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Diagnosis and management of neonatal purpura fulminans

V.E. Price [a,*], D.L. Ledingham [b], A. Krümpel [c], A.K. Chan [d]

[a] Division of Pediatric Hematology/Oncology, Department of Pediatrics, IWK Health Centre, Dalhousie University, Halifax, Canada
[b] Division of Hematopathology, Department of Pathology and Laboratory Medicine, Dalhousie University and Capital District Health Authority, Halifax, Canada
[c] Department of Pediatric Hematology/Oncology, University Children's Hospital, Muenster, Germany
[d] Division of Pediatric Hematology/Oncology, Department of Pediatrics, McMaster University, Hamilton, Canada

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S U M M A R Y

Neonatal purpura fulminans is a rare, life-threatening condition, caused by congenital or acquired deficiencies of protein C or S. The condition is often fatal unless there is early recognition of the clinical symptoms, prompt diagnosis, and judicious replacement therapy is initiated. The clinical presentation is that of acute disseminated intravascular coagulation and hemorrhagic skin necrosis. The management includes an acute phase of replacement therapy with fresh frozen plasma or protein C concentrate and a maintenance therapy that includes anticoagulation with warfarin or low molecular weight heparin. This review focuses on the management of severe protein C deficiency.

1. Introduction

Neonatal purpura fulminans describes a clinico-pathological entity of dermal microvascular thrombosis associated with disseminated intravascular coagulation (DIC) and perivascular hemorrhage, occurring in the newborn period. The clinical presentation is that of acute DIC and hemorrhagic necrosis of the skin. This is a rare condition, but it is often fatal if it is not treated early and effectively. Therefore early recognition with prompt investigation and treatment is of paramount importance. This is a review of the diagnosis and management of neonatal purpura fulminans, specifically focusing on protein C deficiency.

2. Etiology of neonatal purpura fulminans

Purpura fulminans was first described in a neonate in 1962 and the etiology was presumed an inherited disorder as three siblings had similar skin lesions.[1] It was only in 1983 that a possible link between the clinical findings of purpura fulminans and protein C deficiency was described in a child, and soon after this the first child with confirmed homozygous protein C deficiency was successfully treated with protein C replacement therapy.[2,3] The first association of homozygous protein S deficiency and purpura fulminans was reported in 1990.[4,5] There are both congenital and acquired causes of neonatal purpura fulminans, outlined in Box 1. Inherited causes are due to a homozygous protein C or S deficiency; compound heterozygosity and co-inheritance with other inherited thrombophilias have been described.[6,7] Acquired causes are more common and often associated with severe infection causing a consumptive coagulopathy and a relative deficiency of protein C and/or S.

Protein C is a vitamin K-dependent coagulation protein that is synthesized in the liver. Plasma protein C is activated by complex formation with thrombin bound to an endothelial cell surface receptor, thrombomodulin (TM). TM and endothelial protein C receptor (EPCR) are both expressed on endothelial cells and regulate the protein C pathway. Thrombin binds TM and acts as a catalyst for the activation of protein C by thrombin. EPCR binds to protein C and enhances the activation of protein C by TM–thrombin complexes by 10-fold. Activated protein C (APC) inactivates factor (F)Va and FVIIIa by limited proteolysis, resulting in a down-regulation of thrombin generation. APC activity is enhanced by protein S.[8,9] Therefore, protein C or S deficiency predisposes to a decreased capacity to reduce thrombin generation and a hypercoagulable state.

3. Diagnosis

3.1. Clinical presentation

Neonatal purpura fulminans usually presents with a rapid onset of cutaneous purpuric lesions after birth and DIC. If the

* Corresponding author. Address: Dalhousie University, Department of Pediatrics, Division of Hematology/Oncology – IWK Health Centre, 5850/5980 University Ave., P.O. Box 9700, Halifax, NS B3K 6R8 Canada. Tel.: +1 902 4707290; fax: +1 902 470 7216.
E-mail address: vicky.price@iwk.nshealth.ca (V.E. Price).

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Box 1. Etiology of neonatal purpura fulminans.

Congenital/inherited states
1. Homozygous protein C deficiency
2. Homozygous protein S deficiency

Acquired causes
Increased consumption:
1. Infection, e.g. group B streptococcus infection
2. Disseminated intravascular coagulation
3. Acute venous thrombosis
4. Antiphospholipid antibodies
5. Cardiac bypass
Decreased synthesis:
6. Severe hepatic dysfunction
7. Galactosemia
8. Severe congenital heart disease
9. Warfarin therapy

condition is not recognized and treated promptly, it is usually fatal. The clinical severity may vary depending on the underlying cause, e.g. genetic variability of severe congenital protein C and S deficiencies. The onset of symptoms is usually within 2–12 h after birth. However, infants presenting with a delayed onset of purpura fulminans, between 6 and 12 months of age, are reported.[10,11] The skin lesions initially appear dark red and then become purple-black and indurated; they occur at previous sites of trauma, e.g. intravenous cannula insertion sites, and they may initially be mistaken as bruising. There is a predilection for the limbs, although buttocks and thighs are often affected. In time the areas may become necrotic and gangrenous resulting in loss of extremities (Figure 1).[11,12] 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.[13,14] These two complications can occur as antenatal events.[15] Large vessel venous thromboses may also occur, e.g. renal vein thrombosis. Similar vitreoretinal findings have been described in neonatal purpura fulminans due to severe congenital protein S deficiency.[16]

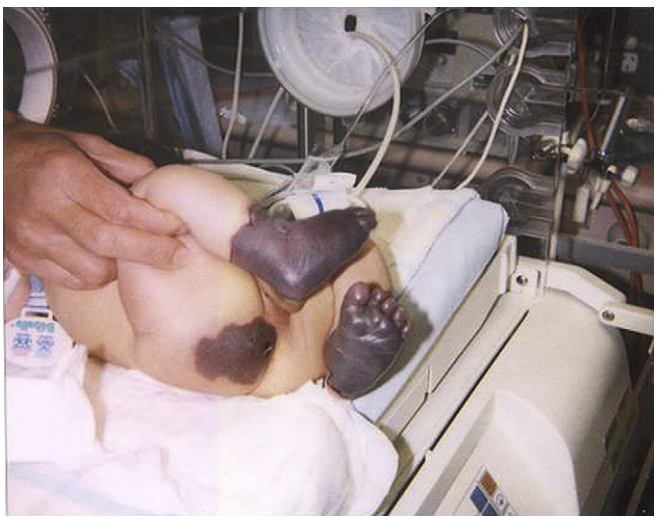

Figure 1. Typical skin lesions of neonatal purpura fulminans, courtesy Dr Paul Monagle.

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.[17] There may be no family history of thrombosis as there is wide variability in heterozygous phenotype.[18,19] 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.[20–22] Neonatal purpura fulminans due to an acquired protein C deficiency has been reported secondary to liver disease in an infant with galactosemia as well as in newborns with severe congenital heart disease.[23,24]

3.2. Laboratory diagnosis

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.[3,11,25] Distinction between congenital and acquired causes of protein C and S deficiency is often challenging in the setting of acute thrombosis. Genetic testing of the child and family members can be useful to 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 (see Goldenberg and Manco-Johnson[19] for a short list of laboratories offering this testing). Testing of a citrated plasma sample, collected prior to initiation of treatment, is therefore crucial for accurate diagnosis. Functional (activity) assays are recommended for initial screening.[26,27] Antigen levels may be contributory if interfering factors (e.g. factor V Leiden mutation, antiphospholipid antibodies, direct thrombin inhibitors) are present.[26,27] Unlike testing in adults, the interpretation of protein S levels in neonates is not complicated by binding to C4b, which is present at very low levels at birth.[28,29] Protein C and S activity levels are undetectable in homozygotes.[4,11] It is essential that the laboratory use age-specific reference ranges for interpretation (Table 1[30–32]). Levels of protein C and S in healthy

Table 1
Reference ranges for proteins C and S in the pre- and postnatal periods.

Age/gestation	Protein C Mean (95% CI)	Protein S Mean (95% CI)
Fetuses[a]		
19–23 weeks	Activity: 9.6% (7–13)	Free: 21.7% (13–32)
24–29 weeks	Activity: 10.4% (8–13)	Free: 27.9% (19–40)
30–38 weeks	Activity: 14.1% (8–18)	Free: 27.1% (18–40)
Premature infants[b]		
Day 1	Antigen: 28% (12–44)	Antigen: 26% (14–38)
Day 5	Antigen: 31% (11–51)	Antigen: 37% (13–61)
Full-term infants[c]		
Day 1	Chromogenic: 36% (24–44) Clotting: 32% (24–40)	Clotting: 36% (28–47)
Day 3	Chromogenic: 44% (28–54) Clotting: 33% (24–51)	Clotting: 49% (33–67)

[a] Data obtained using chromogenic assay (protein C activity) and enzyme-linked immunosorbent assay (ELISA) following precipitation of C4bBP-bound protein S (free protein S).[39]
[b] Data obtained using ELISA (protein C) and immunoelectrophoresis (protein S) methods.[31]
[c] Data obtained using Stachrom Protein C, Staclot Protein C and Staclot Protein S.[30]

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neonates are significantly below adult reference ranges, as low as 0.12 and 0.14 U/mL respectively.[31] These physiologically low levels combined with acquired causes (see Box 1) can lead to abnormal results. The usual recommendation of repeat testing in three to six months for confirmation is clearly impractical in this setting; testing of parents is therefore essential.

Confirmation of a heterozygous state in both parents is complicated by slightly different pitfalls. Particularly with protein C testing, there is overlap between heterozygous carriers and normal adults.[27] Pregnancy has an unpredictable effect on protein C levels[27]; in fact, diagnosis of an affected infant was delayed by an initial low–normal result in the mother.[33] Protein S activity is predictably decreased in states of elevated estrogen,[26] and there is difficulty distinguishing heterozygous carriers from normal pregnant women based on standard reference ranges.[34] Acute inflammation also lowers protein S activity due to binding with C4b.[26] Finally, treatment with oral vitamin K antagonists is a well-known acquired cause of both protein C and S deficiency. Given these issues, abnormal results should be confirmed by repeat assays, and testing of extended family may be necessary to demonstrate the inherited nature of the deficiency. Experts have recommended testing of siblings and grandparents.[11,19]

4. Prenatal diagnosis of severe protein C or S deficiency

If the causative mutation of protein C or S deficiency within a family is known, prenatal diagnosis is available for women at risk of having a child with homozygous deficiency. This requires chorionic villous sampling that is associated with a 1% risk of fetal loss.[35] Despite the identification of almost 200 unique mutations in the protein C gene and 131 in the protein S gene,[6,36,37] the underlying defect is not always identified.[38]

Fetal blood sampling offers an alternative method; however, fetal protein C levels in the second trimester may be as low as 8%[39] and the detection limit for many of the commercially available assays is 3%. This, combined with the risk of sample contamination with maternal blood, makes the distinction between heterozygous and homozygous states challenging.[39,40] As complications of congenital protein C deficiency in the central nervous system may occur in the third trimester, antenatal diagnosis may provide an opportunity for early intervention, through timely delivery and initiation of replacement therapy, and prevention of devastating consequences of severe protein C deficiency.[15,38]

5. Treatment of neonatal purpura fulminans

Management of DIC should be based on the clinical and associated laboratory findings. The platelet count should be maintained $>50{,}000 \times 10^9$/L and the fibrinogen level >1 g/L. If the etiology is secondary to severe infection, appropriate intravenous antibiotics should be administered.

6. Fresh (frozen) plasma (FFP/FP) and protein C concentrates

6.1. Treatment of neonatal purpura fulminans

If the infant has the classical signs of purpura fulminans, blood samples of the infant and parents should be drawn into citrated tubes for antigen and activity levels of protein C and protein S, before replacement therapy is commenced. There is no protein S concentrate available. FFP/FP (10–20 mL/kg every 12 h) or cryoprecipitate is used as replacement therapy.[5] The mainstay of management of severe acquired, transient deficiencies of protein C or S is aggressive treatment of the underlying cause, although replacement therapy has been used in such cases. This review will focus primarily on the treatment of congenital protein C deficiency.

6.1.1. Fresh (frozen) plasma

Protein C replacement should be commenced promptly using FFP/FP, or a human plasma-derived, viral inactivated protein C concentrate.[17] FFP/FP should be given at a dose of 10–20 mL/kg every 6–12 h until a protein C concentrate is available. The most common associated side-effect is fluid overload. Exposure to large numbers of donors potentially increases the risk for exposure to blood-borne pathogens and allergic reactions to donor proteins in FFP/FP. The use of solvent detergent-treated plasma may avoid this, but it is not universally available. There is evidence that the haemostatic qualities of solvent detergent-treated plasma and FFP/FP are similar, but the protein S activity may be lower in solvent detergent-treated plasma and the relevance of this is unclear when considering this product for replacement therapy.[41–43] A total of 1 mL/kg of FFP/FP will increase the plasma protein C concentration by 1 IU/dL. The aim is to have a trough protein C activity of >10 IU/dL while awaiting the protein C concentrate.[11,19]

6.1.2. Protein C concentrates

There are two human plasma-derived, viral-inactivated protein C concentrates available: Ceprotin (Baxter Bioscience, Glendale, CA, USA) is licensed for use in congenital protein C deficiency in the USA and Europe; and Protexel (LFB, Lille, France) is licensed for use in Europe. Unfortunately, these products are not widely available in many countries. The dose for both products is an initial 100 U/kg followed by 50 U/kg every 6 h.[19] The dosing is based on the fact that 1 IU/kg of protein C concentrate increases plasma protein C by 1 IU/dL and the half-life of plasma protein C is 6–10 h. The target protein C activity is a trough level of 50 IU/dL. Although both products are licensed for use for replacement of protein C in congenital deficient states, both have been used off label in the management of severe acquired protein C deficiency.[44,45] Recombinant activated protein C (APC) is not recommended to treat neonatal purpura fulminans due to the possible increased risk of bleeding that was reported in a randomized controlled trial of APC in children with sepsis. In this study, there was a trend to increased major bleeding particularly in infants.[46] However, there are reports of its use in the management of neonatal purpura fulminans.[47]

The treatment during the acute phase should continue until all lesions, including skin, CNS and ocular lesions, have resolved.[11] Reliable venous access may be difficult and there are reports of protein C concentrate administered subcutaneously.[48] Early referral to an ophthalmologist for management and follow-up of the ocular lesions is recommended.

6.1.3. Liver transplant

Liver transplant has been performed as a successful treatment of homozygous protein C deficiency when replacement therapy was not readily available.[49]

6.2. Prophylaxis for surgical procedures

Protein C concentrate: 100 U/kg as an initial bolus, then 30–50 U/kg every 12–24 h with a target therapeutic range (trough level) for protein C activity of 20–50 IU/dL.[19]

6.3. Maintenance therapy

Maintenance therapy consists of either secondary prophylaxis with oral anticoagulation alone or protein C concentrate: 30–50 U/kg every 1–3 days with warfarin therapy.[19] Reliable

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venous access to facilitate long term protein C replacement therapy is a challenge and often requires the insertion of central venous line (CVL). The presence of a CVL may increase the risk of thrombosis and infection, due to the underlying hypercoagulable state and the risk:benefit ratio of a CVL requires serious consideration prior to insertion. Subcutaneous administration of protein C concentrates might offer further opportunities for long term treatment. First experiences show good acceptance, tolerability and pharmacokinetic data similar to intravenous therapy.[48,50,51]

7. Anticoagulation

7.1. Initial therapy

Anticoagulation therapy should be initiated with administration of protein C replacement therapy (protein C concentrate or FFP/FP) and is an effective long term secondary prophylaxis. Initial anticoagulation consists of either unfractionated heparin (UFH) or low molecular weight heparin (LMWH). UFH should be administered at a dose of 28 U/kg/h with a target anti-Xa level of 0.3–0.7 U/mL. The recommended dose of LMWH is 1.0–1.5 mg/kg/dose every 12 h with a therapeutic target anti-Xa level of 0.5–1 U/mL.[17,19,52] Initiation of warfarin therapy should overlap and only commence after several days of anticoagulation with UFH/LMWH to avoid warfarin-induced skin necrosis and other thrombotic complications. Warfarin is a vitamin K antagonist and therefore, on initiation of therapy, protein C levels are decreased, increasing the risk of thrombosis.

7.2. Maintenance

Warfarin therapy is recommended. If protein C concentrate is not concurrently administered as prophylaxis, the aim of an international normalized ratio (INR) is between 2.5 and 3.5. A smaller dose of warfarin, to maintain a target INR of 1.5–2.5, is recommended with protein C replacement therapy.[19]

8. Monitoring of therapy

The therapeutic target activity levels for monitoring of protein C replacement therapy as well as anticoagulation therapy are mentioned above. Due to the risk of bleeding or recurrent purpura fulminans, INRs often need to be monitored on a weekly basis. Point-of-care testing for INR enables such patients to be monitored at home.[53] D-Dimer is a useful marker for activation of the coagulation cascade and has been a helpful indicator both of adequate replacement and anticoagulation therapy in neonates.[19,52,54] A rising or elevated D-dimer may be the first sign of recurrent purpura fulminans.

9. Conclusion

Neonatal purpura fulminans, whether caused by congenital or acquired deficiencies of protein C or S, remains a life-threatening condition. Fortunately it is a rare disorder. Early recognition of the clinical symptoms, prompt diagnosis and judicious replacement therapy decreases both the morbidity and mortality associated with this condition. Every effort should be made to increase awareness of this rarely diagnosed condition and its treatment, so that affected infants and their families will derive maximum benefit, even if replacement therapy with protein C concentrate is not widely available.

Practice points

- Early recognition and treatment prevents excess morbidity and mortality.
- The clinical presentation is that of acute DIC and hemorrhagic skin necrosis.
- Etiology is due to a congenital or acquired deficiency of protein C or S.
- Management of congenital protein C and S deficiency includes an acute phase of replacement therapy and well as ongoing maintenance therapy that includes anticoagulation therapy with warfarin.
- Human plasma-derived, viral-inactivated protein C concentrates are approved for use in congenital protein C deficiency.
- Initiation of warfarin therapy must always overlap replacement therapy.

Research directions

- To develop an international registry of neonatal purpura fulminans.
- To better define the use of LMWH and other new anticoagulants in the homozygous protein C deficiency.
- Define a consensus treatment protocol that is easily accessible.

Conflict of interest statement

None declared.

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