Case Report

Neonatal purpura fulminans: A rare, life-threatening, and rapidly progressing disorder of coagulation

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ABSTRACT

Background: Neonatal purpura fulminans (NPF) is a life-threatening rare disease, which can be caused by deficiencies of protein C or protein S in a congenital or acquired manner. It is characterized by thrombosis of microvasculature, peri-vascular hemorrhage, and disseminated intravascular coagulation (DIC) occurring in the neonatal period. **Clinical Description:** A term female baby presented at 40 h of life with multiple purpuric rashes over the left foot which over 1 day extended until the knee. Over the next 3 days, there was rapid progression to involve extensive areas of necrosis with gangrene of toes of left foot, both forearms, bilateral temporal areas, peri-orbital regions, and left ear, in addition to multiple hemorrhagic blebs. **Management and Outcome:** Investigations showed anemia and thrombocytopenia with normal leucocyte count. DIC was suspected (INR 2), sepsis screen was negative, and fresh frozen plasma (FFP) was transfused 8th hourly. Arterial and venous Doppler was normal and blood culture showed no growth. Suspecting NPF, protein C, protein S, and anti-thrombin levels were sent, which showed a low protein C and protein S value. Mutations involving factor V Leiden, prothrombin gene, and MTHFR gene were not detected. The baby was started on low molecular weight heparin and, FFP and platelet concentrate replacement were continued, but she succumbed to the illness. **Conclusion:** NPF is a rare life-threatening entity which is fatal without prompt recognition of the condition. Therefore, it is necessary to recognize it early and initiate treatment.

Key words: Disseminated intravascular coagulation, Neonatal purpura fulminans, Protein C deficiency, Protein S deficiency

Neonatal purpura fulminans (NPF) is a rare entity with very high mortality, which can be caused by deficiencies of protein C or protein S in either a congenital or acquired manner [1]. The entity of NPF was described for the 1st time in 1962 with the presumed etiology of an inherited disorder. In 1983, protein C deficiency was found to be linked with NPF and was treated using protein C replacement therapy. It was in 1990 that homozygous protein S deficiency and fulminant purpura were found to be associated [2]. The hereditary form secondary to protein C deficiency is very rare and is known to occur in 1:1,000,000 live births [3].

This condition is usually fatal, without the prompt recognition of clinical features, early diagnosis, and initiation of replacement therapy. They present clinically such as disseminated intravascular coagulation (DIC) and hemorrhagic necrosis of the skin. The mainstay of treatment is with fresh frozen plasma (FFP) or protein C concentrates replacement and the maintenance therapy with anticoagulants such as low molecular weight heparin (LMWH) or warfarin. Death is usually due to rapid progression to multi-systemic thrombosis [4]. Although the fatality rate has a reducing trend with improved supportive care, treatment of complications, and targeted management modalities, it continues to be a significantly disabling problem usually needing multiple amputations among the survivors [5].

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CASE REPORT

A term female baby, 1st born to a non-consanguineous marriage, with a birth weight of 3.2 kg, presented at 40 h of life with multiple purpuric rashes over the left foot feet which over the next day extended till the knee. DIC was suspected, and hence, a sepsis screen and blood culture were sent, and parenteral antibiotics and FFP transfusion were started. The anthropometric measurements and Apgar scores at birth were normal. By the 3rd day, the purpuric rashes progressed rapidly to involve extensive areas of skin necrosis with gangrene of the toes of the left foot, and left forearm, in addition to multiple hemorrhagic blebs (Fig. 1). In view of progressing gangrenous and necrotic changes, evaluation for vascular pathology and hypercoagulable states was done. By day 6, there was further involvement of the forearms, bilateral

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temporal areas, peri-orbital regions, and the left ear (Fig. 2). With the above clinical findings, the diagnosis of NPF was suspected and protein S, protein C, and anti-thrombin level estimation were done.

In our case, the onset was at 40 h of life. The course of skin lesions is from dark red initially to purple-black later with induration. These areas can, then, become necrotic and gangrenous leading to loss of extremities. They are usually noted at sites of prior trauma such as cannulation sites and are hence initially mistaken to be bruised. Limbs are the predicted sites of involvement as were the scenario in our case.

MANAGEMENT AND OUTCOME

Initial investigations showed hemoglobin of 10 g/dL leukocyte count of 13,000 cells/mm^3, platelet count of 46,000/mm^3, PT 28 s, aPTT 44 s, and INR 2. Parenteral antibiotics Amoxyclav and Gentamycin were started as per our NICU protocol and the 8th hourly FFP transfusion was started. Arterial and venous Doppler studies were normal. The sepsis screen was negative and the blood culture showed no growth. Mutational analysis of factor V Leiden, prothrombin gene, and MTHFR gene (methylene tetra hydrofolate reductase) were negative. Suspecting NPF, activities of protein C and S, and antithrombin were done, which were 65%, 52%, and 67%, respectively. Although protein C and protein S levels were below the laboratory reference range; in this case, estimation in parents was required. However, due to financial constraints, evaluation of family members could not be done. The baby was started on LMWH 1 mg/kg/dose Q12 h for 4 days and platelet concentrate replacement was continued, but she succumbed to the illness.

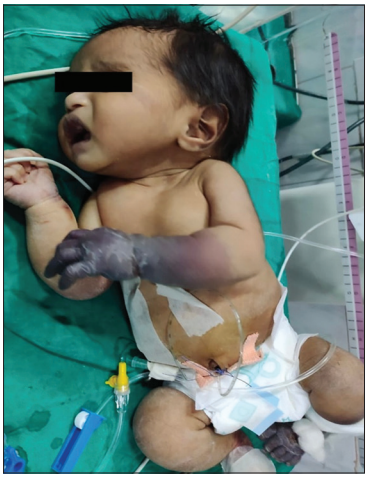

Figure 1: Gangrenous and necrotic changes involving left foot and left upper limb

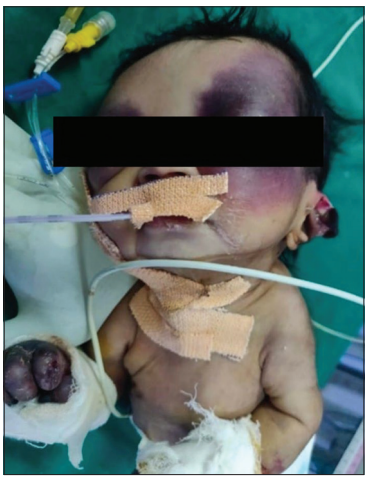

Figure 2: Hemorrhagic skin necrosis involving bilateral temporal, periorbital areas, and gangrene of the left ear and right hand

DISCUSSION

NPF presents as a rapid-onset progression of purpuric skin lesions and DIC postnatally. The spectrum of severity can vary from symptom onset within 12 h after birth, which is the usual scenario, but, there are reports of delayed presentation around 6–12 months [6]. Protein C and protein S are dependent on Vitamin K and are synthesized in the liver. Activated protein C, by limited proteolysis, inactivates factors Va and VIIIa thus leading to downregulation of generation of thrombin. Activated protein C activity is further enhanced by protein S [7]. Hence, a deficiency of protein C or protein S results in a hypercoagulable state.

Inherited causes of NPF include homozygous deficiency of protein C or S, co-inheritance with other thrombophilias, and compound heterozygosity [8]. Consanguinity can point towards homozygosity, whereas compound heterozygosity may be seen in off-springs of non-consanguineous marriages. Acquired causes are usually associated with severe sepsis leading to consumptive coagulopathy (DIC) and a relative protein C and/or protein S deficiency. Other acquired causes include acute venous thrombosis, severe liver dysfunction, antiphospholipid antibodies, warfarin therapy, and galactosemia [2].

For initial screening, a citrated plasma sample for functional assay must be collected before initiating treatment [2]. Levels of protein C and protein S activity in homozygotes are undetectable. Since the option of repeating the test after 3–6 months for confirmation is practically not possible in this condition, it is essential to test the parents. The diagnosis can be made on the basis of the clinical picture of cutaneous purpura fulminans, estimation of protein C or protein S levels, and detection of the molecular defect. A family history of thrombosis may not be obtained due to the variability in the heterozygous phenotype. In case of a known familial mutation, prenatal diagnosis by chorionic villous sampling can be done for those with a risk of a baby being born with homozygous deficiency. Although about 200 mutations in the protein C gene and over 130 for the protein S gene are identified, recognition of the defect may still be missed in a given case [8]. CNS complications of severe congenital deficiency of protein C can occur antenatally in the third trimester. Severe protein C deficiency can be complicated in the form of cerebral thrombosis, vitreous hemorrhage, and retinal detachment resulting in blindness [9]. These ophthalmic complications have also been reported in cases of congenital severe protein S deficiency. Death

is usually due to severe multi-systemic thrombotic phenomenon. Hence, antenatal diagnosis provides a valuable opportunity for beginning early treatment.

Apart from treating the underlying cause, replacement therapy forms the mainstay treatment. While protein S concentrate is not available, FFP, cryoprecipitate, or protein C concentrates are used for replacement therapy in those with the classic features. Platelet count must be maintained above 50,000/mm^3, while the fibrinogen level should be over 1 g/L [2]. Intravenous antibiotics for the treatment of NPF secondary to sepsis should be administered. FFP is given at a dose of 10 mL/kg every 8 h. 1 mL/kg of FFP increases the plasma level of protein C by 1 IU/dL. The protein C concentrate is given at a dose of 100 U/kg initially followed by 50 U/kg 6th hourly. The target trough protein C activity with FFP and the protein C concentrate is >10 IU/dL and 50 IU/dL respectively [10]. Replacement therapy is continued until all the lesions involving the skin, CNS, and eye have resolved. Liver transplant can be a treatment modality for homozygous deficiency of protein C. Maintenance therapy is with oral anticoagulation (Warfarin) with or without protein C concentrate.

CONCLUSION

Irrespective of the etiology, NPF remains to be a rare entity with a very high mortality rate. The clinical presentation is in the form of a highly thrombotic form of DIC. Since prompt clinical recognition, early diagnosis, and initiation of replacement therapy can reduce morbidity and mortality, increasing the awareness of this condition becomes important.

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