Study of hemostasis in pediatric patients with portal vein thrombosis

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We describe the behavior of hemostatic variables in children with portal vein thrombosis (PVT) and in a control pediatric population. Hereditary protein C (PC) or protein S (PS) deficiency was not a etiologic factor for PVT in children. Minor signs of comsumption of coagulation factors II, V, fibrinogen and hyperfibrinolysis were detected. One child had lupus anticoagulant (LA).

PVT is responsible for the majority of cases of portal hypertension and upper gastrointestinal tract hemorrhages in children.[1,2] PC and PS have not previously been investigated as an etiologic factor for PVT, but a hereditary tendency to thrombosis may lead to PVT. The hemostatic system may be altered due to a hepatic proteic synthesis insufficiency and/or disseminated intravascular coagulopathy due to thrombosis. As the main objective, we evaluated whether PC and PS deficiencies were etiologic factors for PVT. We also studied components of hemostasis in children with PVT in order to determine the mechanism involved in coagulation abnormalities, if present.

This study comprised all patients with PVT that were diagnosed by Pediatric Clinics at the University Hospital of Unicamp/Campinas, between 1987 and 1995. The patient group consisted of 20 children (8 males and 12 females) diagnosed as having PVT at the median age of 77 months (2→136). An age- and sex-matched control group comprised 20 children and another was composed of 61 normal children, 24 males and 37 females at the median age of 95 months (43→177). PC was measured by a coagulation method and total and free PS were determined by rocket immunoelectrophoresis.[3]

Prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), coagulation factors II, V, VII, IX, X, XII and fibrinogen concentration were determined by coagulation methods. Euglobulin lysis time (ELT),[4] and lysis area on fibrin plate (LAFP) were performed by described procedures.[5] D-dimer was measured by latex method.[6] LA was screened by kaolin clotting time and dilute Russell viper venon time (dVVT) and confirmed by DVV confirm®, and frozen-thawed platelets.[7] For statistical analysis we used Student's *t* test.

There was no difference in PC and PS between patients and controls. None of the patients had a congenital deficiency of PC or PS. One patient demonstrated an acquired decreased PC level (62%); his parents were normal. One patient had LA which was reconfirmed later on. PT and TT were increased and coagulation factors II and V were decreased in patients when compared to the control group. Seven patients had D-dimer levels greater than 0.5 µg/mL. Prealbumin levels were decreased in patients.

Table 1.

	Patient group mean±SD	*Matched group mean±SD*	*Control group mean±SD*
APTT (R)	1.13±0.17	1.12±0.09	1.09±0.11
PT (R)	1.24±0.22°*	1.03±0.08*	1.04±0.08°
TT (R)	1.10±0.08*	1.02±0.07*	1.07±0.13
Factor II (%)	83.4±13.8°*	99.4±16.15*	97.0±14.57°
Factor V (%)	71.4±17.83°*	95.2±19.62*	94.4±22.28°
Factor VII (%)	106.95±35.57	106 ±19.59	97.4±26.10
Factor IX (%)	101.07±37.26	118.1±38.7	I107.2±35.24
Factor X (%)	88.82±19.65	91.3±15.29	85.8±12.66
Factor XII (%)	88.97±37.51	89.6±16.46	90.8±17.05
LAFP (mm^2)	240.7±79.43°*	75.9±38.02*	102.4±51.02°
ELT (min)	290±211.8°*	390±146.9	410±102.89°°
Fibrinogen (mg %)	200.7±61.97	245.5±69.21	280.9±66.31
Protein C (%)	100.8±31.04	101±34.93	109.2±21.48
Total protein S (%)	99.5±15.06	81.8±8.48	88.1±12.86
Free protein S (%)	94.76±11.83	86.1±11.95	100.6±21.77
Prealbumin (%)	66.4±21.5°*	78±19.32*	85.2±23.87°

LAFP-lysis area on fibrin plateELT-euglobulin lysis time;
R-relation of time obtained between patient and controls SD-standard deviation;
**p< 0.01; **p< 0.05; *between patient group and matched group;*
°p< 0.01; °°p< 0.05; °between patient group and contrlos.

The importance of inherited prethrombotic states such deficiencies of antithrombin, PC, PS and factor V Leiden has been realized.[8] We had previously investigated factor V Leiden in these 20 children with PVT but none of them carried this mutation, suggesting it was not a risk factor for PVT in our children.[9] The analysis of coagulation inhibitors could reveal congenital disorders but also changes secondary to deficient liver synthesis resulting from the PVT. In this study, congenital deficiencies of coagulation inhibitors, potentially implicated in the etiology of PVT, were not found. Only one patient had low PC levels which were not congenital, since his parents had normal PC levels. This deficiency was, therefore, a consequence and not the cause of his PVT. His low factor V, prealbumin level, increase in TT and TP suggested a decrease in protein synthesis and/or intravascular coagulation. Our data suggest that intravascular coagulation had occurred, associated with decreased factor II, V and fibrinogen levels, hyperfibrinolysis and increased D-dimer. Changes in liver synthesis function cannot be ruled out, since prealbumin was diminished in these patients. Vitamin K

metabolism was unaffected since factors VII, IX, X, PC and PS were within the normal range. LA was found in one patient and may have been the cause of the PVT. Due to the importance of LA in thrombosis, this raises the question of whether LA could be investigated in children with PVT.

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Hyperammonemic encephalopathy in multiple myeloma

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We report two cases of hyperammonemic encephalopathy in patients with multiple myeloma. This rare complication, whose pathophysiology remains unknown, is associated with disease progression and so with a very bad prognosis. We believe that this complication should be included in the differential diagnosis of encephalopathy occurring in multiple myeloma.

Hyperammonemia is usually found in chronic liver diseases with portal-systemic shunts and acute fulminant hepatic failure.[1] It has also been described in hematologic malignancies such as acute leukemia,[2] following bone marrow transplantation[3] and in eleven patients with multiple myeloma (MM).[4-10] We report two new cases of hyperammonemic encephalopathy in MM.

Patient #1. IgG λ MM was diagnosed in a 56-year-old woman. Five courses of vincristine, adriamycin and dexamethasone (VAD) resulted in good partial remission. Three months later she presented with a one-week history of alternating lucidity and delirium, lethargy and inappropriate behavior. Serum electrolytes and creatinine were normal. Serum IgG λ spike amounted to 1920 mg/dL. A lumbar puncture and a computed axial tomography were unremarkable. The electroencephalogram presented changes compatible with metabolic encephalopathy. Plasma ammonium concentration was 170 mg/dL (normal < 82 mg/dL). Bilirubin, liver transaminases, coagulation tests, viral hepatitis serology, an abdominal ultrasound and a transjugular liver biopsy showed no alterations. Dietary nitrogen was eliminated and oral lactulose therapy was started, but mental status and plasma ammonium levels did not improve. A bone marrow (BM) aspirate showed 84% plasma cells. Three days after reinstituting chemotherapy (VAD), plasma ammonium decreased to normal and the patient became rapidly asymptomatic. Three months later the patient developed the same symptoms and died of disease progression.

Patient #2. IgA κ MM was diagnosed in a 51-year-old man. Chemotherapy (VAD) and local radiotherapy to the ribs and lumbar spine were started. After 6 courses he presented with disorientation, bradypsychia and myoclonus. Neurological examination and a lumbar puncture were normal. A magnetic resonance imaging scan showed diffuse edema in the brain. The electroencephalogram recorded triphasic waves. Serum electrolytes and renal and liver function were normal. Plasma ammonia level was 233 mg/dL. Serum IgA κ spike amounted to 4000 mg/dL. There were progressive osteolytic lesions and 100% plasma cells in BM aspirate were demonstrated. The clinical manifestations were ascribed to hyperammonemic encephalopathy and treatment with dexamethasone (8 mg/day) was started. Hyperammonemia and the neurologic alterations improved immediately after chemotherapy (VAD) was instituted. One month later the patient again presented with hyperammonemic encephalopathy and died of dis-