues\textsuperscript{61} have not been reproduced by others,\textsuperscript{62} but work in this area continues. Patient selection may be one cause of discrepant results. The French subjects were predominantly suffering from alcoholic cirrhosis and were in good condition. Beta blockade has not been formally studied in hepatosplenic schistosomiasis. Because in this condition the vascular problem of portal hypertension can be examined distinct from the often confusing issue of liver cell failure, hepatosplenic schistosomiasis would be an ideal model in which to study this pharmacological approach to portal hypertension. For the time being, the use of beta adrenergic blockade for the prevention of variceal haemorrhage is best restricted to controlled clinical trials.

Complications and associations

DECOMPENSATED HEPATOSPLENIC SCHISTOSOMIASIS

Endstage hepatosplenic schistosomiasis may be complicated by features of hepatocellular failure, ascites often being the most obvious clinical sign. While this may all result from severe schistosomiasis, the possibility of other coexistent liver disease must be remembered. In Nairobi,\textsuperscript{1} two of 25 patients considered to have schistosomal portal hypertension also had histological evidence of cirrhosis. Areas endemic for schistosomiasis have a high prevalence of hepatitis B virus (HBV) infection. Work from Brazil\textsuperscript{63} and from Egypt\textsuperscript{64} suggests that HBV infection may be more frequent in patients with hepatosplenic schistosomiasis than in controls, and that patients with hepatosplenic schistosomiasis who have chronic HBV infection develop more severe liver disease. Presumably their basic disease is made worse, in addition to which they may develop chronic active hepatitis or cirrhosis. This possible association between HBV infection and hepatosplenic schistosomiasis deserves further attention.

RENAL INVOLVEMENT, SALMONELLOSIS

Proteinuria has frequently been noted in hepatosplenic schistosomiasis, and nephropathy associated with hepatosplenic schistosomiasis has been histologically documented both in man and in experimental animals.\textsuperscript{65 66}
Although studies are few, clinically significant renal disease is probably uncommon in hepatosplenic schistosomiasis.

An association also exists between chronic salmonellosis and schistosomiasis. The bacteria may be harboured by the parasite itself, and antischistosomal chemotherapy may have to be given for antibiotics to be effective in eradicating the bacterial infection. Salmonellosis seems particularly associated with cases of hepatosplenic schistosomiasis where nephropathy is also present, and it is possible that the bacterial infection alters the clinicopathological course of the renal lesions.

Conclusions

Although hepatosplenic schistosomiasis affects only a small proportion of all those with schistosomal infection, study of the condition is appropriate because it is patients with hepatosplenic schistosomiasis who make the greatest demands on medical facilities. As a disease of the liver, hepatosplenic schistosomiasis has been neglected by academic hepatologists, although its study could increase understanding of many aspects of liver disease. Portal hypertension, and recent non-surgical therapeutic approaches, can be examined uncomplicated by liver cell failure. The question of HBV infection in hepatosplenic schistosomiasis requires clarification. Hepatosplenic schistosomiasis is of interest to clinical immunologists, and allows study of hepatic fibrogenesis. Not least, it deserves attention because it is one of the world’s most prevalent forms of liver disease.

The prognosis of the rural African patient with hepatosplenic schistosomiasis is uncertain. Variceal haemorrhage in a small Third World hospital is a formidable challenge. It is to be hoped that clinical research in the management of these patients will be encouraged in tropical institutions.

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