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Case Report

A rare case of protein C mutation causing neonatal purpura fulminans

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ABSTRACT

Congenital protein C deficiency presenting as purpura fulminans is a rare condition in neonates. It is a disorder with autosomal recessive inheritance and is caused by homozygous or compound heterozygous mutations in PROC gene. The authors report a case of autosomal homozygous PROC gene transversion mutation in a newborn baby born to third degree consanguineous parents who presented as purpura fulminans at birth. She had almost undetectable protein C levels. As protein C concentrate was not readily available, she was managed with low molecular weight heparin along with fresh frozen plasma. Despite our best efforts, baby succumbed to her illness on day 21 of life. Autosomal recessive protein C deficiency should always be sought as an explanation for thrombotic disorders in the newborn with manifestations of disseminated intravascular coagulation.

Keywords: Purpura fulminans, Congenital protein C deficiency, PROC gene, Homozygous, Newborn, Thrombosis

INTRODUCTION

Purpura fulminans in neonates is a rapidly progressive thrombotic disorder manifesting as extensive subcutaneous thrombosis and disseminated intravascular coagulation (DIC) manifesting soon after birth. Congenital protein C deficiency presenting as purpura fulminans is a rare condition in neonates with an incidence of about 1 in 4 million.[1] It is caused by homozygous or compound heterozygous mutations in PROC gene with an autosomal recessive inheritance.[2] We reported a case of autosomal homozygous PROC gene transversion mutation.

CASE REPORT

A pre-term, 35 weeks baby girl was born to third degree consanguineous parents by emergency cesarean section due to fetal distress. She had a birth weight of 2055 g. She was born to a second gravida mother who had no miscarriages, risk factors from sepsis or antenatal TORCH infections. There was no family history of thromboembolic events. She required conventional ventilation and CPAP due to severe respiratory distress present since birth.

She had multiple erythematous lesions and purpuric areas over the chest and both flanks (Figure 1), which was noted at birth. Within 3-4 hours, these lesions progressed from being purple to black and necrotic. Swab cultures taken from these lesions were sterile. Further blebs formed over these lesions. Her routine hemogram, coagulation parameters and biochemistry reports showed severe anemia with thrombocytopenia and severe consumptive coagulopathy.

Hence, she received packed cells, Fresh Frozen Plasma (FFP) and cryoprecipitate transfusion. In view of sepsis, she was also on broad spectrum antimicrobials and inotropes. She was weaned from SIMV ventilation to CPAP with improvement in respiratory distress. However, new lesions (Figure 2) started developing over the back, legs, forehead, nose, perineum and groin by the end of the first week. They progressed rapidly and became enlarged, vesiculated and necrotic on day 14. Skin biopsy from the lesion showed features suggestive of purpuric bulla. Serial head ultrasound scans during the first two weeks of life showed bilateral cystic lesions suggestive of periventricular leukomalacia. Her fundus examination

showed bilateral vitreous hemorrhage. Her TORCH IgM assay and HSV PCR were negative for evidence of active infection.

Her protein C, protein S and antithrombin 3 levels were sent which showed almost undetectable protein C levels (<1%). She was further evaluated with mutation profile for thrombophilia which showed mutation on PROC gene. Genomic DNA was isolated from exon 8 which showed presence of autosomal homozygous PROC gene. This mutation was in the homozygous state in our symptomatic baby with asymptomatic parents. The genetic study of parents could not be done and they were lost on follow up.

As protein C concentrate was not readily available, she was managed with therapeutic anticoagulation with low molecular weight (LMW) heparin along with FFP transfusion in view of clinical profile favoring congenital protein C deficiency. Despite our best efforts, baby succumbed to her illness on day 21 of life.

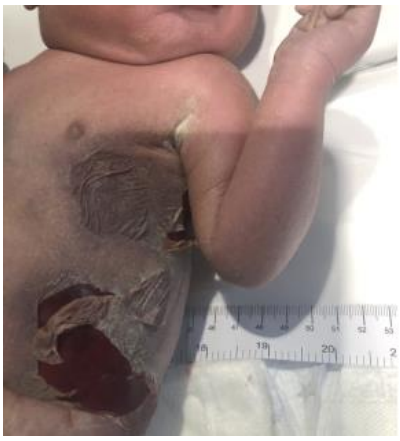

Figure 1: Large bullous echymotic lesions over the lower chest wall, abdominal wall (immediately after birth).

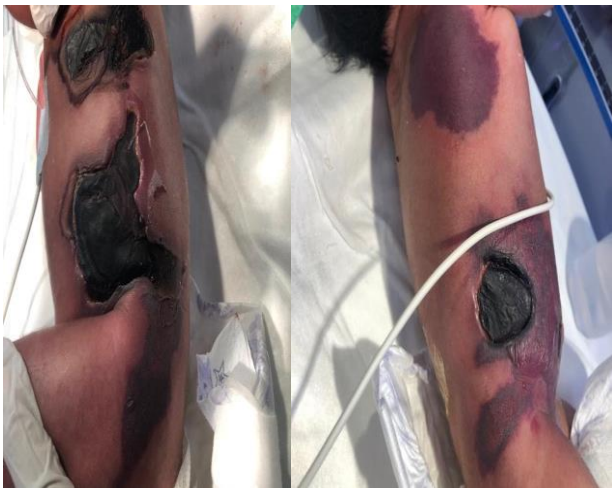

Figure 2: New lesions over the back, legs, forehead, perineum, groin and over the nose (7 days after birth).

DISCUSSION

Neonatal purpura fulminans is a clinical condition of dermal thrombosis associated with DIC. Protein C is a Vitamin K dependent anticoagulant that regulates thrombosis.[3] Protein C deficiency is predominantly an autosomal dominant trait with heterozygous carriers. Autosomal recessive protein C deficiency is less common, due to homozygous mutation and causes a more severe form of the disease with onset of thrombotic manifestations at birth.[4]

Our case report had classic manifestations of neonatal purpura fulminans caused by homozygous mutations in the PROC gene. Since the baby was born to a third-degree consanguineous family, an autosomal recessive protein C deficiency should always be sought as an explanation for thrombotic disorders in the newborn with manifestations of DIC.

In our case, genetic work up showed presence of autosomal homozygous PROC gene. A history of consanguinity may point towards a homozygous state while compound heterozygous gene mutations may be found in neonates born to unrelated parents. Genetic testing of the child and family members can confirm the diagnosis, but it is not readily available in most centers, and the results would not be timely enough to guide management of these critically ill neonates. In our case, we could not do the genetic testing of parents. Genetic testing of siblings, parents and grandparents are recommended.[4] Molecular diagnosis also gives the parents an option regarding prenatal diagnosis in subsequent pregnancies.

Management of such cases requires a multidisciplinary team effort with the services of a neonatologist, hematologist, pathologist, ophthalmologist and dermatologist. We managed the baby with FFP transfusion and anticoagulation therapy. Protein C replacement should be given using FFP (at a dose of 10-20 ml/kg every 6 hours to 12 hours) or a human plasma-derived protein C concentrate.

The aim was to have a protein C activity of >10 IU/dl while awaiting the protein C concentrate.[5] Protein C concentrates are unfortunately not easily available in resource poor settings. Anticoagulation therapy should be initiated with administration of protein C replacement therapy (protein C concentrate or FFP). Initial anticoagulation consists of either unfractionated heparin or LMW heparin.[6] These patient might require long-term oral anticoagulation with warfarin.

CONCLUSION

Neonates with purpura fulminans should be screened for both congenital and acquired causes. Molecular diagnosis and prenatal counseling in neonatal purpura fulminans are vital considering the poor outcome.

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