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NEPHROTIC SYNDROME ASSOCIATED WITH HEPATOINTESTINAL SCHISTOSOMIASIS

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SUMMARY

Schistosomal nephropathy has long been related to the hepatosplenic form of schistosomiasis. In the last few years, 24 patients with hepatointestinal schistosomiasis and the nephrotic syndrome were studied. Aiming at evaluating a possible etiologic participation of schistosomiasis in the development of the nephropathy, this group was comparatively studied with a group of 37 patients with idiopathic nephrotic syndrome. Both groups had a different distribution of the histologic lesions.In the group with schistosomiasis there was a statistically significant prevalence of proliferative mesangial glomerulonephritis (33.3%), whereas in the control group there was prevalence of membranous glomerulonephritis (32.4%). On immunofluorescence, IgM was positive in 94.4% of the patients with schistosomiasis versus 55.0% in the control group ($p<0.01$). In the group with schistosomiasis, 8 patients evidenced mesangial proliferative glomerulonephritis and 5, membranoproliferative glomerulonephritis. In both histological types immunofluorescence showed IgM and C_3 granular deposits in the glomeruli. The data in this study suggests that mesangial proliferative and membranoproliferative glomerulonephritis, with glomerular granular IgM and C_3 deposits, represent the renal lesions of the schistosomiasis associated nephropathy.

KEY WORDS: Schistosoma mansoni; Schistosomal associated nephropathy; Nephrotic syndrome; Hepatointestinal schistosomiasis.

INTRODUCTION

Nephropathy associated with schistosomiasis has long been related to the hepatosplenic form of the disease[1,2,3,7]. In the last few years we observed some patients with nephrotic syndrome concurrent with hepatointestinal schistosomiasis.

The objectives of this study were to determine whether the two diseases are independent or if there is an etiological role for schistosomiasis, even if it is hepatointestinal in the genesis of the nephrotic syndrome in these patients.

PATIENTS AND METHODS

Twenty-four patients with hepatointestinal schistosomiasis and nephrotic syndrome were studied. The diagnosis of schistosomiasis was carried out based on the examination of the stool specimens by Hoffman's method, Kato's method modified by Katz and/or by rectal mucosal biopsy. The usual causes of secondary nephrotic syndrome such as diabetes mellitus, collagen diseases, hepatitis B, Lues, vasculitis and amyloidosis were excluded. The diagnosis of hepatointestinal schistosomiasis was based on absence of splenomegaly on ex-

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amination in 16 patients, on absence of splenomegaly at ultrasonography in 6 patients, on lack of esophageal varices at endoscopy and the absence of splenomegaly on examination in 2 patients. The group was made up by 14 men and 10 women, mean age was 29.9±12.6 years (13 to 64 years) and with mean serum creatinine concentration of 1.4±0.7 mg/dl at entry. Of the 24 patients, 11 (45.8%) had high blood pressure (diastolic > 9.5 cmHg).

Thirty-seven patients without schistosomiasis and with idiopathic nephrotic syndrome were studied as control group. They have never lived in schistosomal endemic areas and all had negative stool examinations. Of this group 21 were men and 16 women, with mean age of 35±15.8 years (16 to 72 years), mean serum creatinine concentration of 1.4±0.9 mg/dl at entry and 11 (29.7%) were hypertensive.

The results of renal biopsy (light microscopy and immunofluorescence) of both groups were comparatively evaluated. All patients were submitted to percutaneous kidney biopsy with Vim-Silverman needle modified by Franklin. For optical microscopy the fragment of kidney tissue was fixed in Duboscq-Brazil solution and stained by HE, PAMS and Masson's Trichrome methods. The renal fragment for immunofluorescence microscopy was submitted to fluorescein-conjugated anti-human globulin sera for IgG, IgM, IgA, C_3, fibrinogen and albumin (Hyland Laboratories, Costa Mesa, California, U.S.A.). The monospecificity of each anti-serum was tested by immunodiffusion.

The chi-square test with Yates correction and Student's "t" test were used for statistical analysis. The significance level was set at $p<0.05$.

RESULTS

There was no significant difference in sex, serum creatinine level and the incidence of hypertension at entry between the two groups.

The histologic findings of 24 patients with hepatointestinal schistosomiasis and of the 37 idiopathic nephrotic patients are shown in Table 1. As it may be observed, the patients were not distributed evenly among the several renal pathologic types of nephrotic syndrome. In the patients with schistosomiasis the main kidney histologic form was mesangial proliferative glomerolonephritis (33.3% in the group with schistosomiasis versus 8.1% in the group without schistosomiasis), whereas in the group of patients with idiopathic nephrotic syndrome membranous glomerulonephritis prevailed (32.4% versus 8.3%). The prevalence of proliferative mesangial glomerulonephritis in the patients with schistosomiasis was statistically significant ($p<0.05$) as compared to the group of patients with idiopathic nephrotic syndrome. Focal glomerulosclerosis was the second most frequent form found in both groups. In the group with schistosomiasis 5 patients (20.8%) had membranoproliferative glomerulonephritis.

As to the immunofluorescence, IgM was positive in 17 out of 18 nephrotic patients (94.4%) with hepatointestinal schistosomiasis and was positive in only 15 out of 27 patients (55.0%) with idiopathic nephrotic syndrome (significant by chi square test, $p<0.01$). All patients with schistosomiasis and proliferative mesangial glomerulonephritis, studied by immunofluorescence (6 of 8 patients, two were not done), showed granular pattern Igm and C_3 deposits in the mesangium, global and diffuse, and sometimes along the capillary walls. Four of the 5 patients (one not done) with membranoproliferative glomerulonephritis also evidenced global and diffuse mesangial granular deposits of IgM and C_3 which were also distributed along the capillary walls.

Table 1
Histologic distribution in patients with nephrotic syndrome associated or not with hepatointestinal schistosomiasis.

Histologic Distribution	Hepatointestinal Schistosomiasis	Idiopathic Nephrotic Syndrome
PMGN	8 (33.3%)	3 (8.1%)
FGS	6 (25.0%)	10 (27.0%)
MPGN	5 (20.8%)	6 (16.2%)
MGN	2 (8.3%)	12 (32.4%)
MCD	2 (8.3%)	5 (13.5%)
OTHERS	1 (4.2%)	1 (2.7%)
TOTAL	24 (100%)	37 (100%)

PMGN – proliferative mesangial glomerulonephritis
FGS – focal glomerulosclerosis
MPGN – membranoproliferative glomerulonephritis
MGN – membranous glomerulonephritis
MCD – minimal change disease

DISCUSSION

The results indicate the possibility that schistosomal nephropathy is not caused exclusively by the hepatosplenic form of the disease. The group of patients with nephrotic syndrome and hepatointestinal schistosomiasis showed a different morphologic distribution than the patients with idiopathic nephrotic syndrome. The high prevalence of IgM on immunofluorescence in the group with schistosomiasis also suggests that the corresponding immunocomplexes might take part in the pathogenesis of these glomerular lesions.

ANDRADE et al.[1], in a study of necropsies of individuals with schistosomiasis, without correlation with the clinical data, found mild mesangial changes (thickening and proliferation) in 60% of the kidneys of patients with the hepatointestinal form of the disease.

VAN MARCK et al.[11] and ANDRADE & VAN MARCK[3] reported that the antigen shuting, either specific of the worm or non-specific, by the portal-systemic colateral circulation is important for the genesis of schistosomal glomerulopathy. In other words, the hepatosplenic form of the disease would be essential condition for the development of schistosomal nephropathy. In our opinion, this mechanical barrier is not an essential condition, since the simple state of saturation of the reticuloendothelial system produced by parasitary infestation, with a continuos antigen production, could be responsible for the increase in the antigenic load to the kidneys.

Another possibility of renal injury in the schistosomal infestation is the presence of polyclonal activation of lymphocytes with development of autoantibodies, which could produce immunocomplexes or interact with kidney antigens[5,6].

SILVA et al.[8] studied 8 patients with hepatosplenic schistosomiasis and no clinical evidence of renal disease by means of kidney biopsy. Light microscopy showed essentially normal glomeruli, excepting a few in which there was a slight increase in the number of mesangial cells. Electron microscopy evidenced hypertrophy and hyperplasia of mesangial cells and electron dense deposits were found on subendothelial position near or underneath mesangial cells and in mesangial matrix. The same authors[4] biopsied the kidneys of 11 patients with hepatosplenic schistosomiasis and the nephrotic syndrome and the histological findings were membranoproliferative glomerulonephritis, some with lobular form.

SOBH et al.[9] submitted to kidney biopsy 15 patients with active Schistosoma mansoni infestation and with proteinuria as the single manifestation of renal disease. They found focal mesangial proliferation and immunofluorescent deposits which were mainly IgM and C_3 in 8 cases. The same group[10] studied 42 patients with hepatointestinal and hepatosplenic schistosomiasis, of which 16 had a symptomatic proteinuria and 26 had the nephrotic syndrome. They did not observe a correlation between the stage of schistosomal disease and the degree of kidney lesions, neither between the stage of the schistosomal disease and the clinical manifestation of the nephropathy. They concluded that a schistosomal-specific nephropathy does exist, in which they identified a circulating anodic antigen and a circulating cathodic antigen of the worms in the glomeruli of the patients. In its very early phases there could not be light microscopic changes. Later on, this could progress to mesangioproliferative and finally to membranoproliferative glomerulonephritis.

In our patients with the hepatointestinal form of the infestation and the nephrotic syndrome we found 8 with mesangial proliferative glomerulonephritis and 5 with membranoproliferative glomerulonephritis. This distribution of renal lesions is significantly different from that found in the patients with idiopathic nephrotic syndrome (table 1). In both histological types immunofluorescence evidenced IgM and C_3 granular deposits in the glomeruli. These data suggest that schistosomiasis, even in the early stages, might produce glomerulopathy with increased proteinuria, enough to develop a nephrotic condition. Therefore, the presence of portal hypertension and portosystemic collateral circulation is not essential to the development of membranoproliferative glomerulopathy in schistosomal patients.

Our results are based on a small number of patients, but we are convinced, as SOBH et al.[10] do, that a schistosomal-associated nephropathy does exist and the specific kidney lesions are mesangial proliferative and membranoproliferative glomerulonephritis, with IgM and C_3 granular deposits in the glomeruli at immunofluorescence. SOBH et al.[10] admit that mesangioproliferative may progress to membranop-

roliferative glomerulonephritis. It has not been proven yet that this transformation occurs, since both histological types could run independently. However, if the progression really occurs its causes are yet unknown.

RESUMO

Síndrome nefrótica associada à esquistossomose hepatointestinal.

A nefropatia esquistossomótica está classicamente vinculada à forma hepatoesplênica da esquistossomose. Ao longo dos últimos anos 24 casos de pacientes esquistossomóticos hepatointestinais e portadores de síndrome nefrótica foram estudados. Com o objetivo de verificar a possível participação etiológica da esquistossomose na gênese da nefropatia, analisamos este grupo comparativamente ao grupo de 37 doentes portadores de síndrome nefrótica idiopática. Ambos os grupos apresentaram distribuição distinta dos tipos histológicos de glomerulopatia. No grupo de esquistossomóticos houve predomínio estatisticamente significante de glomerulonefrite proliferativa mesangial (33.3%), enquanto no grupo controle houve predomínio da glomerulonefrite membranosa (32.4%). A positividade para IgM à imunofluorescência foi de 94.4% nos doentes esquistossomóticos versus 55.0% no grupo controle ($p<0.01$). No grupo de esquistossomóticos 8 pacientes evidenciaram glomerulonefrite proliferativa mesangial e 5, glomerulonefrite membranoproliferativa. Em ambos os tipos histológicos a imunofluorescência mostrou depósitos granulares de IgM e C_3 nos glomérulos. Os dados do presente estudo sugerem que as glomerulonefrites proliferativa mesangial e membranoproliferativa, com depósitos glomerulares de IgM e C_3 representam as lesões renais específicas da nefropatia esquistossomótica.

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