TROPICAL GASTROINTESTINAL DISEASE: HEPATOSPLENIC SCHISTOSOMIASIS – PATHOLOGICAL, CLINICAL AND TREATMENT REVIEW

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ABSTRACT

S. mansoni and S. japonicum complex schistosomes cause hepatosplenic and hepatointestinal schistosomiasis. The prevalence and incidence of this disease is increasing in all the endemic areas. Hepatosplenic schistosomiasis is seen in a small subset of clinically infected patients and represents a good model of intrahepatic portal hypertension characterised by a presinusoidal portal block and a well preserved liver parenchyma.

Symmers' fibrosis is seen in a significant proportion of patients with high worm load. While the pathogenesis of Symmers' pipe stem fibrosis has not been well established, experimental and clinical data point to egg induced granulomata.

The main consequences are presinusoidal portal hypertension, oesophageal varices and hepatosplenomegaly. The most striking symptoms are haematemesis or melena secondary to variceal and gastrointestinal bleeding.

Cofactors associated with the pathogenesis include aflatoxins, malnutrition, alcoholism, hepatitis B and C virus.

While stool examination is the best technique for diagnosis, a number of immunological tests though sensitive are not specific. Ultrasonography is sensitive for detection of Symmer's fibrosis.

Praziquantel and oxaminiquine are drugs found to be effective in the treatment of hepatosplenic schistosomiasis. Recently beta-blockers have been found to be effective in the treatment of gastrointestinal rebleeding. Endoscopic sclerotherapy has been found to be effective for treatment of bleeding oesophageal varices. The treatment of choice for portal hypertension is oesophagogastric devascularization with splenectomy (EGDS).

Keywords: *hepatosplenic schistosomiasis, pathology, clinical aspects, treatment*

INTRODUCTION

Schistosomiasis is a chronic debilitating disease complex caused by any one of the blood flukes namely *Schistosoma mansoni, S. japonicum, S. mekongi* and *S. malayensis* which causes intestinal schistosomiasis and *S. haematobium* which causes urinary schistosomiasis. The illness maybe acute or chronic with slow progression reflecting the host response to the continuing intravascular deposition of eggs and to the continued elaboration of excretions by the worms. Hepatosplenic schistosomiasis refers to a major complication of chronic intestinal schistosomiasis. This condition is usually associated with hepatosplenomegaly and is the commonest cause of portal hypertension worldwide and has caused death from gastrointestinal bleeding in Egypt[1]. The pathogenesis and pathology of human *S. japonicum* infection is less well defined than the pathology of *S. mansoni* infection and descriptions of *schistosomiasis japonica* often base assumption on *schistosomiasis mansoni*. The paper reviews the current literature available on hepatosplenic schistosomiasis emphasising the epidemiology, pathogenesis, pathology and clinical aspects with special reference to *S. mansoni* and the *S. japonicum* complex of schistosomes.

EPIDEMIOLOGY

It is estimated that over 250 million people in 76 countries throughout the world are affected by schistosomiasis especially children and young people. The global distribution of schistosomiasis is determined by the distribution of snails appropriate as intermediate hosts, the pattern of discharge into fresh water of eggs containing faeces or urine and the water contact habits of people. Laughlin[2] estimated that 1.5 billion human beings live in endemic areas, while the World Health Organisation (WHO) quotes 600 million people who are in constant threat of acquiring this protean diseas [3,4]. Out of this, 5% of the world's population reside in S. japonicum endemic areas[5]. The mortality and morbidity rates due to schistosomiasis are between 500-1,000/year and 20,000/year[6]. From these data, it is obvious that this man-made disease is increasing in frequency of occurrence as irrigation schemes and man-made lakes are developed in tropical regions. Schistosomiasis, thus, is one of the most threatening parasitic diseases of warm countries and ranks eleventh in terms of world's major disease prevalence.

Hepatosplenic schistosomiasis in the Asian region is caused mainly by *S. japonicum* which exists as four distinct strains and closely follows the distribution of *Oncomelania* snails. The endemic areas stretch from the Tone River basin in Japan to Lake Lindu in Central Sulawesi. China has the largest endemic area. In Japan, the disease is endemic in five areas in two of Japan's five islands. In the Philippines, six of the thirteen main islands are endemic for *S. japonicum* and 16.5% of the population is believed to be infected[1]. A 50% prevalence rate has been recorded in the Lake Lindu and Napu Valley in Central Sulawesi, western Indonesia. New endemic foci have been discovered in Laos, Kampuchea and Thailand and associated with a new schistosome species named *S. mekongi*[8] with *Tricula aperta* as the snail host. Similarly, in Peninsular Malaysia, a new species existing as two separate strains (*Baling & Koyan*) identified as *S. malayensis*[9] with *Robertsiella* species as snail intermediate hosts were discovered recently. While the morphological features

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of the newly found species are characteristically similar in certain ways, the pathological changes induced both in human and animal hosts are no different from *S. japonicum* and hence are placed within the *S. japonicum* complex of schistosomes.

Pathogenesis and pathology of hepatosplenic schistosomiasis

S. japonicum -- complex of schistosomes and *S. mansoni* are usually located in the mesenteric and portal veins. The paired adult worms migrate to the smaller mesenteric venules of the intestinal mucosa where oviposition takes place. Frequently, eggs and adult worms are carried into the hepatic portal veins to be retained within the portal and periportal regions. It takes approximately 10 days for the schistosome eggs with the intact miracidia trapped within tissue to mature. Between 2-3 weeks, several proteolytic enzymes and antigenic materials are released which induce host sensitisation. The frequency and intensity of hepatic damage in schistosomiasis mansoni and japonica varies not only among individuals but also geographically. It has been estimated that only about 10% of patients with proven infection develop severe hepatosplenic schistosomiasis.

The basic pathological lesion is a granulomatous response surrounding the eggs (pseudotubercles) deposited in the tissues and stimulated by egg-derived antigen including immune-complexes released into the tissue. The granulomas contain lymphocytes, plasma cells, macrophages and their derivatives such as epitheloid and multinucleated giant cells, granulocytes especially eosinophils and fibroblasts. The relative proportion and organisation of these cells vary not only with the species of host and parasite but also with respect to the type of tissue in which the granulomas form as well as the immunological status of host. Accumulated granulomata are later followed by a strong fibrotic response in the affected tissue chiefly in the liver and bowel. Immunopathogenesis of the granuloma is related to a subpopulation of specific suppressor T lymphocytes in schistosomiasis mansoni while in schistosomiasis japonica it is thought to be related to antibody-mediated inflammatory response. Granulomatous reactivity is sometimes modulated in chronic infections, an effect that may be due to suppressor T cell activity and antibody-mediated blockade.

The transition from granuloma formation to fibrous tissue deposition marks the establishment of the permanent fibro-obstructive lesions. The hepatic fibrosis results as a consequence of a reparative process after cell necrosis and further parenchymal collapse and/or when the equilibrium between collagen synthesis and degradation is disturbed[10]. The liver parenchyma is normal and lobular architecture is essentially without any changes though widening of portal triads, fibrosis and numerous capillaries in the fibrous portal tissues have been observed in pure *S. japonicum* infections. Marked destruction and distortion of small portal branches, especially in the periphery of the liver, have been observed[11]. Corresponding histological section often show occlusion or apparently absent portal vein radicles. The arterial branches increase in size and number, explaining that normal hepatic blood flow is maintained in the majority of patients with hepatosplenic schistosomiasis.

The intensity of infection, the number of worms and quantum of eggs in tissues and excretions correlate closely, both clinically and pathologically in hepatosplenic schistosomiasis. Although a direct relationship between the number of eggs and the amount of fibrosis has been reported[12], individual host reaction to the parasite may regulate the severity of the fibrotic response[13,14]. In liver biopsies, portal inflammation, mild stellate fibrosis emanating from the portal tracts, Kupffer cell hyperplasia and variation in the number and size of nuclei in parenchymal cells have been observed[15]. In the spleen, hyperplasia of reticular

tissue is followed by diffuse fibrosis. Portal hypertension follows with marked congestive splenomegaly and development of portal-systemic collateral circulation, as accompanied by oesophageal varices without any impairment of liver function.

The mechanisms leading to the development of hepatosplenic schistosomiasis is yet to be understood. Andrade[12] had shown a peculiar pattern of vascular intrahepatic lesions which depends on two mechanisms: egg embolism with a partial blocking of portal vasculature and appearance of small portal collaterals along the intra-hepatic portal systems. The arrival of these eggs into these thin and anastomosing blood vessels leads to vascular obstruction and periportal fibrosis. In chronic cases, a thin septal fibrosis that dissects the parenchyma in several directions has been observed. In hepatosplenic schistosomiasis presinusoidal block to liver blood flow with a high portal pressure has been confirmed[16].

Sulit et al[17] conducted excellent studies on schistosomiasis japonica and associated the problem with portal hypertension. Their study showed the clinical picture of hepatosplenic schistosomiasis japonica to be similar to that of schistosomiasis mansoni. In Nairobi, hepatosplenic schistosomiasis was the cause of portal hypertension in one-third of 85 patients with documented oesophageal varices[18].

In endemic areas, schistosome infection may coincide with any form of liver disease and morbidity is primarily due to schistosomal pipe-stem fibrosis (PSF) of liver (Symmer's clay pipe stem fibrosis)[19]. This form of extensive periportal and perilobular fibrosis has been most often seen in human infections with *S. mansoni* and *S. japonicum*[20]. Portal fibrosis was correlated with heavy egg deposition in the portal triads and intra-hepatic portal radicles, accompanied by granulomatous as well as diffuse inflammation.

The development of Symmer's periportal fibrosis is the most important complication of intestinal schistosomiasis because it leads to the formation of esophageal varices and other associated complications. In Symmer's fibrosis, varying degrees of inflammation and collagen deposition surround the portal vein and its tributaries. In the most florid cases, there is virtual replacement of the portal system.

Whether clay-pipe stem fibrosis causes portal hypertension or the clinical state of patient is a subject for discussion. In approximately 100 autopsied cases of portal hypertension caused by schistosomiasis, all had pipe stem fibrosis of the liver and no patient with schistosomiasis and without pipe stem fibrosis had portal hypertension not explained by other lesions[21]. Andrade and Cheever[11] thus conclude that pipe-stem fibrosis and the vascular lesions causing portal hypertension are intimately related and suggest that granulomatous endophlebitis could be responsible for portal hypertension. Others are of the opinion that clay-pipe stem lesions are not themselves the cause of portal hypertension[19,22].

Controversy surrounds the role of granulomata in causing chronic portal fibrosis. Warren[23] is of the opinion that granulomatous inflammation around the eggs and subsequent fibrotic reaction are enough to cause portal hypertension. Evidences against this theory is the observation that fibrosis were seen distant from granulomas[12], in the absence of Symmer's pipe stem fibrosis. ova do not always accumulate in portal tracts in heavily infected cases[1] and that fibrosis preceded egg deposition in portal tracts in experimentally infected chimpanzees[24]. Another interesting feature observed is the excessive deposition of collagen independent of any granuloma in the space of Disse, producing fibrosis at the sinusoidal level[25].

The lack of major hepatocellular damage and the relatively good preservation of liver function in human schistosomiasis

led to the search for an alternate explanation for the development of fibrosis. Wyler et al[26] showed that extracts of isolated egg granulomata from livers of experimental *S. mansoni* mice stimulated in vitro proliferation of fibroblasts. This finding strongly suggests an association between direct action of granulomatous complex in induction of fibrosis. Recently, Rodrigues and Galle[27] showed the inflammatory processes that develop during advanced stages of hepatic schistosomiasis mansoni to be related to accumulations of siderosomes, capacity of the ferrous/ferric ions to unleash the formation of free radicals, peroxidation of membrane lipids and reduction of stability of membranes of several components of the hepatic lysosomal compartment. While more work need to be carried out to elucidate the pathogenesis of schistosomiasis, other factors have been recently suggested.

In endemic areas, repeated infection are very often associated with other cofactors which include protein deficient diets, alcohol, aflatoxin and hepatitis B and C virus. Biempica et al[28] demonstrated more severe parenchymal damage in cases of schistosomiasis associated with chronic hepatitis. Recently, evidence has accumulated to indicate that hepatic lesions are more severe in patients with hepatosplenic schistosomiasis and hepatitis B virus (HBV) than in those with isolated HBV[29-33].

The role played by this infection in raising morbidity of schistosomiasis is increasing. Patients who are carriers of hepatitis B antigen present with more clinical signs of chronic liver disease (cirrhosis) and inflammation of the portal spaces than in those with severe hepatosplenic schistosomiasis mansoni when compared to controls. El-Raziky et al[34] found HBsAg, anti-HBs and HBV exposure rate significantly higher in *S. mansoni* patients than controls and that HBsAg positivity rate was not significantly different between those with active and inactive infections. Li[35] and Li et al[36] detected HBsAg and HBcAg in liver biopsies in patients with schistosomiasis japonica complicated by hepatocellular carcinoma and concluded that HBV infection may be one of the major causes of hepatocellular carcinoma in these patients. Uemura et al[37] suggested a causative association between HCV infection and hepatocellular carcinoma. On the otherhand, Domingo et al[38] found that increasing intensity of *S. japonicum* infection was not associated with either decreasing or increasing HBV exposure and HBsAg positivity. They further postulated that HBV infection does not contribute to the production of hepatosplenic schistosomiasis japonica mainly because HBV infection occurs at a much earlier age than infection with *S. japonicum*. Madiwar et al[39] are of the opinion that the higher frequency of hepatitis B virus markers in hepatosplenic form as compared to hepatointestinal form is due to therapeutic measures in patients who seek medical care. On the other hand, Ghaffar et al[40] proposed that acute viral hepatitis frequently converts uncomplicated intestinal schistosomiasis to hepatosplenic schistosomiasis. Community based studies have not been able to demonstrate an increased risk for HBV in those with schistosomiasis mansoni or japonica[36,41]. Eltoum et al[42] affirmatively showed that in an endemic area there was no association between HBV infection and schistosomiasis, with or without periportal fibrosis. The association between HBV infection and hepatosplenic schistosomiasis japonica and mansoni warrants further investigation.

Genetic factors, such as between both histocompatibility antigen type HLA-A1 and B5 antigens, have also been associated with hepatosplenic mansonic schistosomiasis[43-47]. This condition was found more frequently in whites than in blacks having similar infection dose in a study in Brazil[44] and with blood group A[45]. Cabello et al[48] found no apparent correlation between chronic form of schistosomiasis and the expression of antigen. However,

this group found an association of histocompatibility antigen with splenomegaly to be consistent and significant only for HLA-B5 and not HLA-A1. Hafez et al[49] suggest that schistosomiasis can affect any person without predilection or association with HLA antigens. The same group investigating host factors that might influence the development of schistosomal hepatic fibrosis concluded that the low responsiveness to schistosomal antigen is probably controlled by an HLA-linked Is-gene via the suppressor T cell that prevents the individual from developing post-schistosomal hepatic fibrosis. They attribute the high responsiveness to schistosomal antigen to inherited HLA-linked Ir-gene and/or lack of an HLA-linked Is-gene in the homozygous state, predisposing to post-schistosomal hepatic fibrosis. Similarly, Sasazuki et al[50] found an association between B12-DEn and hepatic cirrhosis due to *S. japonicum*.

The production of cytokines such as tumour necrosis factor alpha (TNF-alpha) is a key event in inflammation of human infectious disease and malignancy. Monocytes that are the potent producers of TNF-alpha has been found to be the factors contributing to the progression of hepatosplenic schistosomiasis[51]. Amiri et al[52] showed that schistosome worms require TNF-alpha for egg laying and for excretion of eggs from the host. They implied that the parasite has adapted successfully to its host and uses a host derived immunoregulatory protein as a signal for replication and transmission.

CLINICAL FEATURES

The hepatosplenic schistosomiasis (HSS) is divided into compensated (uncomplicated) and decompensated (complicated) forms. In the decompensated form, the signs and symptoms of chronic liver disease are not uncommon and is characterised by muscular wasting, low serum albumin and occasionally chronic ascites, the most obvious clinical sign. In patients with compensated HSS, the hepatic parenchyma is normal and ammonia levels in these patients remain within normal limits even during episodes of repeated haematemesis[53]. Anaemia with delayed somatic and sexual development is often observed in young people. This may result from occult gastrointestinal blood loss and hypersplenism. Gynaecomastia, spidex nevi, palmer erythema jaundice, altered hair distribution, neuropsychiatric manifestations and a bleeding diathesis are rare in uncomplicated schistosomiasis[54].

The main presenting symptom of HSS is congestive splenomegaly and haemorrhage. Spontaneous ascites appears usually after bleeding episodes or infection or in association with other liver lesions. The spleen is firm and smooth to palpation, and when it is large, more than one notch may be evident[18]. In some instances the lower border reaches the iliac crest.

A hard enlarged liver with a predominant increase of the left lobe is usually palpable. Leucopenia, pancytopenia and thrombocytopenia are a common feature of HSS. Electrophoresis of serum proteins obtained from patients with high worm load may show an intermediate fraction between beta and gamma globulins[55]. In HSS, the clotting defects are due to impaired rate of protein synthesis by the liver and localised consumption coagulopathy or both[55]. However, the role of these two factors is yet to be established.

The portal hypertension in HSS is of presinusoidal type with splenic pulp and portal vein pressures being raised while the wedge hepatic vein pressure remains normal. Portal hypertension is considered elevated when the portal vein pressure is raised to 5mm Hg above the inferior vena caval pressure, when the intrasplenic pressure is above 15mm Hg or when the portal vein pressure measured directly at surgery is above 30cm H_2O[56]. The contention that large varices appear more likely to bleed than

small ones was disputed by Lebrac et al[57] who are of the opinion that there is no relationship between bleeding risk and size of oesophageal varices. Whether these observations are seen in HSS has not been studied.

Patients infected with schistosomes may develop a clinical picture of chronic salmonellosis[58]. The schistosomes share a symbiotic relationship and behave as reservoirs of bacteria and can cause bacterial discharges followed by a long carrying period. It has also been found that *S. mansoni* infection alters phagocytosis and intracellular destruction of *Salmonella*.

DIAGNOSIS

Epidemiological and clinical data of patients with hepatosplenic schistosomiasis from endemic areas are important considerations for assessment. Aetiological diagnosis can only be confirmed by the demonstration of characteristic eggs in the stool using the Kato-Katz's technique with the hatching test. In light infections, rectal mucosal snips taken with a currette through a protoscope is sensitive. Squash preparations of biopsy materials can be examined between two slides immediately for embryonated and calcified eggs under a microscope. Endoscopic biopsy and wet mount preparation maybe useful when stool examination is unrewarding or the laboratory is inexperienced in stool analysis. The intensity of schistosomal infection is currently measured by quantitative egg counts which are highly variable and may depend on the immune status of the host.

Immunodiagnostic tests of use include indirect haemagglutination, immunofluorescence, the circumoval precipitin test, radioimmuno-assay and ELISA. The ELISA has been found to be cheap, easy to do, highly sensitive and the most successful immunodiagnostic technique for *S. mansoni* and *S. japonicum* though it lacks specificity. Cross reactions with *S. haematobium* occur. In schistosomiasis, infection does not necessarily signify pathology and serology is incapable of distinguishing between simple infections and hepatosplenic disease[18]. Antibody titres are usually higher in the hepatosplenic form than in the hepato-intestinal form. However, because of cross reactivity with other helminthic antigens, the tests are not specific enough for individual patient management. Besides this, in an endemic area the tests cannot distinguish past from present infection. Currently, ELISA and radioimmunoassays are techniques used for epidemiologic studies. Molecular biological techniques such as the use of Polymerase chain reaction (PCR) has been recently introduced in schistosomiasis diagnosis. Dias Neto et al[59] demonstrated the use of PCR as an alternate approach to identification of schistosomes at strain and species level.

In patients with splenomegaly, the diagnosis of portal hypertension can be made by the radiological or endoscopic demonstration of oesophageal varices[60,61]. Since 1979, ultrasonography has become a reliable and sensitive method to demonstrate Symmer's fibrosis and to assess portal hypertension in hepatosplenic schistosomiasis[62,63]. It has also been shown to be as sensitive as liver biopsy[63]. Liver biopsy and fine needle biopsy have also been utilised in the diagnosis of HSS. Needle biopsy is an insensitive method of diagnosing Symmer's pipe stem fibrosis as the perivascular changes are patchy and centrally sited and the intervening parenchyma is frequently normal.

TREATMENT

While a multi-pronged method of control using health education, sanitation and snail control has been used, chemotherapy and chemoprophylaxis play the most important and crucial role in containing/preventing the transmission of the disease[64]. Chemotherapy is useful not only for individuals but also for the control of morbidity in hyperendemic areas. Therapeutic cure is the term used to refer to termination of an existing parasitic infection with permanent cessation of egg excretion[64]. The two most effective drugs that have been found for the treatment of *S. mansoni* and *S. japonicum* infections are praziquantel and oxamniquine. Praziquantel and 4-hydroxypraziquantel, an isomer, are highly effective antischistosomal drugs which are effective against all major schistosome species and can also be used in advanced cases of *S. japonicum* and *S. mansoni* where patients present with portal hypertension and ascites[65,66]. For *S. japonicum* and *S. mekongi* it is given orally as 3 divided doses at 20mg/kg body weight at 4 hourly intervals or as a single dose of 60mg/kg body weight. For *S. haematobium*, a single dose orally of 40mg/kg body weight is effective. For *S. mansoni*, 2 doses of 25mg/kg body weight given 4 hourly give a cure rate of between 63 and 97%. The therapeutic efficacy of praziquantel was recently shown to prevent appearance of Symmer's fibrosis and also to reverse schistosomal induced pathology[65]. Zwingenberger et al[66] provided evidence that the fibrogenic process ceased after praziquantel therapy and showed that portal vein pathology regressed in hepatosplenic schistosomiasis cases.

Until the advent of praziquantel, oxamniquine was the best drug available for the treatment of acute, subacute, chronic and complicated infections with *S. mansoni*. It has been used for individual patient therapy as well as for mass chemotherapy. The dose used is 15 mg/kg body weight as a single dose in South America and 15 mg/kg twice daily for 2 days in Africa. Oxamniquine may considerably improve even established hepatosplenic diseases[67]. No contraindications to oxamniquine have been observed but medical supervision is required. While both drugs have been effectively used in the treatment of major schistosome species, its cost limits its use in developing countries.

TREATMENT OF PORTAL HYPERTENSION

Two related problems warrant consideration: management of acute variceal haemorrhage and prevention of recurrent bleeding. The surgical treatment of portal hypertension suggested by Da Silva et al[68] were esophagogastric devascularisation with splenectomy (EGDS), classical (proximal) splenorenal shunt with splenectomy (SRS) and distal splenorenal shunt (or selective shunt-DSRS). After comparing the three operations. the same group recommended the following:

(1) the best treatment of variceal bleeding in HSS in *S. mansoni* is EGDS although the risk of rebleeding persists;
(2) classical (proximal) splenorenal shunt should be abandoned;
(3) a complication of DSRS is hepatic encephalopathy, although it is later and occurs at a lesser rate than in SRS[69].

Ezzat et al[69] concluded that DSRS is superior to EGDS but that the latter operation is a good alternative to DSRS. Endoscopic sclerotherapy is becoming the favoured treatment for oesophageal varices. Sakai et al[70] concluded that previous surgical treatment for portal hypertension in patients with mansonian schistosomiasis greatly benefited the treatment of rebleeding esophageal varices by endoscopic sclerotherapy.

Recently, it has been shown that beta adrenergic blockade with propranolol reduced portal pressure and the frequency of variceal haemorrhage. Mies et al[71] showed that propranolol appeared to protect patients with schistosomiasis against gastrointestinal rebleeding during the short time that preceded definitive surgical treatment.

VACCINATION

Extensive investigations aiming at molecular characterisation and identification of potentially protective molecules against schistosomiasis have been developed in the last five years. Several molecules using rat monoclonal or polyclonal antibody probes of specific isotypes have been selected and cloned and found to afford protection in vaccination experiments. Further research is still needed. However, the future of antischistosome human vaccine will rely on an indepth analysis and comparison of the basic mechanisms underlying the suppression of immunity in experimental models and in the natural infection in humans[72]. The possibility of achieving this goal by using different parasite stages holds promise and the development of a schistosome vaccine is not far off.

CONCLUSION

Hepatosplenic involvement in schistosomiasis is associated with infection with *S. mansoni* and *S. japonicum* complex of worms and leads to portal hypertension, oesophageal varices and hepatosplenomegaly. Gastrointestinal bleeding is the most frequent cause of death. Only a small proportion of those infected develop serious chronic disease. While extensive literature on experimental and human mansonic schistosomiasis exist, similar literature on *S. japonicum* is scarce. Thus our understanding of the pathophysiology of human schistosomiasis japonica warrants further investigation. Some of the research questions that require highlighting are:

1. The basic assumption that the pathogenesis and pathology of *S. japonicum* is similar to *S. mansoni* cannot hold true based on new knowledge that has emerged from studies carried out on the parasite, reservoir hosts and status, egg laying capacity of the female worms, host parasite relationships, immunological differences, intensity of infection, egg quantum in tissues etc.

2. Differences in the granulomatous response exist. In *S. mansoni* it is believed to be an immunologic reaction of the cell mediated type with delayed hypersensitivity. The host response interferes with the egg metabolic and immunologic activities. On the other hand, in schistosomiasis japonica it is thought to be related to antibody-mediated inflammatory response.

3. The aetiologic relationship between HBV infection and HSS has brought about a lot of controversy. Asian workers in particular have linked HBsAg and HBcAg with HSS and even HCC whereas workers working with mansonic schistosomiasis have affirmatively shown that there is no association between HBV infection and schistosomiasis. Probably community-based studies looking into various variables need to be conducted to come up with the exact role of HBV infection in the causal relationship of hepatocellular carcinoma. Besides, is there a link between HBV and cirrhosis seen in some HSS cases and can it be linked to HCC? It is very unlikely that there is a link, for schistosomiasis does not involve the hepatic parenchyma but the portal tract.

4. The reparative process that follows destruction caused by the intravascular and perivascular portal granulomas is not sufficient to explain the extensive fibrosis seen in the classic pipe stem pattern. The natural history of periportal fibrosis also needs to be defined possibly by carrying out field studies and longitudinal studies in *S. japonicum* endemic areas where patients with established periportal fibrosis exist.

5. Are constitutional factors and/or HLA phenotypes predisposing factors for HSS in schistosomiasis japonica? Controversy surrounds this factor.

6. The relationship between bleeding risk and oesophageal varices, an observation in HSS in mansonic schistosomiasis needs to be studied for schistosomiasis japonica.

7. The impact of antischistosomal chemotherapy on the most important complication of intestinal schistosomiasis, Symmer's periportal fibrosis has not been determined, especially in the Asian region.

8. Liver images for human schistosomiasis japonica by the use of ultrasonography require inputs from hepatologists. Are the ultrasonographic patterns of hepatic fibrosis in *S. japonicum* similar or different from that of *S. mansoni*?

9. Finally, the evaluation of side effects due to praziquantel therapy in mass treatment campaign should be investigated. Is there any progression of hepatic lesions after praziquantel therapy? Or is there a reversibility of hepatic fibrosis in HSS patients?

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