Journal of Blood Disorders

Open Access

Austin Publishing Group

Special Article - Acute and Chronic Myeloid Leukemia

Protein C Deficiency: The Dramatic in Utero Clinical Presentation

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Received: July 12, 2017; **Accepted:** August 17, 2017; **Published:** August 24, 2017

Abstract

Protein C has a major role in regulating hemostasis and modulating blood coagulation and its deficiency has been associated with micro and macro vascular thrombosis. Congenital protein C deficiency is a life threatening condition with pronounced coagulopathy and increased risk of thromboembolic events.

Management of patients with protein C deficiency is challenging because of the competing risks of bleeding and thrombosis. Replacement of the deficient protein C, in addition to anticoagulation, is an established therapy for congenital protein C deficiency.

We describe the case of a newborn with severe congenital protein C deficiency that presented antenatally and was born with evidence of in utero coagulopathy and experienced further events of intracranial hemorrhage and retinal hemorrhage. Identified to have low protein C activity and was treated with protein C concentrate and fresh frozen plasma. Long-term therapy was provided.

Introduction

Protein C is a vitamin K-dependent protein, synthesized in the liver and circulates in the plasma as the key component of the natural anticoagulant pathway. It is converted by thrombin into its active form (Activated Protein C) that functions as an anticoagulant. It cleaves and inhibits coagulation factors FVIIIa and FVa, which result in down regulation of the activity of the coagulation system [1].

Congenital Protein C deficiency is a rare but life threatening disorder, presenting in the neonatal period with progressive purpurafulminans and disseminated intravascular coagulation with concomitant venous thromboembolism [2].

Protein C deficiency subdivided according to whether the deficient activity is due to reduced protein levels (type I) or to reduced protein function with normal protein levels (type II). Type I is more common than type II deficiency. There is marked phenotypic variability among patients with protein C deficiency [3].

Therefore, in this report, we are presenting a case of severe Protein C deficiency in a newborn with intracranial hemorrhage and retinal hemorrhage. Our objective is to provide an overview of this rare disease and highlight the treatment options available.

Case Report

A late preterm female baby, a product of consanguineous marriage, born at 36+6 weeks of gestation to a 28 years old healthy mother, para 2, living 2, abortion 0, with negative serology screen. Her pregnancy was uneventful; however, the antenatal ultrasound study has unveiled a risk previously not known, the presence of a hyper echoic left intracranial mass measuring 4.9 cm x 1.8 cm.

The family history is positive for the eldest sibling, who is 1 year and 4 months old boy, born at Term with a birth weight of 2.9 Kg, via vaginal delivery and good Apgar score. He had a history of brain cyst diagnosed after delivery, complicated by intracranial hemorrhage (intraventricular and intraparenchymal hemorrhage) with subsequent seizure, hemiplegia and bilateral vitreous hemorrhage causing retinal detachment and blindness. He was later diagnosed with severe protein C deficiency as his laboratory tests revealed low protein C activity 0.03 IU/ml (normal value 0.7 – 1.3 IU/ml) and since then started on regular subcutaneous injection of Low Molecular Weight Heparin - LMWH (Enoxaparin) twice daily after control of the bleeding with regular follow up in outpatient clinic.

She underwent emergency caesarean section due to the abnormal ultrasound finding and the risk of having intracranial bleeding if she goes into vaginal delivery, as well as avoiding instrumental delivery. At delivery, the female baby was vigorous, received routine care and had an Apgar score of 9, 10 & 10 at 1, 5 and 10 minutes respectively, and admitted to Neonatal Intensive Care Unit for further evaluation and assessment. Her birth weight was 2.180 kg, length was 43 cm and head circumference was 31.5 cm which were appropriate for gestational age.

On admission she was stable, active, maintaining the blood pressure and oxygen saturation on room air. In view of the antenatal ultrasound finding, head ultrasound was performed and confirms the presence of left temporal lobe parenchymal hemorrhage, likely of sub-acute to chronic in nature. On an urgent basis, brain computed tomography was done which document that the bleeding is involving the left temporal lobe extending through the occiput and the left lateral ventricle with surrounding vasogenic edema and adjacent mass effect. Pediatric Hematology service and Neurosurgery service were consulted and brain magnetic resonance imaging was arranged and carried out instantly. It demonstrates the presence of Left-sided temporal, parietal, and occipital hemorrhagic changes, which is likely

Citation: Alansari E, Almidani E, Saleh M and Khadawardi E. Protein C Deficiency: The Dramatic in Utero Clinical Presentation. J Blood Disord. 2017; 4(2): 1047.

to have occurred intrauterine, and no midline shift; space-occupying lesions or hydrocephalus were seen and there are no obvious signs of arteriovenous malformations. There was a significant hemorrhagic transformation within the hematoma itself which provides further proof that the hemorrhage had taken place during the intrauterine period. Serial head circumference measurements were taken and it was similar to the first measurement.

On the second day of life, she was noticed to have ecchymosis and bruises over the posterior aspect of her both thighs. Abdominal ultrasound was performed to assess the possibility of intra-abdominal hemorrhage and was negative. An evaluation by the ophthalmologist revealed bilateral retinal hemorrhage of different levels with incomplete retinal vascularization and a vascular retina in zone 3 (Retinopathy of Prematurity - ROP like picture of stage 1, zone 3, no plus disease). She was found to have a heart murmur, evaluated by echocardiography that identified the presence of an atrial septal defect and a follow up required afterward.

A thorough hematological workup was done including serum prothrombin time (PT 20.3 seconds), Activated Partial Thromboplastin time (APTT 45.4 seconds), international normalized ratio (INR 1.7), fibrinogen level (0.73 g/L), D. Dimer (>20 mg/L) and ant thrombin III level (54%), along with Factors level, Protein C level and activity and Protein S level and activity. Her coagulation profile was deranged and the Protein C activity was low <0.10 IU/ml (normal value 0.7-1.3 IU/ml), accordingly a diagnosis of severe Protein C Deficiency was proposed and established.

She received a replacement therapy of Vitamin K, cryoprecipitate of 5 ml/kg with Fresh Frozen Plasma as a repeated infusion of 10 ml/kg, initiated every 8 hours on a daily basis and later on reduced to 12 hourly with close monitoring of her coagulation profile. She was started on intravenous Protein C Concentrate with an initial dose of 100 IU/kg, followed by 60 IU/kg every 6 hours for 3 doses, then maintenance of 45 IU/kg every 12 hours.

A follow-up Head ultrasound showed involution of the bleeding in the left temporal horn and left occipital horn with small cystic changes within them and no new bleeding. The bruises gradually heal over a period of days and fade away to yellow then disappeared. Repeated ophthalmological assessment revealed slow resolution of the retinal hemorrhage with residual fibro vascular proliferations in the temporal zone and persistent a vascular retina in zone 3 (similar to stage 1 ROP, no plus disease).

Protein C concentrate was continued on a daily basis for three weeks, later on, discontinued and she was maintained on twice daily FFP that controlled her bleed. With normalizing her coagulation profile, the patient condition stabilized, FFP stopped and started on subcutaneous injection of LMWH (Enoxaparin) twice daily. The patient discharged home and followed as an outpatient case.

Discussion

Under normal conditions activated protein C is a natural anticoagulant, plays an important role in the reversal of the clotting cascade, it cleaves 2 activated coagulation factors, factor Va and factor VIIIa, inhibiting the conversion of factor X to factor Xa and of prothrombin to thrombin. Activated protein C has also been shown to induce tissue plasminogen activator mediated fibrinolysis by inhibition of plasminogen activator inhibitor-1, resulting in an increase in circulatory plasminogen activator levels [4]. Thus the overall net effect is to interrupt the clotting cascade.

Deficiency of protein C leads to a hyper coagulable state, resulting in numerous thrombi, predisposing to thrombo-embolic events with the location of the thrombi determines patients' clinical symptoms.

Protein C deficiency is inherited in an autosomal pattern. The gene for protein C is located on chromosome 2 (2q13–14) [5]. Two major subtypes of protein C deficiency have been delineated. Type I deficiency, the most common, is characterized by the parallel reduction of protein C activity and antigen level. Type II deficiency, have normal plasma protein C antigen levels with decreased functional activity. There also appear to be both dominant and recessive forms of protein C deficiency [6].

Based on the clinical expression of the disease homozygous and heterozygous forms have been identified. Homozygous and compound heterozygous forms often have a similar phenotype of severe protein C deficiency evident in the neonatal period. Simple heterozygous form is often asymptomatic but may involve recurrent thromboembolic episodes, most often triggered by clinical risk factors [7].

Onset of severe protein C deficiency is usually within the first few days of life and can occur within hours of birth. The thrombotic event involves the skin, central nervous system, eyes and kidneys. The microcirculation of the skin is characteristically affected first with the development of purpura fulminans associated with laboratory evidence of DIC. Cerebral and renal vein thromboses are common and can be presenting features. Ocular manifestations are also characteristic [8]. Although purpura fulminans is almost always a feature; major vessel thrombosis occasionally occurs in isolation [9]. It is likely that cerebral and ophthalmic thrombosis often occur as intrauterine events as in our case.

The baseline laboratory results are frequently indicative of DIC. The definitive diagnosis can be difficult in the neonate and it is possible that affected infants die from DIC before assignment of the diagnosis. Protein C levels are physiologically reduced at birth and are further reduced in the presence of DIC, during which protein C, in particular, can reach very low levels. The diagnosis is therefore based on finding undetectable protein C activity with heterozygous levels in the parents [10]. When the molecular defect is known, prenatal diagnosis can be offered to families when there is a prior history of similar illness.

Management includes monitoring coagulation studies with the replacement of clotting factors with FFP when DIC is ongoing and adequate replacement of the deficient inhibitor (Plasma derived Protein C concentrate) to bring protein C activity to normal levels. Long-term anticoagulant therapy is indicated to avoid further micro vascular damage. This can be accomplished with protein C concentrate or therapeutic anticoagulation using either low molecular weight heparin or warfarin [11].

This case report points out to the peculiar antenatal presentation of severe Protein C deficiency with intracranial hemorrhage. In the

medical literature, there are only a few reports on severe protein C deficiency in neonates with the age of onset of the first symptom has ranged from a few hours to two weeks after birth. Skin involvement is frequently seen as an early manifestation of disease process and purpura fulminans is the presenting feature [12]. Dreyfus et al. [13] analyzed nine cases of neonates with severe congenital protein C deficiency presenting with purpura fulminans associated with disseminated intravascular coagulation and some progress to multi-organ failure. Unlike our case the bruises didn't progress topurpura fulminans and regressed with treatment. The ophthalmic complication was also observed in our newborn. Hattenbach LO et al. [4] reported two cases of protein C deficiency with ocular and extraocular manifestation in full term neonates.

In conclusion, severe congenital protein C deficiency is a rare but life-threatening disorder of coagulation with severe impact on quality of life, which has serious implications for the patient morbidity and mortality and requires prompt recognition and treatment to optimize outcomes of affected patients.

Work Plan

The roles and responsibilities of the Principle Investigator (PI) and the co-investigators can be summarized as follows:

The PI is responsible for writing the Case report. She will ensure that the final case report and publication form as well as other required forms will be sent to Office of Research Affairs (ORA) at KFSHRC for approval.

1. E. Khadawardi is a Pediatric Neonatology at KFSHRC. He will be the corresponding author, supervising the whole work and is responsible for writing the case report and final approval of the version to be published.

2. E. Alansari is a pediatric neonatology fellow at KFSHRC. She is the primary author, involved in writing the case report and a substantial contribution to the design, review; critical writing and submission for publication.

3. E. Almidani is a Pediatric Neonatology at KFSHRC. He is a substantial contribution to review the manuscript, revising the intellectual content before final approval of the version to be published.

4. M. Saleh is a Pediatric Hematologist at KFSHRC. She is a substantial contribution to review the manuscript, revising the intellectual content before final approval of the version to be published.

5. All co-authors will be notified about the results and conclusion.

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