CASE REPORT

Extra Hepatic Portal Hypertension Due To Familial Protein S Deficiency

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Portal vein thrombosis (PVT) is a common cause of portal hypertension in children. A majority of children with PVT of unknown etiology have functional Protein C deficiency or abnormally elevated levels of anti-cardiolipin antibodies. We report an 8 years old Indian girl with portal cavernoma due to hereditary Protein S deficiency. We documented familial deficiency of Protein S in 2 asymptomatic siblings suggesting that this deficiency is the primary cause of portal vein thrombosis.

Keywords: *Portal vein thrombosis, Protein S.*

Portal vein thrombosis (PVT) is a common cause of portal hypertension in children from developing countries(1). It was initially proposed that umbilical sepsis or catheterization of the umbilical veins in the neonatal period were responsible for PVT. However, such history is available in only a minority of patients with PVT. Further, PVT is uncommon on follow-up in patients with umbilical infection or umbilical vein catheterization(2). Deficiencies of the natural anticoagulant proteins, protein C, protein S and antithrombin have been reported as strong risk factors(3). Deficiencies of the natural inhibitors of the procoagulant system are rare with less than 0.4% reported in healthy individuals and 1-3% of patients with deep vein thrombosis(4). We report a child with extra hepatic portal hypertension due to deficiency of protein S.

Case Report

An 8 year-old girl born of non consanguineous marriage presented with abdominal pain. An ultrasound abdomen showed splenomegaly with portal cavernoma. Esophageogastroscopy did not reveal varices. There was no history of hematemesis, malena, jaundice, severe dehydration or neonatal umbilical catheterization. Family history was non-contributory. On examination, she was well nourished and had splenomegaly. Other systemic examination was normal. The liver function tests were normal and her hemogram showed anemia (hemoglobin 8.8 g/dL), with leucopenia (white cell count 2,700/cumm) with normal platelet count (2,75,000/cumm) with reticulocyte count of 2%. Repeat ultrasonography of abdomen revealed multiple perigall bladder varices with portal cavernoma and splenomegaly. A thrombophilia workup revealed absent urine homocysteine with normal protein C (levels 81.6%) and antithrombin III levels (84%). Her ANA, ds DNA, anti phospholipid antibodies, anti cardiolipin antibodies were negative. Total protein S levels were low [53.7% (normal 60-120%)] as measured by ELISA [Diagnostica Stago, Asniers, France]. Her two younger siblings (one boy and one girl) who were asymptomatic were also screened for Protein S deficiency and were found to be deficient (52.2% and 31.9%) respectively. Parents were not tested. The patient was started on folic acid, beta blockers and advised pneumococcal vaccine as a preventive measure in case of future need for splenectomy. The child was advised regular follow up with monitoring for hypersplenism and

increasing portal pressures. Both siblings were not treated as they were asymptomatic.

DISCUSSION

Protein S is a natural inhibitor of the procoagulant system along with Protein C and Antithrombin III. Deficiencies of these inhibitors are estimated to increase the risk of deep vein thrombosis by approximately 10-fold(4). An Indian study has found that majority of children with PVT have functional protein C deficiency or abnormally elevated anti cardiolipin antibodies(1). Similarly in Mexican patients with non-cirrhotic PVT, 31% had protein C deficiency(5). However, a French study has found that in non-cirrhotic PVT, deficiency of Protein S was found in maximum number of patients(6) and in a study from UK, protein S deficiency was found to be 38% of patients with portal vein thrombosis(7).

Regardless of whether or not there is an associated precipitant, patients presenting with PVT should also be investigated for an underlying thrombophilic condition such as hereditary thrombophilic state. Hereditary thrombophilias that are known to predispose to PVT include certain mutations of the prothrombin or factor V genes, or deficiency of one of the natural anticoagulant proteins C, S, or antithrombin(7).

Our patient did not have any hepatic impairment and thus the reduced Protein S level was not due to liver dysfunction. A study in patients with PVT with normal liver function tests found single or combined deficiencies of protein C, protein S and antithrombin in 62% of cases, but family studies suggested that majority of these were acquired, rather than hereditary(7). However, a minority of cases of PVT may have a true underlying hereditary anticoagulant protein deficiency and this can only be confirmed by careful investigation of family members, as seen in our patient where family study suggested that the protein S deficiency was hereditary.

Though our patient did not have any thrombus in the portal vein on ultrasonography, it is likely that the acute thrombosis may have been missed and when the child presented to us, cavernous transformation had already taken place. Formation of collaterals occurs rapidly and has been described as early as 12 days after acute thrombosis, though average time to formation is approximately 5 weeks(3). Thus, the portal cavernoma in our patient could be secondary to a thrombotic episode with underlying Protein S deficiency.

Management of patients with portal hypertension with underlying thrombophilia state consists of sclerotherapy, adjunctive propanolol therapy and portosystemic shunt with severe bleeds(7). Role of warfarin in PVT remains debatable.

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REFERENCES

1. Yachha SK, Aggarwal R, Sharma BC, Misra RN, Aggarwal A, Nair SR. Functional Protein C and anti-cardiolipin antibody in children with portal vein thrombosis. Indian J Gastroenterol 2001; 20: 47-49.
2. Yadav S, Dutta AK, Sarin SK. Do umbilical vein catheterization and sepsis lead to portal vein thrombosis? A prospective, clinical and sonographic evaluation. J Pediatr Gastroenterol Nutr 1993; 17: 392-396.
3. Sald A. Portal vein obstruction. E-medicine. Available on URL:http://www.e-medicine. Accessed on 18th August, 2005.
4. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet 1999; 353: 1167-1173.
5. Majluf-Cruz A, Hurtado Monroy R, Sansores Garcia L, Labardini–Mendez J. The incidence of Protein C deficiency in thrombosis related portal hypertension. Am J Gastroenterol 1996; 91: 976-980.
6. Denninger MH, Chait Y, Casadevall N, Hillaire S, Guillin MC, Bezeaud A, *et al*. Cause of portal or hepatic venous thrombosis in adults: the role of multiple concurrent factors. Hepatology 2000; 31: 587-591.
7. Fisher NC, Wil de JT, Roper J, Elias E. Deficiency of natural anticoagulant proteins C, S and antithrombin in portal vein thrombosis: a secondary phenomenon? Gut 2000; 46: 534-539.
8. Condat B, Pessione F, Erlinger S, Valla D. Portal vein thrombosis: outcome in 94 adult patients [abstract]. Hepatology 1997; 26: 204A.