

Fibrinolysis and the bleeding tendency in patients with hepatosplenic schistosomiasis

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Abstract

Fifty seven patients with schistosomiasis of the liver and spleen in both the compensated and decompensated states and 15 non-bilharzial subjects were studied. Fibrinogen, plasminogen, fibrinogen/fibrin degradation products, α_2 -macroglobulin, antithrombin III and Cl-activator concentrations were evaluated in an attempt to assess abnormalities at various stages of the disease. The results showed a progressive decrease in fibrinogen and plasminogen concentrations; fibrin degradation products showed a progressive increase as the disease progressed. Together with a falling platelet count, these data indicate the possible occurrence of disseminated intravascular coagulation with enhanced fibrinolysis which was most pronounced in those who vomited blood. Antithrombin III concentration showed a progressive decrease in parallel with the progress of the disease, possibly due to decreased synthesis or increased consumption, or both. Cl-activator concentration showed no significant change from that in normal controls at any stage of the disease. These findings provide further evidence that disseminated intravascular coagulation and enhanced fibrinolysis in the late stages of schistosomiasis may contribute to the haemorrhagic diathesis seen in the liver and spleen.

A major health problem in various parts of the world and in Egypt is schistosomiasis of the liver and spleen.¹ The disease is well known for the bleeding tendency that may result from diminished synthesis of coagulation factors, fibrinolytic system activation, and consumption coagulopathy.²⁻⁴ Acute attacks of haematemesis from ruptured oesophageal varices are often life-threatening and are probably exacerbated by impaired haemostatic and fibrinolytic mechanisms.⁵

We studied some variables of the fibrinolytic system, both in compensated and decompensated states of the disease, to clarify the part played by fibrinolytic activity during the acute attacks of haematemesis secondary to ruptured oesophageal varices.

Methods

This study included 72 subjects: 15 normal controls, and 57 patients with schistosomiasis in whom disease was confirmed by urine and

stool analysis, sigmoidoscopic examination, rectal biopsy, ultrasonography and by liver biopsy whenever possible. Patients were further classified into compensated and decompensated groups: the former were subdivided into 15 patients with enlarged liver and spleen (group 1) and 15 with an enlarged spleen only (group 2); and the latter comprised patients with advanced hepatic fibrosis with ascites (15 cases, group 3) and 12 patients who had acute attacks of haematemesis from ruptured oesophageal varices (group 4). Blood differential, platelet count, prothrombin time and liver function tests were carried out and antibodies to hepatitis B surface antigen (HBsAg) were measured in all members of the study. The patients included in groups 1-4 were negative for HBsAg. Plasma fibrinogen concentration was determined by a modified Clauss method,⁶ using the Multifibren test kit (Behring Institute, Mannheim, West Germany). Plasminogen concentration was estimated by M-Partigen immunodiffusion plates (Behring Institute). The quantitative determination of α_2 -macroglobulin, Cl-activator, and antithrombin III was done with Nor-Partigen immunodiffusion plates (Behring Institute). Estimation of fibrin degradation products was done with staphylococcal clumping test⁷ using a Fibro Tec Combipack Kit (Behring Institute).

Results

The results obtained from this study showed a progressive decrease in platelet count and fibrinogen, plasminogen and antithrombin III concentrations as the disease progressed, while fibrin degradation products progressively increased. The α_2 -macroglobulin concentration was raised in group 1 patients, group 2 patients, and in those with ascites (group 3), and was normal in group 4 patients. Cl-inactivator was within the conventional range of normal in all of the groups (table).

Statistical analysis (Mann-Whitney U test)⁸ showed a significant difference between the control group and the group 1 in fibrinogen degradation products and α_2 -macroglobulin concentration ($p < 0.001$) and a significant difference in fibrinogen, plasminogen, and antithrombin III concentrations ($p < 0.01$). The difference between the control group and the other diseased groups was significant for all the aforementioned variables ($p < 0.001$), except for α_2 -macroglobulin during acute attacks of haematemesis ($p > 0.05$). The difference between group 1 and group 2 was significant for antithrombin III ($p < 0.001$), significant for plasminogen ($p < 0.01$), but

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Tested variables in normal controls and disease groups

		Fibrinogen (mg/dl)	Plasminogen (mg/dl)	Fibrin degradation products (μ g/ml)	α_2 -macro- globulin (g/l)	Anti- thrombin III (g/l)	Cl-inactivator (g/l)	Platelets ($10^9/l$)	Prothrombin time (seconds)
Normal controls (n=15)	Range	253-412	10.6-20.0	2.88-5.76	1.86-2.9	0.272-0.375	0.240-0.288	200-350	11-12.7
	Median	331	11.8	5.76	2.63	0.300	0.252	280	11.9
	Mean (SD)	333.47 (48.37)	12.53 (2.46)	4.61 (1.46)	2.6 (0.32)	0.315 (0.035)	0.253 (0.015)	278 (44.51)	11.89 (0.45)
<i>Compensated form:</i>									
Group 1 (n=15)	Range	196-358	6.0-12.6	5.76-46.08	2.9-6.15	0.168-0.344	0.154-0.449	21-380	12-14.9
	Median	253	10.6	23.04	3.93	0.231	0.217	140	13.3
	Mean (SD)	266.7 (53.16)	9.64 (2.31)	23.42 (13.15)	4.06 (1.05)	0.242 (0.05)	0.253 (0.094)	146.13 (97.97)	13.1 (0.93)
Group 2 (n=15)	Range	180-307	3.0-10.6	23.04-46.08	2.36-5.78	0.111-0.218	0.154-0.313	26-166	11.4-17.9
	Median	227	7.4	23.04	3.78	0.168	0.262	55	14.5
	Mean (SD)	233.53 (36.94)	7.12 (2.69)	30.72 (11.2)	3.78 (0.98)	0.174 (0.029)	0.24 (0.055)	78.06 (41.19)	14.82 (1.87)
<i>Decompensated form:</i>									
Group 3 (n=15)	Range	139-269	3.0-10.6	46.08-92.16	2.63-6.52	0.06-0.168	0.134-0.352	38-90	13.5-20.4
	Median	196	5.2	46.08	3.48	0.144	0.240	71	15.8
	Mean (SD)	197.07 (36.61)	5.71 (2.26)	64.51 (23.37)	3.76 (1.08)	0.129 (0.039)	0.242 (0.063)	69.82 (15.2)	15.89 (1.74)
Group 4 (n=12)	Range	83-259	3.0-4.6	92.16-368.6	1.29-3.18	0.06-0.144	0.125-0.288	30-90	15.8-25
	Median	151.5	3.6	184.32	2.62	0.116	0.240	51.5	17.9
	Mean (SD)	164.33 (61.3)	3.5 (0.52)	215.0 (120.0)	2.47 (0.68)	0.11 (0.03)	0.227 (0.05)	56.25 (17.75)	18.63 (2.66)

not for fibrinogen, fibrinogen degradation products, and α_2 -macroglobulin ($p > 0.05$). The difference between group 1 and the groups 3 and 4 was significant for plasminogen, fibrinogen degradation products, antithrombin III ($p < 0.001$) and fibrinogen ($p < 0.01$), and that for α_2 -macroglobulin was significant for group 4 ($p < 0.01$), but not for group 3 ($p > 0.05$). The difference between group 2 and group 3 patients was significant for fibrin degradation products ($p < 0.001$), fibrinogen, and antithrombin III ($p < 0.01$), but not for plasminogen and α_2 -macroglobulin ($p > 0.05$). As regards groups 2 and 4, the difference was significant for plasminogen, antithrombin III, and fibrin degradation products ($p < 0.001$), as well as for fibrin and α_2 -macroglobulin ($p < 0.01$). Groups 3 and 4 patients showed a significant difference in concentrations of fibrin degradation products ($p < 0.001$), plasminogen, and α_2 -macroglobulin ($p < 0.01$) but not in fibrinogen or antithrombin III ($p > 0.05$). Cl-inactivator was the same for all groups tested.

Discussion

This study attempted to shed light on the part played by fibrinolytic mechanisms in causing the haemostatic abnormalities seen in hepatosplenic schistosomiasis. The results obtained showed a progressive decrease in fibrinogen concentration as disease advanced which was more obvious in groups 3 and 4. More than one factor is responsible for the hypofibrinogenaemia occurring in chronic liver disease: decreased hepatic synthesis; increased consumption during intravascular coagulation; destruction by abnormal plasma fibrinolytic activity; and unreplaced loss during massive haemorrhage from oesophageal varices.⁹ Exchange of plasma fibrinogen into ascitic fluid or increased catabolism will also hasten the rapid disappearance of fibrinogen from plasma.¹⁰ The progressive decrease in plasminogen concentration as disease advanced could be explained by decreased synthesis owing to hepatic fibrosis or increased consumption by enhanced fibrinolytic activity, or both. Fibrin degradation products were increased in

patients' sera, being the lowest in group 1 and the highest in group 4. The existence of the progressively increasing concentrations of fibrin degradation products on the one hand, and the progressive decrease of fibrinogen and plasminogen concentrations and platelet count on the other, could be accounted for by the enhanced fibrinolytic activity or disseminated intravascular coagulation, or both, which often accompany hepatic fibrosis in patients with schistosomiasis, especially in the advanced ascitic and haemorrhagic groups. The occurrence of disseminated intravascular coagulation could be attributable to exposure of blood to the expanded collaterals and the distorted splenic circulation in conjunction with impaired hepatic clearing of the pro-coagulants.¹¹ Localised intravascular coagulation might also be the outcome of microthrombi present in hepatic venules at the site of schistosomal granulomas, or pressure necrosis affecting the peripheral hepatocytes.¹² The α_2 -macroglobulin concentration was increased in groups 1-3, reverting to normal in group 4, which differs from that of other acute phase proteins such as haptoglobin, transferrin, or α_1 -antitrypsin. These are known to decrease in chronic liver disease due to diminished synthesis by the liver—their main site of synthesis. The significant increase in α_2 -macroglobulin can thus be attributed to immunomodulatory functions,¹³ while its decrease in group 4 might be due to increased consumption in the complexes formed with excess plasmin and thrombin.¹⁴ Antithrombin III concentration progressively decreased as the disease advanced, probably as a result of impaired hepatic synthesis and increased consumption.¹⁵ Cl-inactivator concentration showed no significant difference between the disease groups and normal controls in any stage of the disease.

The data obtained from group 4 during acute attack of haematemesis showed low concentrations of fibrinogen, plasminogen, and α_2 -macroglobulin, a low platelet count and very high concentration of fibrin degradation products. These data indicate that increased fibrinolysis or disseminated intravascular coagulation, or both, may be present during an acute attack of haematemesis. This suggests

that disseminated intravascular coagulation and increased fibrinolysis are important factors that underlie the haemorrhagic diathesis seen in hepatosplenic schistosomiasis.

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