Spectrum of hemostatic derangements in Budd-Chiari syndrome

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Background: Hemostatic abnormalities have been reported in various hepatocellular diseases. We evaluated the hemostatic functions in patients with Budd-Chiari syndrome. Methods: Biochemical liver function tests, and measurement of prothrombin time, activated partial thromboplastin time, and plasma levels of anti-thrombin III (antigen) and activity of protein C were done in 36 patients with Budd-Chiari syndrome. Results: Liver biochemistry was abnormal in 34 patients. Plasma prothrombin time and activated partial thromboplastin time were prolonged in 17 (47%) and 23 (64%) patients, respectively. Anti-thrombin III antigen levels and protein C activity were reduced in 15 (50%) and 25 (83%) patients, respectively, among the 30 patients studied. Albumin levels showed significant correlation with coagulation test results, levels of anti-thrombin-III, and protein C activity. Conclusion: Hepatic synthesis of coagulation factors and anticoagulants is reduced in Budd-Chiari syndrome; this may play a role in recurrence of thrombosis. [Indian J Gastroenterol.2003;22:59-60]

Key words: Activated partial thromboplastin time, antithrombin III, protein C, prothrombin time

Budd-Chiari syndrome (BCS) results from occlusion of the hepatic veins (HV) and/or inferior vena cava (IVC). Sinusoidal dilatation and centrilobular congestion of liver parenchyma lead to ischemia, pressure necrosis and atrophy of centrilobular hepatocytes; this may lead to derangement of liver function.

Liver disease is associated with hemostatic abnormalities like prolonged plasma prothrombin time (PPT) and activated partial thromboplastin time (APTT), and reduction in levels of natural anticoagulants like anti-thrombin III (AT III) and protein C. These abnormalities have not been documented in patients with BCS. The available studies in BCS have focused on hereditary defects in AT III and protein C.

Methods

Thirty-six consecutive patients with BCS (18 men) were studied. The diagnosis was confirmed by ultrasonography, liver biopsy and inferior vena cavaography with pressure measurements. Obstruction of the IVC alone was found in 21 (58%) patients and that of HV alone in 6 (17%) patients; 9 (25%) patients had combined HV and IVC block. Venous thrombosis at other sites was observed in 5 (14%) patients; one had deep vein thrombosis of leg veins, 2 had renal vein thrombosis with nephritic syndrome, and one patient each had obstruction in splenic and portal veins. No patient had family history of venous thrombosis. All patients except one presented in the chronic phase of the disease, with duration of illness varying from 6 weeks to 14 years.

Platelet count was checked in all patients. Biochemical investigations included serum bilirubin, alkaline phosphatase (SAP), AST, ALT and albumin. For PPT, APTT, fibrin degradation products (FDP). AT III, lupus anticoagulant and protein C activity, 4.5 mL of blood was collected in 0.5 mL of 3.8% sodium citrate and was immediately centrifuged at 4°C. PPT and APTT tests were performed on fresh platelet-poor plasma using a technique described previously. The remaining plasma was stored in aliquots at -70°C for estimation of AT III and protein C activity. Plasma levels of AT III antigen were estimated using Laurell's rocket immuno-electrophoresis, and protein C activity using a chromogenic substrate assay kit (Diagnostica Stago, France); for these assays, pooled plasma from 20 healthy subjects was used as control and levels below 70% of that in the control were considered as abnormal. FDP levels were estimated in 19 specimens using a semiquantitative method. Tests for lupus anticoagulant were done in patients with prolonged APTT by Russell's viper venom time and platelet neutralization tests.

Pearson's correlation coefficient was used to assess the relationship of serum albumin levels with PPT, APTT, AT III and protein C levels.

Results

The presenting clinical features were: ascites 28 patients (78%), hepatomegaly 26 (72%), splenomegaly 21 (58%), prominent anterior abdominal wall veins 18 (50%), pedal edema 15 (42%), abdominal pain 11 (31%), history of gastrointestinal bleeding 9 (25%), and jaundice 8 (22%).

Levels of both AST and ALT were increased in 6 patients (Table). The platelet count was within normal limits (150-400 x 10^9/L) in 31 patients; it was low (100-130 x 10^9/L) in 3 patients and high (420-480 x 10^9/L) in 3 patients.
2 patients. PPT was prolonged (>3 s above control) in 17 (47%) patients and APTT (>6 s above control) in 23 (64%) patients. None of the 23 patients with prolonged APTT had lupus anticoagulant. Increased serum FDP levels (10-40 μg/mL) were observed in 15 of 19 specimens studied.

AT III levels were low in 15 of 30 (50%) patients; the levels in these patients were 12% to 55%. Protein C activity was low in 25 of 30 (83%) patients; the activity in these patients varied from 4% to 55%.

A positive correlation was observed between PPT and APTT (r=0.82, p<0.001). Albumin levels had negative correlation with both PPT (r=0.56; p<0.001) and APTT (r=0.39; p<0.05), and positive correlation with AT III levels (r=0.49; p<0.02) and protein C (r=0.49; p<0.02).

On keeping the values of APTT, AT III and protein C constant, a significant negative correlation (r = -0.428, p<0.05) was found between PPT and albumin. Similarly on keeping the values of PPT, protein C and AT III constant, a negative correlation was observed between APTT and albumin (r = -0.467, p<0.05), suggesting that these changes were independent of each other.

Discussion

Liver is the major site of production of most of the coagulation factors and of natural anticoagulants, namely, AT III and protein C. Therefore, defective synthetic function of liver may result in abnormal in vitro coagulation tests such as prolonged PTT and APTT, and low levels of plasma AT III and protein C. These test abnormalities have been reported in patients with acute and chronic liver disease, and hepatic encephalopathy.

Mohanty et al.\(^7\) in a study of 53 patients with BCS, found low serum albumin levels (<3.0 g/dL) in 4, raised ALP in 4, elevated AST in 8 and elevated ALT in 9 patients. In our study, low serum albumin was more frequent. However, in that study, 23 of 53 patients had acute BCS, whereas only one of our patients had acute disease. PPT and APTT were prolonged in 47% and 64%, respectively, of our patients; the correlation between these parameters and serum albumin suggests that deranged PPT and APTT in our patients may be attributable to defects in synthetic function of the liver. Similarly, reduced levels of AT III and low activity of protein C could also have resulted from poor synthetic function of the liver. It is however possible that some of our patients had hereditary deficiency of AT III or protein C. However the much higher frequency of deficiency of these factors (50% and 83%, respectively), as compared to previous reports (0%-3.8% and 9.3%-13.2%, respectively),\(^8\) makes this unlikely.

Many patients with BCS develop venous thrombosis at other sites.\(^3\) Five of our patients also had thrombosis at sites other than the HV and IVC. These might be a result of the abnormalities in AT III and protein C. Also, these consequences of reduction in liver function may predispose patients to thrombosis of surgically created porta-systemic shunts.\(^1\)

References