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PREALBUMIN, PREKALLIKREIN AND PROTHROMBIN IN HEPATOSPLENIC SCHISTOSOMIASIS: INCREASED TURNOVER OF THE CLOTTING PROTEINS? (*)

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SUMMARY

Prealbumin, prekallikrein and prothrombin were evaluated in 20 patients with the hepatosplenic form of schistosomiasis and in 18 subjects of a control group. With the prealbumin concentration values obtained in the latter group a reference interval (0.5 — 99.5%) of 97 to 389 mg/L was calculated and plasma levels below 97 mg/L assessed in 2 patients a deficiency in hepatic synthetic capacity. Mean (± SEM) prealbumin concentration in the 18 remaining patients (232 ± 13 mg/L) did not differ ($p > 0.05$) from that of the control group (243 ± 11 mg/L). Otherwise these 18 patients had both mean plasma prekallikrein (34 ± 1.3 μKat/L) and prothrombin-antigen (81 ± 3 mg/L) concentrations lower ($p < 0.01$) than those of the control group (40 ± 1.4 μKat/L and 100 ± 3 mg/L, respectively). The present findings do not necessarily rule out the possibility that prekallikrein and prothrombin may asses a minimal hepato-cellular damage earlier than prealbumin; but, since the latter protein have a shorter half-life than the formers and is a reliable index of hepatic synthetic capacity, the present report supports the hypothesis of an increased turnover of clotting proteins in some patients with the hepatosplenic form of schistosomiasis.

INTRODUCTION

Schistosomiasis is prevalent in large world areas affecting 200 million persons; in Brazil, **S. mansoni** affects about 10 million persons (ca 10% of the Brazilian population). Abnormal laboratory clotting tests are frequently observed among patients with the hepatosplenic form of the parasitosis although hepatocellular function remains good [14]. The importance of understanding these clotting alterations is clear when we consider that the main cause of death is bleeding (hematemesis and/or melena which follows gastro esophageal varices rupture); clotting laboratory abnormalities may even preclude, in these patients, necessary propedeutic and/or surgical procedures.

In schistosomiasis the clotting defects have been assigned either to impaired rates of protein synthesis by the liver and/or to localized consumption coagulopathy. Improvement, in some patients, of clotting tests after heparin administration or splenectomy supports the hypothesis that consumption of clotting factors may occur in an anatomically and hemodynamically altered spleno-portal venous systems [7].

Chronic consumption coagulopathy has been described in other diseases accompanied by splenomegaly [6] as well as in liver cirrhosis [16]. But the role of these two variables (synthesis and turnover of clotting proteins) in schistosomiasis patients has not yet been clearly distinguished.

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In this paper we have compared plasma levels of two clotting proteins (prekallikrein and prothrombin) with those of prealbumin both in schistosomiasis patients and in subjects of a control group; prothrombin time (PT), activated partial thromboplastin time (APTT) and albumin were also assayed. Prealbumin was selected because it is a true index of liver function [9].

MATERIAL AND METHODS

Thirty eight adults were studied: 20 ambulatory patients with the compensated form of hepatosplenic schistosomiasis and 18 healthy subjects from the same social-economical class as the diseased ones. The diagnosis of the parasitosis was confirmed by the finding of **S. mansoni** ova in feces and/or rectal mucosa; all patients had enlarged spleen (at least 5 cm from the left costal border). From each individual venous citrated blood was collected by a double-syringe technique: after 2 to 4 ml of blood have been drawn with the first syringe, it was removed leaving the needle in place; the second plastic syringe was then attached to the needle and the specimen collected. The contents of the latter syringe was presumed to be free of tissue factors that may contaminate specimens during venipuncture [11]. After a room-temperature centrifugation plasma was assayed for PT, APTT, prekallikrein and albumin; plasma aliquots were stored at -20°C for ulterior assay of prealbumin and prothrombin-antigen. Prothrombin time was measured by a one-stage technique using human brain thromboplastin prepared as described by POLLER & THOMSON [13]; APTT was performed using Activated Thrombofax from Ortho Diagnostics; results of these two clotting assays were expressed as a ratio (subject time: normal time). Albumin was determined by densitometry after cellulose acetate gel electrophoresis. Prealbumin and prothrombin-antigen were measured by radial immunodiffusion [12] using plates M-Partigen from Behring Institute (W. Germany). Plasma prekallikrein was activated by a 100 mg/L solution of dextran-sulphate (Mr 500 000, Pharmacia, Sweden) in 70% acetone and the kallikrein amidolytic activity was measured [1] on the chromogenic substrate S2302 (H-D-Pro-Phe-ArgpNA) from Kabi Diagnostica, Sweden.

Mean values were compared by Students "t" test.

RESULTS

With the prealbumin values obtained in the control group (Table I) a reference interval (0.5 — 99.5%) of 97 to 389 mg/L was calculated. In two schistosomiasis patients (No. 7 and 15, Table II) prealbumin plasma levels lower than 97 mg/L were interpreted as the result of impaired rate of protein synthesis by a diseased liver; these two patients had also the lowest levels of prekallikrein and prothrombin antigen (Table II) and were excluded when means showed in Table I were calculated. The remaining 18 schistosomiasis patients had similiar ($p > 0.05$) prealbumin levels than those of the control group (Table I); in these 18 patients the mean (± SEM) albumin level (44 ± 0.6 g/L), PT ratio (1.14 ± 0.03) and APTT ratio (1.08 ± 0.03) did not differ ($p > 0.05$) from those of the control group (46 ± 1 g/L, 1.08 ± 0.02 and 1.03 ± 0.02 respectively). Otherwise both mean prekallikrein and mean prothrombin-antigen levels were lower ($p < 0.01$) in the schistosomiasis group when compared with the control one (Table I). One schistosomiasis patient (No. 17, Table II) with a plasma prealbumin concentration only marginaly "normal", i.e., inside the reference interval adopted, must be considered a borderline case.

TABLE I

Mean (± SEM) values of prealbumin, prekallikrein and prothrombin-antigen in the 2 studied groups

Group	Prealbumin mg/L	Prekallikrein μKat/L	Prothrombin-antigen mg/L
Control (n=18)	243 ± 11	40 ± 1.4	100 ± 3
Schistosomiasis (n=18)	232 ± 13	34 ± 1.3	81 ± 3
"t"	0.61	2.92	5.45
p	>0.05	<0.01	<0.01

DISCUSSION

The schistosomiasis coagulopathy may be attributed to at least two variables: decreased synthesis rate and increased turnover of clotting proteins. In order to distinguish between

TABLE II
Prealbumin, prekallikrein and prothrombin-antigen in the schistosomiasis group

Patient No.	Prealbumin mg/L	Prekallikrein μKat/L	Prothrombin-antigen mg/L
1	255	28	60
2	198	34	70
3	198	41	84
4	275	37	94
5	265	32	74
6	226	36	84
7	87	14	51
8	285	37	89
9	236	36	74
10	236	36	89
11	245	28	79
12	339	44	97
13	295	37	92
14	226	36	83
15	94	18	50
16	172	39	94
17	116	32	58
18	265	41	83
19	172	25	88
20	181	23	66

the effects of these two variables on a group of patients with the hepatosplenic form of the parasitose, albumin, prealbumin, prekallikrein and prothrombin were assessed. Prekallikrein acts at the very initial (contact) phase when the intrinsic clotting pathway is activated [8] while prothrombin acts at the final step of the coagulation cascade; prealbumin, obviously not part of the clotting system, is a sensitive index of hepatic synthetic capacity [9]. In two patients (No. 7 and 15, Table II) an impaired synthesis was then admitted. Although a normal prealbumin plasma level indicates a normal rate of protein synthesis by the liver a decreased plasma level may reflect either impaired synthesis or a poor nutritional condition [10]. Anyway data from these 2 patients were not included in the means showed in Table I. The remaining 18 patients had "normal" prealbumin and albumin plasma concentrations, i.e, they do not differ from the control group; PT and APTT mean values were also "normal" in these 18 patients. It must be emphazised that global clotting tests are not sensitive to minor deficiencies of clotting factors; indeed prekallikrein and prothrombin mean values were only 15% and 19% respectively lower than those found in the control group, although these differences are statistically significant ($p < 0.01$). Since we had determined prothrombin immunoreactive protein but not its coagulant activity we could not evaluate a possible impaired carboxylation as had been previously found in other liver diseases [2].

A normal prealbumin plasma level of the schistosomiasis group was in variance with decreased prekallikrein and prothrombin concentrations. Measurement of circulating levels of prothrombin antigen is an excellent indication of hepatic synthetic capacity [5]; although we cannot rule out the possibility that this clotting protein may asses a minimal hepato-cellular damage earlier than prealbumin, there are no reason to suppose that prealbumin synthesis may be selectively preserved in schistosomiasis patients. As a matter of fact the 2,8 days of prothrombin biologic half-life [15] is longer than the 1,9 days of prealbumin half-life [9]. Prekallikrein half-life is supposed to be around 36 h in rats [3] but there are no human data available. These facts may altogether indicate that in schistosomiasis patients with well preserved hepatic synthetic capacity a decreased concentration of a clotting protein is secondary to an increased turnover. Such a situation had already been described in cirrhosis [4] where liver functions are not as well preserved as in schistosomiasis. We can conclude by stating that, facing the "dilemma" decreased synthesis versus increased turnover of clotting proteins in schistosomiasis:

a) global clotting tests may not be useful; and
b) prealbumin as well as individual clotting proteins must be evaluated.

The correct interpretation of laboratory clotting tests in patients with the hepatosplenic form of schistosomiasis is fundamental when propedeutic and/or surgical decisions must be made.

Unfortunately the evaluation of isolated clinical cases will seldon be simple, mainly in borderline cases (as exemplified by patient 17, Table II) and in patients with moderate to severe degree of undernutrition, a situation commonly found in countries where schistosomiasis is prevalent.

RESUMO

Prealbumina, precalicreína e protrombina na forma hepatesplênica da esquistossomose: ca-

tabolismo aumentado de proteínas da coagulação?

No plasma de 20 doentes portadores da forma hepatesplênica da esquistossomose mansônica, assim como no de 18 indivíduos normais, foram avaliados pré-albumina, precalicreína (atividade amidolítica) e protrombina-antígeno. Os valores da concentração plasmática de pré-albumina obtidos no grupo controle permitiram que se estabelecesse um intervalo de referência (0,5 — 99,5%) de 97 — 389 mg/l. Valores anormalmente diminuidos de pré-albumina encontrados em 2 dos doentes indicaram nestes uma disfunção hepatocítica de síntese protêica.

Nos 18 doentes restantes a média da pré-albumina (232 ± 13 mg/l) não diferiu ($p > 0,05$) da do grupo controle (243 ± 11 mg/l) enquanto as médias da atividade de pré-calicreina (34 ± 1 μKat/l) e protrombina (81 ± 3,0 mg/l) estavam significativamente diminuídos no grupo de esquistossomóticos ($p < 0,01$).

Estes dados não excluem a possibilidade da pré-calicreina ou da protrombina-antígeno serem marcadores de síntese protêica pelo hepatócito mais sensíveis que a pré-albumina; se entretanto a concentração plasmática normal desta proteína indicar preservação desta função, a diminuição de fatores de coagulação poderá ser secundária a um "turnover" aumentado dos fatores de coagulação na forma hepatesplênica da esquistossomose.

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