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Case Report

A Novel Missense Variant c.125G>A on Exon 3-Presenting as Neonatal Purpura Fulminans with Persisting Fetal Vasculature

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ABSTRACT

Neonatal purpura fulminans due to severe congenital protein C deficiency is a rare autosomal recessive disorder which can be fatal if untreated. Here, we discuss a case report of a 10-month-old male child, born via 3rd degree consanguineous marriage, with a history of tractional retinal detachment and persistent fetal vasculature (PFV) now presenting with neonatal purpura fulminans and DIC who was managed with fresh frozen plasma (FFP) and Low Molecular Weight Heparin (LMWH). Genetic evaluation identified a novel PROC mutation c.125G>A(p.Arg42His). This report also emphasizes the significance of molecular analysis in genetic counselling and prenatal diagnosis.

Keywords: PROC, purpura fulminans, persisting fetal vasculature, newborn

Introduction

Neonatal purpura fulminans describe a clinicopathological entity of dermal microvascular thrombosis associated with disseminated intravascular coagulation (DIC). Neonatal purpura fulminans associated with congenital protein C deficiency is an exceedingly rare condition with a predicted incidence of 1 per 4 million births (1).

Biallelic (homozygous or compound heterozygous) PROC mutations lead to autosomal recessive Protein C Deficiency which occurs in 1 in 40,000 to 250,000 individuals. Autosomal recessive protein C deficiency, which is a more severe but rarer form compared to autosomal dominant protein C deficiency, is associated with a very low level of protein C and typically presents in the neonatal period with neonatal purpura fulminans (2).

Herein, we describe an infant who presented with neonatal purpura fulminans with retinal detachment secondary to persistent fetal vasculature and was found to have autosomal recessive protein C deficiency caused by a novel homozygous PROC mutation.

Case Report

A 10-month-old male child with normal development, born via 3rd-degree consanguineous marriage, with a family history of recurrent abortion in his maternal grandmother, presented to our center with a history of bluish discoloration of the left lower limb for 3 months following trivial trauma. The child had a history of similar episodes in the neonatal period on postnatal day 3, and it healed by 1 month of age. At 6 months of age, the mother noticed white reflex in the right eye and on evaluation, it was found that the child had

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leukocoria and complete vision loss in the right eye due to tractional retinal detachment caused by persistent fetal vasculature. Over a one-week period, the lesion progressed - became edematous, tender and there was oozing of serous fluid. The child was admitted, and on examination had a black eschar on the left lower limb, with a few vesicles and surrounding erythema (Figure 1). Ecthyma gangrenosum was suspected, and treatment was started with ceftazidime and vancomycin, along with other supportive measures. Initial investigations were unremarkable except for a marginally positive C-reactive protein. However, on the following day, the child worsened clinically, with the spreading of the lesions, new lesions in the scrotum and forehead, and the child appeared pale. Further investigation revealed anemia (Hb: 7.4 g/dL, reference range 11-13 mg/dL), thrombocytopenia (platelet count: 77×10^9/L, reference range 150-450$\times10^9$/L), elevated INR: 5 (reference range 0.9-1.2), elevated APTT: 70 seconds (reference range 24-36 seconds), elevated D-dimer: 8.9 mg/L (reference range <0.5 mg/L) and low fibrinogen: 76 mg/dL (reference range 180-410 mg/dL), suggestive of a child going into DIC.

In light of the family history of recurrent abortions, consanguineous marriage, similar past history, skin lesions similar to neonatal purpura fulminans, and the presentation in DIC, inherited thrombophilia including Protein C/Protein S deficiency was suspected. Protein C level assay was performed and was found to be low (Protein C level: 8 IU/dL, reference range for <5 years: 40-92 IU/dL). The child was started on fresh frozen plasma (FFP). Low molecular weight heparin was started at a dose of 1 mg/kg for 2 weeks and later bridged to warfarin. Escharotomy was carried out after 1 month. Following discharge, the patient returned to his usual state of health and has continued prophylactic LMWH. The PROC gene was sequenced and a novel homozygous missense mutation (c.125G>A; p.Arg42His) on Exon 3 was identified. A genetic study of both the parents was carried out and both were heterozygous for p.Arg42His mutation, confirming the diagnosis of autosomal recessive protein C deficiency.

Discussion

Protein C is a vitamin K-dependent serine protease anticoagulant which plays a critical role in the regulation of thrombosis by degrading activated procoagulant factors V and VIII (3). PROC, the gene encoding protein C, is located on chromosome 2q14.3 (4). Individuals with autosomal recessive protein C deficiency carry biallelic PROC mutations and have a very low level of protein C, whereas individuals carrying heterozygous PROC mutations have protein C levels at about 50% of reference values (2).

Neonatal purpura fulminans due to congenital protein C deficiency usually present within hours of birth with rapidly progressive cutaneous purpuric lesions and DIC. Most affected infants present with blindness and prenatal arterial ischemic stroke resulting from thrombosis in the developing vitreous vein. Douglas et al. (5) identified 12 cases where severe protein C deficiency was associated with ophthalmic signs compatible with a diagnosis of persistent fetal vasculature. The identified PROC novel mutation c.125G>A(p.Arg42His) had not been previously reported. This p.Arg42His variant has an allele frequency of 0.00079% in the gnomAD and is novel in the 1000 genome database. The amino acid arginine at position 42 is changed to histidine, changing the protein sequence and it might alter its composition and physicochemical properties (6).

The classic presentation of autosomal recessive protein C deficiency is often neonatal purpura fulminans and early recognition is critical in preventing morbidity and mortality. Although the identified p.Arg42His mutation in PROC was not previously reported, its pathogenicity is supported by biochemical and clinical phenotypes which are consistent with autosomal recessive protein C deficiency. Therefore, p.Arg42His in PROC is a novel mutation causing autosomal recessive protein C deficiency which presented in this infant

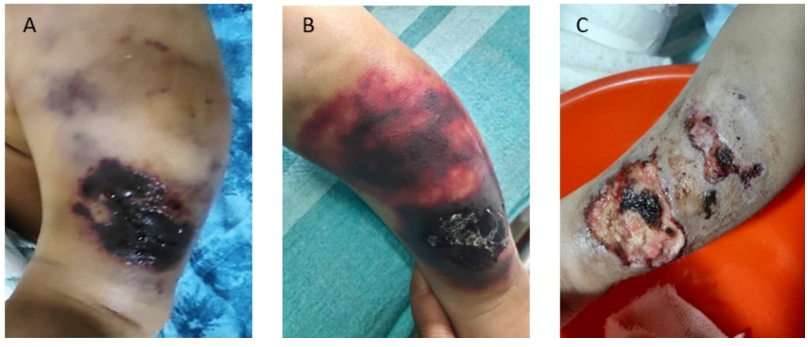

Figure 1. Skin changes at various stages: (A) At presentation in our hospital; (B) After progression into DIC; (C) After escharotomy

with neonatal purpura fulminans along with persistent fetal vasculature. This report also emphasizes the significance of molecular analysis in genetic counselling and prenatal diagnosis.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.B., R.I., S.H., Concept: R.I., Design: S.H., Data Collection or Processing: A.B., Analysis or Interpretation: R.I., S.H., Literature Search: A.B., Writing: A.B.

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