Schistosomiasis and Associated Infections

JR Lambertucci/+ AAM Rayes, JC Serufo, R Gerspacher-Lara, G Brasileiro-Filho, R Teixeira, CMF Antunes, AM Goes*, PMZ Coelho**

Departamento de Clínica Médica, Faculdade de Medicina *Departamento de Imunologia e Bioquímica **Departamento de Parasitologia, ICB, UFMG, Av. Alfredo Balena 190, 30130-100 Belo Horizonte, MG, Brasil

In hospital-based series viral hepatitis B has been frequently described in association with schistosomiasis whilst in field-based studies the association has not been confirmed. The association between schistosomiasis and Salmonella bacteraemia has been well documented. More recently, acute schistosomiasis has been shown to be a facilitating factor in the genesis of pyogenic liver abscesses caused by Staphylococcus aureus. New evidences indicate an interaction between the acquired immunodeficiency syndrome (AIDS) and schistosomiasis. In this paper, data on the association of schistosomiasis with other infections are updated.

Key words: schistosomiasis - salmonellosis - staphylococci - AIDS - liver abscesses

ASSOCIATION WITH VIRAL HEPATITIS B

Patients with hepatosplenic schistosomiasis have been reported to be more frequent carriers of hepatitis B surface antigen than patients with other forms of schistosomiasis or uninfected individuals (Lambertucci 1993).

It is generally accepted that Schistosoma mansoni infection alone does not lead to cirrhosis or chronic active hepatitis. Interaction between hepatitis B virus (HBV) and S. mansoni infection was suggested to cause a more serious form of chronic liver disease (Bassily et al. 1979). Liver biopsy studies have shown a significant increase of chronic hepatitis and hepatic decompensation in S. mansoni infected subjects (Lyra et al. 1976, Chen & Mott 1988). Patients with this dual infection more often develop jaundice, intractable ascites and hepatic failure. The clinical management is more complicated and the prognosis more guarded than for chronic hepatosplenic schistosomiasis alone.

Different reasons have been advanced to account for the S. mansoni-hepatitis B association: (1) impaired cell-mediated immunity which reduces host resistance (Lyra et al. 1976, Colley et al. 1986); (2) low socioeconomic conditions and educational levels which increase the risk of exposure; (3) repeated treatments in the past with intravenous or parenteral drugs or blood transfusions (Madwar et al. 1989).

Some patients were negative for HBsAg but had the typical liver biopsy histological picture of chronic active hepatitis (Coelho et al. 1985); the role of hepatitis C or the existence of other aetiological factors should be investigated (Pereira et al. 1997).

In a controlled study, treatment of schistosomiasis with oxamniquine did not result in disappearance of the antigenaemia (Lyra et al. 1976).

Studies from Egypt suggest that patients with hepatosplenic schistosomiasis and infant born to mothers with active schistosomiasis present a weak or failed response to the hepatitis B vaccine (Ghaffar et al. 1989, 1990). These studies await confirmation.

The positive relationship between HBV and S. mansoni infection has been questioned by a few investigators (Serufo & Lambertucci 1997). Domingo et al. (1983) studying a nonhospitalized population found no difference in HBV exposure and HB surface antigen positivity between individuals with S. japonicum infection, including hepatosplenic disease, and individuals without schistosomiasis. A lack of association between schistosomiasis mansoni and HB has also been reported from Egypt (Hyams et al. 1986, Eltoum et al. 1991).

Summing-up, in hospital-based studies the carrier rate of HBV in patients with hepatosplenic schistosomiasis was higher than in the controls, whilst in field-based studies an association between these organisms has not been found (Serufo 1997). Further observations with well-designed studies are necessary to clarify this controversy.

Partially supported by CNPq/Brazil.
+Corresponding author. Fax: +55-31-273.4985. E-mail: lamber@net.em.com.br
Received 4 May 1998
Accepted 31 August 1998
ASSOCIATION WITH SALMONELLA

Chronic persistent Salmonella bacteraemia has been described in association with S. mansoni infection (Neves & Martins 1967, Salih et al. 1977). The most common characteristics of the clinical syndrome are: (i) an indolent febrile disease (from several weeks to a few years); (ii) bacteraemia with one of many species of the genus Salmonella; (iii) chronic active schistosomiasis. It occurs most commonly in males between the ages of 10 and 30 years. Patients complain of fatigue, malaise, weight loss and fever. Even with bacteraemia for many months they do not look toxicemic; hepatosplenomegaly has been described in most cases, but many patients with the hepatointestinal form have also presented with the syndrome. Oedema and a petechial rash on the lower limbs are common. Prostration and delirium never occur. Localized infections, as are found in the osteomyelitis of sickle cell disease, and chronic cholecystitis do not occur. The clinical features of this peculiar association have been described as being more like kala-azar than typhoid fever (Lambertucci et al. 1991a).

Salmonella are easily recovered from the blood; in 25% of cases they have also been isolated from the faeces or urine. The Widal test, positive in 25% of cases, is not helpful in the diagnosis of the syndrome (Lambertucci et al. 1985a). Eosinophilia increases after treatment with antibiotics.

The bacteria are found in the tegument or in the intestinal tract of S. mansoni adult worms. The role of schistosomes as a source and vehicle of Salmonella infection has been suggested (Lo Verde et al. 1980), and sera from patients with hepatosplenic schistosomiasis were found to have reduced antibody activities against S. typhi and S. cholerasuis compared with normal controls (Rocha et al. 1971, Muniz-Junqueira et al. 1996).

Mortality is rare, and the response to antibiotic therapy is dramatic. However, recurrent Salmonella bacteraemia is common if the underlying schistosome disease is not treated. Effective treatment of schistosomiasis alone deprives the Salmonella of favourable foci for growth and eliminates both infections in more than 90% of the cases (Lambertucci et al. 1985b).

Renal involvement is common in patients with Salmonella-S. mansoni association. At least two patterns of clinical and histological renal involvement have been described. Barsoum et al. (1977), in Egypt, categorized their Salmonella-positive cases in two groups: (1) those with clinical, laboratory and histological evidence of interstitial nephropathy, without glomerular involvement, that probably resulted from Salmonella pyelonephritis. These findings have not been confirmed by Brazilian studies (Lambertucci et al. 1988), and before accepting this as a distinct pattern it would be desirable to define the importance of concomitant S. haematobium infection in the pathologic findings reported in patients from Egypt; (2) those with overt glomerular disease, usually proliferative glomerulonephritis with minimal or no basement membrane thickening, being the nephritic syndrome the presenting clinical picture (Lambertucci et al. 1988).

The association of S. mansoni with Escherichia coli has also been described (Teixeira et al. 1976, Farid et al. 1984). After months of febrile attacks, treatment with co-trimoxazole or amoxycillin followed by antischistosomal drugs resulted in cure.

Rocha et al. (1968) inoculated E. coli into mice previously infected with S. mansoni and observed bacteraemia and liver abscesses in the experimental group. The formation of abscesses was interpreted as being derived from suppurative cholangitis.

The number of cases of bacteraemia due to Gram-negative bacteria other than Salmonellae should not increase since it is known that most Gram-negative organisms parasitize and kill the schistosomes (Ottens & Dickerson 1972).

ASSOCIATION WITH STAPHYLOCOCCUS AUREUS

Graham and Orr (1950) described the case of an English Army officer who developed a S. aureus liver abscess associated with schistosomiasis and suggested that the liver damage caused by schistosomiasis may have paved the way for a subsequent pyogenic infection. Lambertucci et al. (1990) described the cases of two children with skin pustules and acute schistosomiasis who also developed multiple pyogenic liver abscesses caused by S. aureus. Liver abscesses were duplicated in the murine model of schistosomiasis when mice were injected with the bacteria 60 days after receiving cercariae of S. mansoni. More recently Teixeira et al. (1996) have confirmed and extended our initial findings. Lima and Maluf (1995) have also reported a case in a patient with chronic schistosomiasis.

The medical charts of 50 patients with pyogenic liver abscesses who were admitted to three general hospitals of Belo Horizonte, State of Minas Gerais, in Brazil, during a period of ten years, were reviewed retrospectively by Lambertucci et al. (1991b). Demographic information, chief complaints, clinical and laboratory findings, and response to treatment were recorded. The age range varied from 2 to 79 years (41% were younger than 15). The main presenting complaints were fever and abdominal pain. Eosinophilia was observed in 15 cases (30%). Parasitological stool examination
was obtained from 28 patients with liver abscesses, and in 20 (71%) the following agents were identified in the stools: *S. mansoni* (36%), *Strongyloides stercoralis* (21%), *Ascaris lumbricoides* (18%), *Entamoeba histolytica* (4%). Ultrasonography had a major role in the diagnosis of liver abscesses and in treatment, directing the percutaneous drainage of the purulent collections. Culture of the material obtained during surgery or by percutaneous puncture in 30 patients revealed: *S. aureus* (14 cases), *S. viridans* (2 cases), Gram-negative bacteria (5 cases), the association of Gram-positive and Gram-negative (2 cases). Two out of the 5 patients submitted to liver biopsy had the necrotic-exudative granulomata of schistosomiasis. The authors conclude that schistosomiasis and migrating larvae of other parasitic diseases (*A. lumbricoides, S. stercoralis, Toxocara*) may be a predisposing factor for pyogenic liver abscesses.

Some mechanisms have been proposed as a probable explanation for the association of schistosomiasis and pyogenic liver abscesses: (1) liver necrosis caused by eggs or dead worms of *S. mansoni* could be colonized by bacteria; (2) there is transient impairment of the cell mediated immunity in the acute phase of schistosomiasis in animal models (Araújo et al. 1977); (3) the literature contains several reports of cases of recurrent infections caused by *S. aureus* in the presence of high IgE levels in the serum (Galandiuk et al. 1995, Lambertucci 1996), and high serum IgE levels have been reported in acute schistosomiasis.

We have noticed regional differences in the clinical presentation of liver abscesses in South America when compared to northern countries (Huang et al. 1996). Nowadays, in developed countries, pyogenic liver abscesses are more often found in individuals of middle age or older, especially those who have underlying biliary tract diseases with obstruction and bile stasis that favour infection. Before antibiotics, appendicitis with obstruction and bile stasis that favour infection, could be colonized by bacteria; (2) there is transient impairment of the cell mediated immunity in the acute phase of schistosomiasis in animal models (Araújo et al. 1977); (3) the literature contains several reports of cases of recurrent infections caused by *S. aureus* in the presence of high IgE levels in the serum (Galandiuk et al. 1995, Lambertucci 1996), and high serum IgE levels have been reported in acute schistosomiasis.

ASSOCIATION WITH HIV

The basis for expecting interactions between HIV infection and schistosomiasis derives largely from our knowledge of the immunology of schistosomiasis and of the effects of HIV on the immune system. HIV infection causes progressive disruption of the immune system with a gradual fall in the number of CD4-positive lymphocytes and increasing functional impairment of cell-mediated immunity. *In vitro*, HIV becomes activated when host lymphocytes or macrophages are stimulated by antigens or mitogens.

Data on the behaviour of schistosomiasis in the immunosuppressed host are rather scarce. It is possible to consider at least four areas of clinical interest concerning this new scenario (Lambertucci & Neves et al. 1993): (1) depression of cell-mediated immune response in the host diminishes granulomatous response to *S. mansoni* eggs. Mice experimentally infected with *S. mansoni* and immunosuppressed by drugs or thymectomy develop diffuse and severe hepatitis. Climent et al. (1994) reported the postmortem histopathological changes in 100 patients with AIDS who died in Puerto Rico from 1982 to 1991. Ten out of their 100 patients had schistosomiasis mansoni and all showed minimal inflammatory or granulomatous tissue reaction. Lambertucci and Neves (1993) reported the complete absence of granulomatous response to eggs and severe hepatic necrosis in a patient who died with the *Salmonella-S. mansoni* association and was found at autopsy to have, in addition, disseminated tuberculosis and *S. mansoni* eggs scattered in multiple organs. The migration of worms to different organs in the human body may explain the finding of a great number of eggs in unusual places. This hypothesis implies that the immune system is important in keeping the adult worms of *S. mansoni* confined to the mesenteric vessels; (2) Lambertucci and Rayes (unpublished observation) have examined the cases of two young men with *Salmonella* bacteraemia, active schistosomiasis and the acquired immunodeficiency syndrome. Liver
biopsy specimens obtained during laparoscopy of one patient revealed in the periportal area poorly formed granulomata around *S. mansoni* eggs and hepatitis of moderate intensity. Treatment of schistosomiasis alone induced consistent clinical improvement and eventual cure of both *Salmonella* and *S. mansoni* infections. Recognition of the *Salmonella*S. mansoni association in patients with AIDS should not be easy because the presenting signs and symptoms (diarrhoea, prolonged fever, hepatosplenomegaly and weight loss) have been described in patients with AIDS alone. The association may help to explain the high prevalence of *Salmonella* bacteraemia in AIDS patients from Africa (Gilks et al. 1992); (3) egg output decreases sharply in mice experimentally infected with *S. mansoni* and immunosuppressed by drugs or thymectomy (Doenhoff et al. 1986). A well formed granuloma facilitates the migration of eggs in the host tissues. Without granuloma formation, *S. mansoni* eggs do not reach (or only in small numbers) the gut lumen. Diagnosis of schistosomiasis, based on parasitological stool examination, in this context, should be reexamined. Rectal or liver biopsies, and ELISA tests for circulating antigens would represent an alternative to stool examination in such cases. Studies in patients with AIDS and low CD4 cell counts are mostly needed either to confirm or exclude this interesting hypothesis; (4) in mice infected with *S. mansoni* and immunosuppressed by thymectomy, the efficacy of schistosomicides is decreased (Lambertucci et al. 1989, Doenhoff et al. 1991). Failure to respond to oxamniquine or praziquantel, in the usual doses, is to be expected in the immunocompromised host infected with *S. mansoni*. So far, this possibility in AIDS patients remains speculative.

**REFERENCES**


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