False findings of low protein C activity in two children with Budd-Chiari syndrome and factor V Leiden mutation

FIGEN ÖZÇAY * and NAMIK ÖZBEK
Department of Pediatrics, Başkent University Faculty of Medicine, Ankara, Turkey

Abstract—Two pediatric patients with Budd-Chiari syndrome are reported, who were heterozygous for factor V Leiden mutation. The first patient was falsely diagnosed with type II protein C deficiency, and the second was initially found to have decreased protein C activity based on a protein C clotting assay. Retesting by protein C chromogenic assay indicated that protein C activity was normal in both children. In patients with Budd-Chiari syndrome, low levels of protein C antigen and activity should be interpreted with caution, and within the context of factor V Leiden mutation status, parents’ results, severity of liver dysfunction, and the type of protein C assay performed in order to avoid misdiagnosing protein C deficiency.

Key words: Budd-Chiari syndrome; factor V Leiden mutation; protein C.

INTRODUCTION

Budd-Chiari syndrome (BCS) is a rare disorder that results from obstruction of hepatic venous outflow. There is a well-established link between BCS and hereditary thrombophilic disorders. Reports have stated that factor V Leiden (FVL) mutation and hereditary protein C (PC) deficiency are important risk factors for BCS and portal vein thrombosis [1, 2]. Protein C, a vitamin K-dependent glycoprotein synthesized by the liver, is one of the main natural inhibitors of the procoagulant system. Once activated on endothelial cells, it rapidly inactivates coagulation factors Va and VIIIa. Type I PC deficiency is characterized by concomitant and proportional decreases in both PC activity and PC antigen level. Type II PC deficiency, also known as dysfunctional PC, is distinguished by decreased PC activity in the face of normal antigen levels. The latter is indicative of a dysfunctional PC molecule. To date, only a small number of type II PC deficiency cases have been published in the literature [3, 4].

*To whom correspondence should be addressed at Başkent University Faculty of Medicine, 6. Cadde 72/3, 06490 Bahçelievler, Ankara, Turkey. E-mail: fozcay@superonline.com
FVL mutation, the most common inherited risk factor for venous thrombosis, is caused by a point mutation in the factor V gene, and results in resistance to activated PC. Combination of the FVL mutation with other acquired or hereditary risk factors, such as PC deficiency, has been reported [1]. However, diagnosing inherited PC deficiency in certain BCS patients is difficult because low PC levels can also reflect failure of hepatic synthesis. In addition, the FVL mutation interferes with functional plasma-based coagulation assays of PC, and mimics type II PC deficiency [5].

Here we describe two children with BCS and FVL mutation who both appeared to have low protein C activity based on their initial work-up. In both cases, repeat testing with chromogenic PC assay of the patient and his parents ruled out any hereditary protein C abnormalities.

CASE 1
An 8-year-old-boy was referred to our hospital for liver transplantation. He had a 1-year history of abdominal distension and, 9 months prior to presentation at our hospital, had been diagnosed with chronic BCS at a local center. According to his medical records, the child had had two episodes of hepatic coma, both of which were treated at his local health facility. There was no known history of dehydration, trauma, surgery, or thrombosis. Physical examination revealed massive ascites, mild jaundice, edema in both legs, and prominent veins in the abdominal wall. The patient was in a grade II hepatic coma, and exhibited slurred speech and agitation. His laboratory results were as follows: hemoglobin 12.1 g/dl, white blood cell count 9 × 10⁹/litre, platelet count 90 × 10⁹/litre, aspartate aminotransferase (AST) 66 U/litre, alanine aminotransferase (ALT) 47 U/litre, total bilirubin 6.6 mg/dl, conjugated bilirubin 1.2 mg/dl, albumin 3 g/dl, ammonia 105 µmol/l, prothrombin time 42 s (normal 10.7–13 s), and activated partial thromboplastin time 147 s (normal 19.9–26 s). Results of serologic testing for hepatitis A, B, and C were negative. Biochemical and microscopic examination of the ascites fluid showed that it was transudate, and a culture of the fluid was sterile. The patient’s alpha-1-antitrypsin level was 106 mg/dl (normal 83–199 mg/dl) and his ceruloplasmin measured 41 mg/dl (normal 20–54 mg/dl). Investigation of the thrombophilia showed that the boy’s PC activity was 9% (normal 70–140%) based on a clotting assay (Dignostica Stago, STA®-Staclot® Protein C) and his PC antigen level was 1.3 mg/l (normal 1.8–3.9 mg/dl) by radial immunodiffusion (Nanorid™, UK). The protein C activity/antigen result was 0.69. Protein S activity was 71% (normal 60–140%), the antithrombin level was 23 mg/dl (normal 24.9–33.1 mg/dl), and the fibrinogen level was 38 mg/dl (normal 200–400 mg/dl). The child tested negative for anticardiolipin antibodies, and his serum homocysteine level was normal. DNA studies revealed that he was heterozygous for the FVL mutation.

Testing of other family members showed that the patient’s mother also had abnormal PC activity (10% as determined by clotting assay), but that her PC antigen level was normal (2.4 mg/l). She was homozygous for the FVL mutation. Her