Homozygous Protein C Deficiency: A Case Report and Review of the Literature.

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Abstract: Homozygous protein C deficiency is a rare autosomal recessive disorder that usually presents in the neonatal period with purpura fulminans (PF) and severe disseminated intravascular coagulation (DIC), often with concomitant venous thromboembolism (VTE). Mutational analysis of symptomatic patients shows a wide range of genetic mutations. We report here a quite rare case of severe homozygous protein C deficiency from Saudi Arabia. Plasma Protein C antigen level was measured by enzyme immunoassay while the protein C activity was measured by using chromogenic assay. Homozygous protein C deficiency state is usually not compatible with long-term survival and often fatal unless there is early recognition of the clinical symptoms, prompt diagnosis, and urgent therapy is crucial to avoid further damage after delivery.
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Introduction

Protein C is a vitamin K-dependent coagulation protein that is synthesized in the liver. Protein C deficiency is a rare genetic trait that predisposes to thrombotic disease. It was first described in 1981.[1] The disease belongs to a group of genetic disorders known as thrombophilias. The prevalence of protein C deficiency has been estimated to about 0.2% to 0.5% of the general population. Homozygous protein C deficiency is usually presents in the neonatal period with purpura fulminans (PF) and severe disseminated intravascular coagulation (DIC), often with concomitant venous thromboembolism (VTE). Recurrent thrombotic episodes (PF, DIC, or VTE) are common [2]. Mutational analysis of symptomatic patients shows a wide range of genetic mutations. The gene for protein C is located on chromosome 2 (2q13–14) and appears to be closely related to the gene for factor IX [3]. The primary effect of activated protein C (APC) is to inactivate coagulation factors Va and VIIIa, which are necessary for efficient thrombin generation and factor X activation [4]. The inhibitory effect of APC is markedly enhanced by protein S, another vitamin K-dependent protein. We report here a quite rare case of severe homozygous protein C deficiency presented by neonatal purpura fulminans, disseminated intravascular coagulation and necrotizing entercolitis.

Case Description:

A Full Term baby boy delivered by breech. Immediately after birth noticed to have hemorrhagic rash over the abdomen. Admitted to nursery for observation. Few days later noticed to have poor feeding and after work up, he was diagnosed as necrotizing entercolitis which required admission to NICU and surgical resection of bowel. Post-operatively (at day 11) the child was referred to hematology for further assessment. In review of the history which revealed parents are first degree cousin. Mother is known to have recurrent DVT and was on anticoagulant during pregnancy; however she was not investigated for thrombophilia. There was history of stillbirth and one abortion. Three siblings are alive and well. Patient Laboratory data at diagnosis are summarized in table 1. Also, the parents characteristics at diagnosis were summarized on table 2.The patient was treated during by FFP at a dose of 15 ml/kg every 12/hours alternating with protein C concentrate, an initial dose of 100 U/kg followed by 50 U/kg every 12 hours, the treatment was continued until all lesions had resolved. Despite supportive measures including protien C infusion, Fresh frozen plasma (FFP), platelets and broad spectrum antibiotics together with mechanical ventilation; the patient died of multiorgan failure and DIC.

Discussion

Protein C deficiency has been estimated to occur in 1 in 200 to 500 persons [2, 5]. More than 160 different genetic abnormalities have been identified [2,7]. Hereditary protein C deficiency is transmitted as an autosomal dominant disorder. The gene for protein C is located on chromosome 2 (2q13–14) and appears to be closely related to the gene for factor IX [8, 9].

Homozygous individuals usually develop PF as newborns; heterozygous protein C-deficient individuals are at increased risk for venous thrombosis and pulmonary embolism. [10].

The neonatal presentation of homozygous protein C deficiency with DIC and PF within hours of birth was reported before [11–13] similar to our case study. In our case, the diagnosis is made by repeated measurements of decreased protein C levels, while all other vitamin K-dependent factors are normal and an acquired protein C deficiency is excluded as reported [14]. Also, monitoring for evidence of coagulation activation with D-dimer was useful to confirm the diagnosis and to monitor adequate replacement or anticoagulation therapy as previously published in the neonate [15], a markedly elevated or rapidly rising D-dimer has important marker for the onset of DIC in neoborn patients with severe PC deficiency as shown in our case study. Also; the diagnosis of homozygous protein C is based on the clinical findings of PF, skin ecchymosis, undetectable levels of protein C, a heterozygous state in the parents, and, if possible, identification of the molecular defect [16].

The family history is important in such cases although there may be no history of thrombosis as there is wide variability in heterozygous phenotype. A history of consanguineous parents may point towards a homozygous state similar to current case. [17, 18].

Table (1): Patient Laboratory data at diagnosis

Laboratory data	Patient	Reference range
Protein C level	0.10	0.70-1.40 U/ml
Protein C activity	0.15 >	0.70-1.40 U/ml
Platelets	53	150-450 $x10^9$/l
Fibrinogen	2.9	2-4 g/l
PT	19	8- 9.9 sec
aPTT	61	21-35 sec
INR	1.5	0.9-1.1
dimer-D	1300<	ml/mg 250>
Liver and renal function	Normal	-
Other coagulation factors (as F V Leiden, protein S, AT III)	Normal	-

Table (2): Parent's characteristics

Parents	**4 Case**
age **father** **mother**	 **37** **33**
Consanguinity	Yes
History of thrombosis	Yes (mother)
Protein C level Father Mother	0.55 U/ml 0.69 U/ml
Protein C activity Father Mother	 0.59 U/ml 0.77U/ml
Other coagulation factors (as F V Leiden, protein S, AT III)	Normal

Conclusion

Homozygous protein C deficiency state is usually not compatible with long-term survival and often fatal unless there is early recognition of the clinical symptoms, prompt diagnosis, and urgent therapy is crucial to avoid further damage after delivery with subsequent decreases both the morbidity and mortality associated with this condition. Every effort should be made to increase awareness of this rarely diagnosed condition and its treatment, so that affected infants will derive maximum benefit.

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