

## Neonatal Purpura Fulminans

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### ABSTRACT

Neonatal purpura fulminans is a rare and life threatening disease that can be inherited or acquired in etiology. It manifests as DIC and extensive subcutaneous thrombosis. The condition is often fatal unless there is prompt diagnosis, and judicious therapy. The most important causes of this condition are infections and congenital deficiency of anticoagulant proteins C and S. In the case of PC (protein C) deficiency, the management includes an acute phase of replacement therapy with fresh frozen plasma (FFP) or protein C concentrate and a maintenance therapy that includes anticoagulation with Warfarin or low molecular weight heparin. Here we report a case of neonatal purpura fulminans due to suspected protein C deficiency.

**Keywords:** protein C, purpura fulmonis

### Introduction

Neonatal purpura fulminans is a rare skin disorder that represents with signs of acute disseminated intravascular coagulation (DIC), tissue necrosis and small vessel thrombosis. This is often a fatal condition, so early diagnosis and prompt treatment is of paramount importance. The etiology of neonatal purpura fulminans consists of both congenital and acquired states. Congenital or inherited causes include homozygous protein C and S deficiency. Acquired conditions are more common with infections being the most important one.

Neonatal purpura fulminans generally presents within the first hours after birth with purpuric lesions and DIC. The skin lesion initially are dark red and then become purple-black and indurated and finally necrotic and gangrenous. Lesions tend to occur mainly on the limbs, but buttocks, abdomen, thighs, scrotum and scalp are often affected. (1,2)

### CASE PRESENTATION:

A full term female newborn with birth weight of 2800gr was referred to our hospital at the first day of her life due to two episodes of generalized seizures 10 minutes apart and echymotic lesions on chest, back, left arm, both legs and left foot up to midfoot. Legs and foot lesions rapidly became

necrotic with sharp borders and induration, ulceration and bullous formation on surface (Figure 1,2,3). The necrotic lesions were tender on palpation. The capillary refill, pulse, color and warmth of distal to the necrotic area were normal. The seizure and dermal lesions occurred within 20 hours after birth. The patient was born through cesarean section delivery and the apgar score at birth was 8 and 10 for minutes 1 and 5 respectively. She was the second child of her mother and the first sibling was a healthy daughter. Her mother had no problem during pregnancy and labor. Both parents were symptom free and they were close relatives (first cousins). There was no family history of any hemorrhagic or thrombotic disorders.

Despite seizure and necrotic lesions, the general condition of baby was good and she continued to feed well. The seizures were controlled with Phenobarbital administration. Laboratory values were: Hct = 38.2% ; WBC count = 7000/mm<sup>3</sup> ; platelet count = 109000/mm<sup>3</sup> ; PT = 18.3 sec ; PTT > 100 sec ; FDP > 20 mcg/ml (normal up to 5) ; D-dimer > 4000ng/ml (normal < 250ng/ml) ; Fibrinogen = 254 mg/dl (normal: 200-400 mg/dl). On the next days the platelet count dropped to 50000/mm<sup>3</sup> and Hct also decreased to 13%. Other laboratory tests including serum Na, K, Ca, Mg, BS, BUN, Creatinin, CRP, blood and urine and CSF

culture, CSF analysis, urinalysis, SGOT and SGPT all were in normal ranges.

Abdominal ultrasound and color Doppler of lower limb arteries were normal. EEG and brain CT scan also were normal but in brain MRI areas of limited diffusion were found near the frontal horn of left lateral ventricle and in the left occipital area suggesting acute ischemic lesions. Eye examination revealed leucocoria and elevation of retina due to vitreoretinal disorders.

Due to presence of laboratory and clinical manifestations of DIC and purpura fulminans the patient was initially treated with broad spectrum antibiotics; packed cell, platelet and FFP transfusions. After correction of Hct and platelet count, packed cell and platelet discontinued but FFP transfusions continued at 10 ml/kg every 12 hours. Serum protein C and S, antithrombin III and factor 5 leiden were measured but unfortunately the specimen was derived after FFP transfusion therefore judgment on results is not accurate { PC activity : 28% (normal:24-51 %); PS total activity : 51%(normal:28-40%); Factor 5 leiden(APC-R) : 132%(neg:>120); antithrombin III : 52%(normal:80-125%)}.MTHFR mutation also were tested that was negative.

After several days of FFP therapy and normalization of PT, PTT, platelet count and Hct; the interval of FFP transfusions was increased to daily. Necrotic lesions gradually healed(Figure 4).Once FFP discontinued new necrotic lesions occurred at thigh and abdomen(Figure 5),therefore FFP again administered and necrotic lesions healed consequently.

With regard to these findings and roll out of infectious causes of purpurafulminans the most likely diagnosis of this patient is PC or PS deficiency; and according to raised level of PS, the suspected diagnosis is likely PC deficiency. repeated measurement of PC and PS levels after discontinuation of FFP and parent's PC and PS measurement is necessary for confirmation of diagnosis.

With a suspected diagnosis of homozygous protein C deficiency, oral warfarin was started in the aim of gradual decrease in FFP transfusions but unfortunately when FFP intervals became 4 day, ecchymotic lesions again occurred. The patient is still in hospital and on warfarin and FFP therapy.

## Discussion:

Neonatal purpura fulminans usually presents with a rapid onset of cutaneous purpuric lesions after

birth and DIC. With purpuric lesions mainly over perineal region, flexor of thighs, and abdomen. Lesions may also appear at pressure sites and also at points of previous punctures. Protein C mutations and inherited deficiency of protein S may lead to neonatal PF.

Protein C is a vitamin K-dependent coagulation protein that is synthesized in the liver. protein C or S deficiency predisposes to a decreased capacity to reduce thrombin generation and a hyper coagulable state.(3)

Severe protein C deficiency is often associated with thrombosis of the cerebral vasculature and ophthalmologic complications including vitreous hemorrhage and retinal detachment that may result in partial or complete blindness (4, 5). These two complications can occur as antenatal events(6).Large vessel venous thromboses may also occur, e.g. renal vein thrombosis.

The diagnosis of homozygous protein C or S deficiency is based on the clinical findings of purpura fulminans, undetectable levels of protein C or protein S, a heterozygous state in the parents, and, if possible, identification of the molecular defect(7).

There may be no family history of thrombosis as there is wide variability in heterozygous phenotype(8,9).Both homozygous and compound heterozygous states have been associated with neonatal purpura fulminans. A history of consanguineous parents may point towards a homozygous state while compound heterozygous gene mutations may be found in neonates born to unrelated parents.

Acquired causes of neonatal purpura fulminans are mainly due to severe infections of which the most commonly associated pathogen in the neonatal period is group B streptococcus(10,11).

During the acute phase, the laboratory findings are that of DIC: thrombocytopenia, hypofibrinogenemia, increased fibrin degradation products and prolonged prothrombin (PT) and activated partial thromboplastin (aPTT) times. There are reports of associated microangiopathic anemia (12,1,13).

Levels of protein C and S in healthy neonates are significantly below adult reference ranges, as low as 0.12 and 0.14 U/mL respectively(14).The usual recommendation of repeat testing in three to sixmonths for confirmation is clearly impractical in this setting; testing of parents is therefore essential. The initial treatment of neonatal purpura fulminans is that of DIC. Management of DIC should be based on the clinical and

associated laboratory findings. The platelet count should be maintained  $>50,000/\text{mm}^3$  and the fibrinogen level  $>1 \text{ g/L}$ . If the etiology is secondary to severe infection, appropriate intravenous antibiotics should be administered. In PC deficiency the initial management is FFP or PC concentrate until all lesions have healed. After that for long term therapy we can give oral anticoagulation with warfarin or PC concentrate replacement. Liver transplant has been performed as a successful treatment of homozygous protein C deficiency when replacement therapy was not readily available (15).



Figure 1



Figure 2



Figure 3



Figure 4



Figure 5

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### References:

1. Marlar RA, Montgomery RR, Broekmans AW. Diagnosis and treatment of homozygous protein C deficiency. Report of the working party on homozygous protein C deficiency of the Subcommittee on Protein C and Protein S, International Committee on Thrombosis and Haemostasis. *J Pediatr* 1989;114:528-34.
2. Manco-Johnson MJ, Abshire TC, Jacobson LJ, Marlar RA. Severe neonatal protein C deficiency: prevalence and thrombotic risk. *J Pediatr* 1991;119:7938.
3. Price VE, Iedingham DL, Krumpel A, Chan AK. Diagnosis and management of neonatal purpura fulminans. *Fetal and Neonatal Medicine* 2011;30:1-5
4. Hattenbach LO, Beeg T, Kreuz W, Zubcov A. Ophthalmic manifestation of congenital protein C deficiency. *J AAPOS* 1999;3:188-90.
5. Seligsohn U, Berger A, Abend M, et al. Homozygous protein C deficiency manifested by massive venous thrombosis in the newborn. *N Engl J Med* 1984; 310:559-62.

6. Kirkinen P, Salonvaara M, Nikolajev K, Vanninen R, Heinonen K. Antepartum findings in fetal protein C deficiency. *Prenatdiagn* 2000; 20:746-9.
7. Monagle P, Chalmers E, Chan A, et al. Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133:887S-968S.
8. Ten Kate MK, van der Meer J. Protein S deficiency: a clinical perspective. *Haemophilia* 2008; 14:1222-8.
9. Goldenberg NA, Manco-Johnson MJ. Protein C deficiency. *Haemophilia* 2008; 14:1214-21.
10. Zenciroglu A, Karagol BS, Ipek MS, Okumus N, Yarali N, Aydin M. Neonatal purpurafulminans secondary to group B streptococcal infection. *Pediatrhematol Oncol* 2010; 27:620-5.
11. Issacman SH, Heroman WM, Lightsey AL. Purpurafulminans following late onset Group B beta-hemolytic streptococcal sepsis. *Am J Dis Child* 1984; 138:915-6.
12. Branson HE, Katz J, Marble R, Griffin JH. Inherited protein C deficiency and coumarin-responsive chronic relapsing purpurafulminans in a newborn infant. *Lancet* 1983; 2:1165-8.
13. Estelles A, Garcia-Plaza I, Dasi A, et al. Severe inherited "homozygous" protein C deficiency in a newborn infant. *Thrombhaemost* 1984; 52:53-6.
14. Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the healthy premature infant. *Blood* 1988; 72:1651-7.
15. Lee MJ, Kim KM, Kim JS, Kim YJ, Lee YJ, Ghim TT. Long-term survival of a child with homozygous protein C deficiency successfully treated with living donor liver transplantation. *Pediatr Transplant* 2009; 13:251-4.