HEPATOSPLENIC SCHISTOSOMIASIS: A REVIEW

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ABSTRACT

Background: Schistosomiasis is a granulomatous disease that is caused by infection with schistosomes. It is a major health threat in tropical and subtropical countries. Due to increased movement, all residents of the universe are at risk of contracting this infection. The infection goes through several stages, but the most life-threatening form and leading cause of mortality is hepatosplenic schistosomiasis (HSS). It is a chronic complication, which develops as a consequence of inflammatory response. This complication has not been adequately addressed or attended to and as a consequence most of patients presenting with this complication in our settings die.

Objectives: To review literature on hepatosplenic schistosomiasis, to give the state-of-the-art management of HSS, to give our own experience on management of this complication and hence impart knowledge to medical personnel on HSS.

Data source: Literature is from Medline database and experience from gastroenterology clinics. Our own experience has been blended on top.

Study selection and data extraction: We have selected material, which have been verified and can be applicable in resource poor-countries, where this problem is a major health threat.

Data synthesis: Based on published studies and meta-analyses and our own experience we have been able to draw conclusions on the current understanding of the subject.

Conclusion: Hepatosplenic schistosomiasis is a deadly complication and occurs mainly in poor countries. Regular reviews and updates of our knowledge is important to enable stakeholders of health sector understand the problem and develop strategies on its management.

INTRODUCTION

Schistosomiasis or bilharziasis is a granulomatous disease that result from infection with parasitic trematode blood flukes denoted as Schistosomes. It is a major health threat and it is estimated that as many as 200 million persons worldwide are infected with schistosome worms(1). Transmission to humans is possible after repeated contact with infected water sources. Invasion of skin of schistosoma species is usually asymptomatic, but mild pruritic dermatitis may result. In most patients this phase passes unnoticed, but acute schistosomiasis or Katayama fever occurs in a minority and coincides with the start of egg production, and is seen three to eight weeks after invasion, depending on the type of species. Acute schistosomiasis is a serum sickness-like syndrome, and clinically characterised by fever, malaise, urticaria, abdominal discomfort, diarrhea, weight loss, mild hepatosplenomegaly, lymphadenopathy and eosinophilia.

Chronic schistosomiasis develops as a consequence of inflammatory response elicited by schistosoma eggs that are deposited in the intestine and swept to the liver through the portal circulation, or may reach the lungs or other sites via the systemic circulation. Schistosoma eggs retained by the hepatic sinusoids elicit a specific granulomatous inflammatory response; also known as Symmer's penportal fibrosis. This may progress to severe 'pipe-stem' portal fibrosis with presinusoidal portal hypertension. Consequently hepatomegaly, splenomegaly, and bleeding from oesophageal varices and ascites can occur(2). Hepatosplenic schistosomiasis (HSS) describes the clinical manifestations from portal hypertension as a result of presinusoidal hepatic fibrosis(1). This form of the disease is a prototype of presinusoidal portal hypertension, although in its more advanced stage it may have components of sinusoidal and postsinusoidal portal hypertension too(2). HSS with portal hypertension is the severest form and the most common cause of morbidity and mortality of
schistosomiasis infection(3-6). This article reviews some of the important aspects of this form of the disease, and focuses on the parasite, the host and discusses prevention and treatment of HSS including our own experience.

The parasite: Almost all cases of human schistosomiasis can be attributed to infection with Schistosoma mansoni, *S. japonicum*, *S. intercalatum*, *S. mekongi*, *S. malayensis* (*S. mekongilike*), or *S. haematobium*. Although all these species have been found to affect the liver, *S. mansoni* and *S. japonicum* are the commonest cause of HSS(7). *S. haematobium* is primarily associated with genitourinary diseases(1,8,9). Schistosoma parasites have a complex life style that requires two distinct hosts; snail and man. Each Schistosoma species can infect only a specific genus of snail. This complex life style of the parasite and the geographic distribution of the snails limit the acquisition of infection to tropical and subtropical climate(1). Apart from their difference in egg morphology, global distribution, preferred location of residence within the human host and snail host, they also differ in their pathophysiology. *S. japonicum*, for instance, can produce as many as 3500 eggs per day in groups, while *S. mansoni* produces fewer and individual eggs. *S. japonicum* for that reason among others, is more pathogenic than *S. mansoni* and produces hepatosplenic schistosomiasis more frequently and much faster(8). *S. mansoni* is the commonest cause of HSS in Africa. In order to develop HSS, several conditions have to be met. (i) a massive infestation by cercariae of Schistosoma species; (ii) migration of the parasite to the mesenteric veins; (iii) deposition of eggs in the hepatic sinusoids with consequent granulomatous inflammatory response, and (iv) haemodynamic changes leading to portal hypertension because of obstruction of portal veins.

As outlined, the basic pathology of chronic schistosomiasis results from granulomatous response by the tissue surrounding the eggs and stimulated by the egg derived antigen release. The daily parasite egg deposition induces hypersensitivity reaction type IV with granulomatous formation and scarring(8,10-12). The extent and severity of chronic liver disease correlates with the intensity and duration of egg production by fertile worm pairs(5). However, when the liver disease is advanced, many patients tend to have low faecal egg count because of senescence of adult worms. When variceal haemorrhage occurs, the granulomatous reaction may have subsided and the clinical picture is predominantly that of fibrosis(8). Nevertheless, HSS can arise in patients with high worm load(5).

The human host: Factors of human host also contribute to HSS. Age has its role in *S. mansoni* HSS. Symmer's periportal fibrosis typical of schistosomiasis has never been reported in children before the age of six years(11). In our endoscopy unit at KCMC hospital we have never seen a HSS patient below the age of 10 years. Liver fibrosis can be divided into three histological categories, grade I (FI) defined by few little inflammation and connective tissue deposits of the portal veins, grade II (FII) by expansion of the connective tissue deposits and grades III (FIII) by bridging fibrosis. The prevalence of FII and FIII increases with the number of years of infection and probably requires prolonged, moderately infection with schistosoma species. Most patients with HSS have harboured the parasites for 5 to 15 years and are adolescent to late 20's at presentation(10). Studies have shown gender differences in susceptibility to HSS and schistosoma infection(10). For instance, prevalence and severity of infection decreases sharply in females beyond 15 years-of-age. This may be due to reduced water contact after puberty and/or some hormonal effects on immunity occurring at puberty or when pregnant.

While the prevalence of FII periportal fibrosis among women aged 20-30 years does not decrease, adult males appear to be more prone to FII even when the infection levels are comparable between them. Further, the prevalence of advanced fibrosis FII and FIII is higher in males than in females. There are evidences for host-specific factors that determine the development of HSS.

Genetics: There are evidences for genetic influence as some families have a higher prevalence of FII and FIII compared to other infected families. Further the disease progresses much faster in these families. Although environmental factors cannot be ruled out it is likely that genetic factors contribute to the development of HSS, and its progression to advanced stage of the liver disease(8,10). For example, it has been found that people of blood group A and HLA A1 and B5 are more involved than other blood groups(13) and only about 10% of infected individuals will eventually present with HSS(14). HSS has a higher prevalence in Caucasians than blacks living in the same environment, even when Caucasians have better socioeconomic status than blacks(5). All these findings point to the genetical component of this form of the disease.

Nutrition: Relatively little is known about the links between nutrition and human schistosomiasis. Evidences show that: the development of the parasite can be inhibited by dietary deficiencies in the host, and that the immune system of the infected host is adversely affected by malnutrition. Lastly, the highest mortality rates occur among malnourished and infected animals; indicating that malnutrition and schistosomiasis often act synergistically. Proof is lacking whether the more severe manifestations of the disease occur in the severely malnourished mice(15). The available evidence on experimental infections indicates that malnutrition of the host is harmful to the parasite, because it results in diminished egg production, laying of defective eggs, and apparent residual damage to the reproductive capacity of the severely malnourished worm(16).
Experimental data show that fewer hepatic granulomas develop in the malnourished mice(15).

Co-infections: The role of other factors such as hepatitis B virus (HBV) and HCV in terms of raising morbidity and mortality in HSS is not yet clear. There are contradicting reports, some in favour and some against(17-19). These tropical and sub-tropical countries where schistosomiasis is endemic, liver pathology due to hepatitis B virus, hepatitis C virus, aflatoxin and alcohol is also a common problem. Acquisition of viral hepatitis may occur in quite a tender age, so is the consumption of poorly stored cereals and groundnuts.

We often see patients even before their third decade presenting with hepatocellular carcinoma, which may be a consequence of the above. Worse enough in these resource-poor countries blood for transfusion is seldom screened for HBV and HCV. And again these countries where schistosomiasis is endemic (Africa, Asia, and Latin America), HIV/AIDS is as well epidemic. The correlation between HSS and HIV/AIDS is as yet not clear; among other things the morbidity in schistosomiasis depends on the immune responsiveness of the host. Egg excretion rate significantly correlates with CD4 levels; it has been found that egg excretion per worm pair is reduced with decreasing CD4 cell counts(20). Fibrosis in HSS depends on both immune responsiveness and also the worm load (and number of eggs), this may therefore mean that less fibrosis occurs in HIV/AIDS patients. Nevertheless the actual outcome of the interaction of the two diseases remains unclear.

Clinical and laboratory changes: The liver function is preserved in HSS unless it is associated with liver disease from other causes, such as hepatitis, liver cirrhosis (5,21). The main symptoms of HSS, are related to splenomegaly and variceal haemorrhage. HSS is one of the common causes of splenomegaly, and when present its size correlates with the severity of the disease(10). Hepatomegaly is seen in the early stages of the disease, but with advancement of the disease it shrinks(8-10, 21). Ascites as a sign of hepatic failure usually appears in advanced HSS especially after repeated variceal bleeding. Neuropsychiatric symptoms common in hepatic failure due to other causes is very rare in HSS(5). Anaemia with delayed somatic and sexual development may be observed in young people. Anaemia is due to sequestration of erythrocytes by the splenomegaly as well as other causes e.g. malnutrition, ankylostomiasis, chronic bleeding and haemolysis. Serum alkaline phosphatase may be elevated, and gamma glutamic transferase may be present. Hypoalbuminemia may be due to hepatic failure, and poor nutrition or a combination of these two(8). Ultrasoundography is a valuable, non-invasive tool for evaluating fibrosis and is regarded as sensitive as histological examination of liver biopsy specimen in diagnosing Symmer's fibrosis(5,9,21-23). There are several studies which have tried to identify predictors of upper gastrointestinal bleeding from periportal fibrosis and its sequel portal hypertension. These predictors may help in planning prophylaxis against bleeding. Advanced fibrosis (i.e. FI and FIII) is associated with an elevated risk of oesophageal varices and with bleeding from the varices. Splenomegally also correlates with advanced fibrosis(9,10,22). Some studies have suggested that variceal size, spleen longitudinal axis, and periportal fibrosis are the most important predictors of variceal bleeding. The presence of congestive gastropathy and red spots on the varices has an increased likelihood to bleed too(21).

In general, combining results from endoscopy (variceal size, red spots congestive gastropathy, fundic varices) and ultrasonography (portal vein diameter and periportal thickness) can be very useful in the evaluation of bleeding risk. The most useful set of clinical data for predicting bleeding in HSS are gastropathy and red spots, portal vein diameter and variceal size, variceal size and gastropathy(21). It is important to identify individuals who are at risk of bleeding, due to the seriousness of this complication and also due to the fact that promptly prophylactic measures can be initiated.

Treatment

Chronic: The medical treatment of HSS is currently based on medical treatment with antischistosoma drugs. Currently, praziquantel, and oxamnique are most commonly used. Praziquantel is effective in killing the parasites and can decrease periportal fibrosis, hepatomegaly and splenomegaly. Depending on the stage of development hepatosplenic schistosomiasis can be reversed or even disappear after praziquantel treatment(1,24). Our practice has been to give praziquantel to all patients presenting with HSS who have not been treated before.

Various agents have been employed for primary prophylaxis of the potentially fatal complication of HSS that is variceal haemorrhage. Non-selective beta-blockers at present are the drugs recommended for primary prophylaxis (e.g. propranolol, nodalol). They block the adrenergic dilatory tone in the mesenteric arterioles resulting into an unopposed alphadrenergic mediated vasoconstriction and consequent decrease in portal inflow(25). At high dose, propranolol decreases heart rate and cardiac output, which contribute to further lowering of portal pressure by decreasing splanchnic blood flow. Propranolol lowers chances of re-bleeding when given to lower resting pulse by 25%(25,27). Selective beta-blockers (e.g. atenoilol) also reduce portal venous pressure; the effect however is not as dramatic as the non-selective ones. While the use of nitrates (e.g. isosorhode-5-mononitrate) as monotherapy is still disputable, combined therapy (non-selective beta blockers and nitrates) has shown to be beneficial. The co-administration is able to bring nearly all-portal hypertensive patients to a reduction of portal flow volume >20%, particularly those who poorly respond
to beta-blockers(28,29). Several randomised trials have shown that combination of beta-blockers and nitrate had better results for re-bleeding than beta-blockers alone. The combination of beta-blockers and nitrate has been found to be better than sclerotherapy in prevention of variceal bleeding(30). Nitrates alone can be recommended for prophylaxis of variceal bleeding only if beta-blockers are contraindicated or ineffective(29). Beta-blockers with or without nitrates therefore should be used for both primary and secondary prophylaxis of bleeding.

Endoscopic variceal ligation as prophylaxis of first bleeding has been found to be beneficial, with reduction of first-bleeding, bleeding-related mortality and all-cause mortality. It even has some advantages as compared with beta-blockers. The development of multiple-band shooers has made the procedure less cumbersome but the expense involved and high chance of variceal recurrence makes it less favourable for primary prophylaxis than beta-blockers, unless the patients cannot tolerate beta-blockers(31,32).

Acute: During acute variceal haemorrhage, several measures have to be taken. Resuscitation includes assessment of blood pressure, pulse rate, and jugular vein pressure. Central line and bladder catheter need to be in place in order to monitor central volume and urinary output respectively. Intubation may be done depending on the level of consciousness, severity of the haematemeses and the degree of haemodynamic instability. Data on haemoglobin and haematocrit parameters, full blood picture, blood grouping and cross matching need to be available. Plasma and/or packed red cell replacement should be performed tailored to the patient’s need.

Several drugs are used in treatment of acute variceal haemorrhage. Vasoconstrictor agents (e.g., vasopressin, terlipressin) when combined with vasodilators (e.g., nitroglycerin) have better therapeutic effects and fewer side effects such as coronary, cerebral and intestinal ischaemia, which are common when vasoconstrictors are used alone(23,24). Vasopressin directly constricts mesenteric arterioles and decreases portal venous inflow leading to reduction of portal pressure, but it has extraplanar vaso-constrictive properties with resultant myocardial, cerebral and intestinal ischaemia. Addition of nitroglycerin attenuates these side effects and further accentuates the portal hypotensive actions of vasopressin(24).

Metoclopramide and domperidone have been shown to decrease azygous blood flow and to reduce oesophageal variceal pressure but have a very limited clinical valuation(35). The natural hormone, somatostatin inhibits the release of vasodilator hormones such as glucagon(36). Intravenous administration (similarly as for synthetic, long acting analogue, octreotide) lowers portal venous inflow, portal pressures, azygous flow and intravascular pressure within seconds. Somatostatin (very short acting) and octreotide have proved to be efficacious in acute variceal bleeding. The mechanism of action and optium dose of octreotide, however, still remains controversial. Somatostatin is more effective in controlling bleeding than vasopressin and has fewer side effects(28,37).

Balloon tamponade is effective as a temporary measure of achieving haemostasis while planning for definitive measures. Compression by the balloon effectively starts the bleeding location in the varices and prevents blood flow through the varices(2). Commonly used balloon tubes are (modified) Sengstaken-Blakemore, Minnesota, and Linton-Nachlas. The first devices possess both oesophageal and gastric balloons, whereas the last tube only has a gastric balloon. Balloon tamponade carries several immediate and late complications. It can result into re-bleeding after deflation of the balloon, result into aspiration pneumonia, compromise respiration and cause necrosis and even rupture of the oesophagus. Furthermore, insertion of the balloon tubes can be complicated in a profoundly bleeding patient. Therefore, remains as an initial, temporary measure until other treatment modalities become feasible.

Endoscopic therapy is currently the definitive treatment of choice for active variceal haemorrhage(12,28). Endoscopy is done as both diagnostic and therapeutic tool and can be done at bedside. Various endoscopic pharmacological methods are used. Endoscopic sclerotherapy is the commonest. A sclerosant solution is injected intravascularly or/and paravascularly. This results in haemostasis through the induction of thrombosis by external compression of the vessel respectively. The commonest sclerosing agents used are sodium morrhuate ethenolamine oleate, polidocanol, sodium tetradecyl sulphate, and 3% ethanol. The first three cause physical irritation to achieve sclerosis while the last is a dehydrating agent. The injection is done at the gastroesophageal junction, the amount of sclerosant depends on the type of sclerosant used. The optimum volume however is between 1-5ml with an average of 3-5 sessions at interval of between 5-7 days each. These agents differ in their effectivenss and complications. Different concentrations of a given agent may as well determine the outcome in terms of haemorrhage control obliteration of varices and complications. The choice of a sclerosing agent to be used by endoscopists is favoured by their personal preference, availability of the agent and affordability than by the definitive supporting data. In our endoscopy unit at KCCH hospital where we attend approximately 2,000 patients per year and the leading cause of upper gastrointestinal bleeding being gastroesophageal varices(38), we use ethenolamine oleate 1%, injecting a maximum of 3ml per point and we hardly exceed 22ml per session. We repeat after two weeks. This regime gives patients time to rest at home, and it has shown to decrease occurrence of big ulcers.
while at the same time not compromising the effectiveness of sclerosis. Disappearance of the varices occurs mainly after five sessions, although we have had cases whereby healing has occurred after only two sessions. We have opted out polymers e.g histocryl, which is a tissue adhesive agent because of risks associated with it (e.g. damage to scope) and cost. Another method used is variceal band ligation; whereby small elastic bands are placed around varices in the distal 5 cm of the oesophagus and eventually obliterate the varices. Several sessions of therapeutic procedures have to be done at an interval of 5-7 days to achieve eradication of the varices followed by maintenance therapy with beta-blockers. Both endoscopic sclerotherapy and endoscopic band ligation have similar outcome in achieving haemostasis and prevention of re-bleeding(39).

Band ligation is superior to sclerotherapy in terms of reducing bleeding rate, and incidence of complication and rate of death due to bleeding(39). Band ligation however, is not a favourable method of achieving haemostasis during active bleeding due to technical difficulties in moving the scope back and forth into the stomach and also the limited visibility by ligator. Band ligation has high chance of variceal recurrence. The main complications of sclerotherapy are ulceration, bleeding, stricture formation, oesophageal perforation. aspiration, mediastinitis and sepsis(40,41). Neodymium yttrium-aluminum-garnet (Nd:YAG) laser has been used in treatment of bleeding varices. Although it is considered easier to use, with less ulceration, it is not effective in obliteration of the varices and it does not appear to offer any benefit over other less expensive and more portable modalities(42).

Other endoscopic methods like fibrin glue, human thrombin, haemoclips, snare and percutaneous catheater obliteration of varices have been used but have not gained wide acceptance(43). With these endoscopic options available from sclerant, polymer to banding, surgical procedures (e.g. portal systemic shunt, oesophageal transection, radiological transjugular portal systemic shunt) become less favourable due to the invasiveness nature of the procedures, high volume of blood transfusion, immediate morbidity and mortality associated with the procedure and initial cost. They are an option for patients who are refractory to medical and endoscopic management(44).

This deadly complication occurs in the environment of ill-health; both in terms of having other endemic and deadly diseases like malaria, tuberculosis and HIV/AIDS and also in terms of poor health services. In certain communities HSS is called the 'angel of death' that is, once it has occurred be it in a hospital setting or otherwise the patient will eventually die. We have witnessed families starting initial preparation for burial ceremony while the patient is still alive in a hospital.

This concept however has started changing in communities where our medical and endoscopy services have reached. If appropriate management is instituted this concept will soon loose its ground. We loose many lives, which otherwise would have been saved.

REFERENCES