Protein C Deficiency: A Case Review

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PRESENTATION/BIRTH HISTORY

Baby Girl W was born to a 19-year-old, gravida 2 para 0 mother. The mother had had a previous spontaneous abortion at 11 weeks for unknown reasons. She received prenatal care beginning in the first trimester of her pregnancy. Her serologies, including hepatitis B sAg, rapid plasma reagin (RPR), rubella, group B Streptococcus (GBS), HIV, and gonorrhea/chlamydia, were all negative. The mother presented to the birth hospital with a placental abruption at 37 weeks gestation and was taken for an urgent cesarean section. At delivery, there was thick meconium in the amniotic fluid. Apgar scores were 8 and 9 at one and five minutes, respectively. The infant received routine delivery room care with drying, stimulation, suctioning, and free-flow oxygen supplementation. The infant’s birth weight was 2,678 g, length was 45 cm, and head circumference was 32 cm (all parameters appropriate for gestational age).

On NICU admission, umbilical arterial and venous lines were placed. Baby Girl W was started on a morphine drip for pain associated with the open skin lesions. Admission lab tests included a complete blood count (CBC) and coagulation studies. The infant’s hematocrit was low (25 percent), and she was thrombocytopenic. Her coagulation studies were abnormal, with elevated prothrombin time (PT) and thrombin time, decreased fibrinogen, and positive D-dimer; these results indicated a state of disseminated intravascular coagulopathy (DIC). A cranial ultrasound done the day of delivery showed right frontal periventricular echogenicity consistent with an in utero hemorrhage or an infarction. At that time, plans were made to administer fresh frozen plasma (FFP) and cryoprecipitate in attempts to correct the infant’s coagulopathy. Finally, on day of life (DOL) 1, an eye exam revealed small scattered retinal hemorrhages in her right eye (left eye was miotic and difficult to visualize).

DIFFERENTIAL DIAGNOSIS

Consultations were placed to pediatric and plastic surgery, hematology, dermatology, and the enterostomal therapist. The differential diagnosis based on the infant’s physical appearance alone included various skin and systemic diseases. Conditions that may present with skin lesions include severe herpes simplex virus infection, staphylococcal scalded skin syndrome, congenital syphilis, and epidermolysis bullosa. Various diseases can present with neonatal purpura: thrombocytopenia, dysproteinemia or inherited thrombophilia,
hemorrhagic disease of the newborn, DIC, congenital rubella syndrome or other toxoplasma, other viruses, rubella, cytomegalovirus, herpesvirus (TORCH) infections, Wiskott-Aldrich syndrome, hemangiomas, and congenital leukemia. The baby may also present with purpura if the mother has idiopathic thrombocytopenic purpura or systemic lupus erythematosus. Based on Baby W’s clinical presentation and obvious coagulopathy, which was present prenatally, inherited thrombophilia was suspected. Levels of protein C (PC) and protein S were obtained. Baby W had <8 percent PC activity, significantly lower than the normal levels of 17–53 percent. Her protein S activity levels were elevated at 87 percent (normal level is 12–60 percent). (Reference ranges were provided for our hospital by the Ohio State University.) The final diagnosis was PC deficiency.

**Figure 1** ■ Baby W's right flank wounds on DOL 1.

**Figure 2** ■ Baby W's left-hip wounds on DOL 1.

**PROTEIN C DEFICIENCY**

**Background**

Protein C (so named because it was the third clotting protein to be isolated from bovine plasma in 1976) is an important part of the anticoagulant pathway. Other members of the anticoagulant pathway include thrombin, thrombomodulin, endothelial cell PC receptor (EPCR), and protein S. Deficiencies of PC can be mild or severe, with significant defects in coagulation noted when PC levels are undetectable.1 Chromosomal analysis has determined the exact location of the PC sequence. It is on the short arm of chromosome 2, at locus 13–14 (2q13-q14). Inheritance of this condition is autosomal dominant with variable expression. Homozygotes are often born to consanguineous parents, but compound heterozygotes (with two different mutations) are more common. De novo (spontaneous) mutations appear to be the most frequent cause of PC deficiency so that parents are frequently unaffected because most are mutations. There are more than 150 documented mutations.2 Among the general population, the incidence of PC deficiency may be as high as 1 in 200–500 people, although the defect is not severe enough to cause clinical illness. People with heterozygous PC deficiency can range from being totally healthy to having single or recurrent venous thromboses, such as deep vein thrombosis, pulmonary embolism, pregnancy-associated thrombosis, or mesenteric thrombi.1 The incidence of clinically significant PC deficiency is estimated to be 1 in 20,000. Such a low incidence of symptomatic PC deficiency may be attributed to fetal demise and early neonatal death before diagnosis.1

Genetics was consulted for Baby W, and a pedigree completed. The infant was determined to have a homozygous condition, but notably her parents were not consanguineous. After genetic testing, both her parents were noted to have low PC levels consistent with heterozygous status. Her mother also admitted to “having a low PC” as well as a family history of thrombosis. Ideally, Baby W’s parents should have been seen by a genetics counselor early in the pregnancy (it was unclear why they were not). In light of this information, genetics counseling might have been beneficial for this family, as genetic testing for thrombophilia could have been done given the previous pregnancy loss and family history.3 Complications of inherited thrombophilia during pregnancy include fetal loss; placental vasculopathy such as abruption, preeclampsia, and intrauterine growth retardation; as well as venous thromboembolic events (VTEs) in the mother.4 Management of pregnant women with increased risk of thrombophilia includes treatment with heparin to prevent VTE or to manage acute thrombotic episodes during pregnancy and postpartum. Mothers with known PC deficiency who have no history of VTE are either monitored clinically or placed on anticoagulation during the last weeks of pregnancy and postpartum.4 Treatment with heparin is aimed at preventing aforementioned complications, which pose risks to both mother and baby. Prophylaxis hopefully avoids formation of clots, and therefore complications in the baby that result from those clots.
There are two different subtypes of PC deficiency that lead to clinical symptoms: (1) Type 1 deficiency results in decreased PC antigen, with correlated decreased function and (2) Type 2 deficiency results in PC activity that is lower than expected for the quantity present, suggesting that an altered protein is less active.

**Pathophysiology**

The clotting cascade is a complex series of enzymatic reactions that culminates with the formation of thrombin and fibrin to create an insoluble clot (Figure 3). Protein C plays an important role in the reversal of the clotting cascade.

Increased clotting leads to increased formation of thrombin. Thrombin can work in two ways: First, it can cause fibrin formation and platelet and endothelial cell activation; all of these lead to formation of an insoluble clot. Secondly, thrombin can bind to thrombomodulin, which is a transmembrane glycoprotein that acts as a cofactor for thrombin.

The thrombin–thrombomodulin complex, which was described earlier, serves to activate PC in an effort to balance or regulate the clotting process. Protein C is synthesized in hepatocytes and circulated within the bloodstream at a low concentration as a preprotein. The preprotein is “activated by thrombin through cleavage of a small activation peptide in the heavy chain of the protein C molecule” (p. 350). Activated PC (APC) binds to EPCR, further enhancing the protein’s functional activity.

Activated PC, along with its cofactor protein S, are the essential molecules that limit clotting. They disable factors Va and VIIIa, leading to decreased production of thrombin and fibrin as shown in Figure 3. In this fashion, PC acts to stop the coagulation cascade. Activated PC can also induce fibrinolysis by neutralizing plasminogen activator inhibitor.

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**FIGURE 3** The coagulation cascade.
Thus, the overall net effect of these actions is to interrupt and stop the clotting cascade.

Deficiency of PC leads to a hypercoagulable state, predisposing the patient to VTEs. Patients with PC deficiency are unable to decrease the production of thrombin via the down-regulation pathway. Because the control of the clotting cascade is disrupted, thrombin formation continues, resulting in numerous thrombi that cause clinical symptoms of PC deficiency. Some common locations for the VTEs are large veins in the limbs and the retinal, cerebral, renal, mesenteric, and portal veins. The locations of the VTEs determine patients’ clinical symptoms. Baby W presented with purpura fulminans (PF), DIC, retinal complications, and intracranial bleeding.

Another potent property of APC is its anti-inflammatory role, which is expressed both directly and indirectly. Direct processes include suppression of monocyte and macrophage signaling. Indirect ways include down-regulation of thrombin-mediated anti-inflammatory activity. Because of its anti-coagulant and anti-inflammatory properties, APC has been postulated as a way to treat adults with acute sepsis. In patients with a systemic inflammatory response, PC works to down-regulate the pro-inflammatory mediators, whereas the anti-inflammatory mediators are up-regulated. This anti-inflammatory action of PC has proved to be a useful adjunct to therapy for patients with sepsis. A large clinical trial has shown that treatment with APC decreases mortality among patients with severe sepsis.

Inflammation can alter regulation of the PC pathway. Inflammation of the vasculature can lead to down-regulation of thrombomodulin and the PC receptor, both of which augment PC activity. Thus, inflammation can decrease APC levels and function. This may account for the PC dysfunction often noted in patients with severe sepsis. Levels of PC increase after birth and for the first six months of life. Thereafter, they decrease, and levels remain low until puberty, when they rise to reach adult levels. Neonates with severe PC deficiency often have undetectable levels of PC, as did Baby W. Although infants with PC deficiency are not inherently at increased risk for sepsis, open lesions do predispose these infants to infection.

CLINICAL PRESENTATION
AND TREATMENT

Baby W’s presentation consisted mainly of four kinds of symptoms: open skin lesions, DIC, retinal hemorrhages, and cranial infarction. These symptoms are all directly caused by PC deficiency. Treatment for this patient consisted of aggressive wound therapy, excellent nutrition, replacement of clotting factors with exogenous PC, as well as supportive care for her overall development. Long-term treatment is indicated for patients with PC deficiency to avoid further complications. The following sections provide more detail about the clinical symptoms and how she was treated.

Skin

Baby W had a very classic appearance of severe PC deficiency, presenting within hours of birth with PF and severe DIC. This infant’s case was remarkable in that her PF was so severe at delivery, with progression of necrosis quickly in the following hours. Purpura fulminans tends to develop over pressure points, like the buttocks or the head. Baby W had severe PF over her hips (see Figures 1 and 2).

Purpura fulminans is a disorder marked by intravascular thrombosis with infarction of the skin; there may be associated DIC and vascular collapse. This disorder results from thrombi in the small veins of the subcutaneous fat of the skin. There are three etiologies of PF: inherited, infectious, and idiopathic. Disorders that can cause PF include inherited coagulopathies, including PC or protein S deficiency or factor V Leiden, which is the most common cause of clots in the microvasculature, or acute bacterial or viral infection (meningococcal, pneumococcal, or varicella). Infectious PF results largely from endotoxin, which alters the delicate balance of pro-thrombotic and anti-thrombotic activity on endothelial cells. Most neonatal cases result from coagulopathies, whereas in older children, the cause is usually infectious.

The lesions start out as purpuric lesions on the surface of the skin, and they quickly enlarge and become necrotic or gangrenous. They are acutely painful to the child, and pain medication is warranted. Secondary infection may also occur, and antibiotics should be started early to treat potential primary or secondary infections. Topical antibiotics may be added to prevent secondary infection of the eschar and further damage to deeper tissues. Laboratory studies to be done on any patient with PF include CBC and coagulation studies (PT, partial thromboplastin time [PTT], fibrinogen, and D-dimer). Tests including PC and protein S levels should also be done to rule out congenital thrombophilia, as well as anemia (related to blood loss and hemolysis), thrombocytopenia, and leukocytosis (related to tissue necrosis).

Treatment includes replacement of clotting factors with FFP and treatment of the underlying disorder. If they are severely necrotic, the lesions may need to be debrided. Vigilant wound care and management are absolutely crucial for these patients. Wound infection may quickly lead to sepsis, which can be fatal. Negative pressure (vacuum-assisted close, or VAC) ranging from −50 to −120 mmHg has been used with some success in avoiding skin grafting. The goal of negative pressure therapy is to decrease wound exudate and edema, thereby increasing perfusion to the wound bed. Another component of this therapy is the mechanical forces; the cells are stretched, enhancing growth of both fibroblasts and epithelial cells. Bacterial contamination, with its subsequent risk of infection, is also decreased.

This type of system may be particularly helpful in infants who are very mobile and cannot comprehend the elaborate skin care they require. Use of VAC on Baby W employed pressure at −100 mmHg. Vacuum-assisted closure devices may be used for weeks to enhance wound healing.

If the negative pressure does not achieve successful closure, other interventions can include placement of dermal regeneration agents, such as Integra (Integra Life Sciences Corporation, Plainsboro, New Jersey). An “engineered skin
substitute” that enhances wound healing, Integra is seen on Baby W in Figure 4, taken at six weeks of age (p. 241e). When this skin substitute is used in conjunction with a wound VAC, adhesion of the artificial layer is improved. After three weeks (or once the silicone layer of the Integra falls off), the wound VAC and the Integra are removed, ideally leaving the wound bed adequately prepared to accept a skin graft. Figure 5 shows application of the skin graft, and Figure 6 (taken five months after Baby W’s birth) demonstrates the final appearance of the left flank wound.

Another important component to treatment is the addition of PC concentrate to bring PC activity to normal levels. Amputation rates and skin grafting rates are much higher in patient populations that cannot be treated with PC concentrate, such as those in countries where the drug is not approved for use. Protein C concentrate is derived from human plasma and was approved by the U.S. Food and Drug Administration (FDA) for treatment of PC deficiency in 2007. Although the diagnosis of PC deficiency was not made until Baby W was four days old, treatment with PC concentrate was started on DOL 2. The goal of PC replacement is to correct the deficient protein. By DOL 7, Baby W’s PC level had increased to 50 percent. Coagulation studies and CBCs were obtained twice daily, and PC levels with d-dimer were monitored daily until the infant’s lab results normalized. Her blood work was followed closely during her entire hospitalization.

A most important element of wound healing is providing excellent nutrition. Poor nutrition in patients with significant wounds can extend the healing process by “prolonging the inflammatory phase, decreasing fibroblast proliferation, and altering collagen synthesis,” as well as by increasing chances of infection (p. 61). Nutrient requirements for optimum wound healing include adequate amounts of energy—namely, glucose and protein. Glucose is the fuel used for collagen synthesis, and protein is required for all stages of wound healing—namely, hemostasis, inflammation, proliferation, and remodeling. Another consideration is protein and fluid losses through exudate if a negative pressure system is used; increased protein and total fluids may be required in these cases. Parenteral nutrition (PN) should be maximized with protein and calories as tolerated. Central intravenous (IV) access may be required for optimal PN. Multivitamins are recommended, with extra amounts of vitamins A and C because these enhance collagen deposition and fibroblast growth, respectively. In Baby W’s case, enteral feedings were started on DOL 6 while her PN was maximized. She was initially a poor bottle feeder and was supplemented with PN to achieve total fluids of 170 mL/kg/day and 135 kcal/kg/day. She was weaned off IV fluids and was taking full volume by mouth by DOL 26; she eventually required approximately 180 mL/kg/day and 120 kcal/kg/day for

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**FIGURE 4** Application of Integra artificial skin layer to left hip.

**FIGURE 5** Application of full-thickness skin graft to left hip.

**FIGURE 6** Final appearance of left hip wound at five months of age.
adequate weight gain of 15–20 g/day. This is at the high end of energy requirements for healthy term babies to gain weight (100–120 kcal/kg/day).15

Eyes

Ocular problems are common in patients with inherited thrombophilias. Some commonly occurring complications include nonreactive pupils, microphthalmos, and periorbital edema. The most frequently seen problem is vitreous hemorrhage. Although the exact cause is unknown, the most likely reason is retinal vein occlusion. Other possible causes include retinal artery occlusion and ischemic optic neuropathy.16

The vitreous fluid is a gel-like substance that fills the inner cavity of the eye, helping to hold the round shape. The vitreous is 99 percent water, inelastic, and avascular. Retinal vein occlusion results in hemostasis and hemorrhage into the vitreous space. Age at the onset of symptoms can range from hours to weeks after birth.17 A clot is rapidly formed with very slow removal of the fibrin, and there can be persistence of red blood cells (RBCs) in the vitreous for months.18 This reaction is likely exacerbated in the patient with PC deficiency. Immune response to a vitreous hemorrhage is also unusual: There is a lack of reaction from the polymorphonuclear cells (PMNs). The PMNs usually act to dissolve fibrin; thus, the absence of PMNs contributes to the persistence of fibrin and RBCs within the vitreous.18

The retinal damage that occurs after a vitreous hemorrhage has an unclear etiology. One theory is that the breakdown of RBCs releases iron, and the excess iron may contribute to “sclerosis and obliteration of retinal vessels with secondary retinal changes” (p. 21).18 It is also postulated that blood, hemoglobin, and iron potentially stimulate proliferation of retinal vessels, contributing to retinal detachment.18 Vitreous hemorrhage can also cause leukocoria (white pupil), another finding often seen in patients with PC deficiency.17

Vitrectomy is done to treat nonresolving vitreous hemorrhage. The goal is to remove debris, scar tissue, or blood from the eye or to alleviate traction on the retina. The amount of vision the patient retains depends on the degree of damage to the retina.18 The vitreous fluid is removed to allow the eye surgeon easier access to repair the retinal detachment. After the vitreous is surgically removed, it is slowly replenished with the body’s own aqueous fluids. This procedure can help to salvage vision in some patients.

Central Nervous System Complications

Pregnancy itself is a thrombophilic state, and the addition of any maternal coagulation defect increases the risk for placental infarction and fetal cerebral infarct, resulting from emboli traveling to the fetus.19 A VTE in the central nervous system of a neonate is essentially a stroke. Cerebral blood flow becomes occluded secondary to a thrombosis in a cerebral artery or vein.19 Such thromboses that occur anywhere between 20 weeks gestation and the 28th DOL can be identified as a neonatal ischemic stroke. They can cause intraparenchymal brain infarction with hydrocephaly.20 Baby W had a head ultrasound on DOL 1, which showed a right frontal infarct, indicating a fetal ischemic stroke. Children with inherited thrombophilia are prone to ischemic head bleeding.19 Additionally, inherited thrombophilia should be considered in term or late preterm patients with intracranial hemorrhage without history of birth trauma.21 Patients like Baby W, with very severe coagulopathy, are at risk for poor outcomes as a result of parenchymal damage.

LONG-TERM TREATMENT

Patients with PC deficiency need long-term anticoagulant therapy to avoid further microvascular damage in the future. This can be accomplished with heparin, warfarin, and continued PC infusions. Low-molecular-weight heparin (LMWH) seems to be the most popular choice for several reasons. It does not require long-term IV access, it requires less monitoring than other choices, and the dose–response relationship is relatively predictable.21 Low-molecular-weight heparin works primarily through antifactor Xa activity. It is administered via subcutaneous injection or an indwelling subcutaneous catheter. These catheters greatly decrease the number of needlesticks for the child. They are a novel intervention with relatively few side effects.

Management includes monitoring coagulation studies. D-dimer monitoring is often used to predict impending recurrence of DIC or PF. Patients with severe disease may also need stress dosing of PC to ensure appropriate levels during subsequent surgeries or times of acute illness. Stress dosing during these times may help to avoid recurrence of thromboses; a goal of 25 percent PC activity should be maintained.22 Both the company that provides exogenous PC as well as the hematologists in-house preferred a goal of 25 percent activity. That is what our team used as the goal for Baby W’s treatment.

Baby W’s Response to Treatment

Baby W’s acute DIC and PF resolved quickly upon treatment with PC infusions. She achieved full enteral feedings by DOL 26. She had a Broviac catheter placed for long-term access for PC infusions. Her PF was very severe, requiring debridement, placement of Integra with wound VAC, and subsequent skin grafting. She underwent a vitrectomy for vitreous hemorrhage and retinal detachment of her left eye. Unfortunately, she lost her vision in that eye. An MRI of her head revealed bilateral frontal infarcts. At three months of age, she was working well with physical and occupational therapy. Baby W was eventually discharged home with her parents and nursing care; she required a Broviac catheter for biweekly PC infusions as well as twice-daily LMWH injections.

LONG-TERM OUTCOMES

There is limited information about long-term outcomes for patients with PC deficiency. For heterozygotes in the general population, whereas survival for patients with homozygous PC deficiency is difficult to determine because of fetal demise and neonatal death prior to...
The literature has shown a clear link between inherited thrombophilias, like PC deficiency, and ocular complications.1,16,17 However, more prospective studies are needed to determine the long-term visual acuity of neonatal patients like Baby W.

A significant problem these patients face is recurrence of VTE. Use of long-term anticoagulation, antithrombotic medication during pregnancy or surgery, as well as avoidance of oral contraceptives can, it is hoped, prevent recurrences.23 One study showed that the incidence of recurrence of VTE in patients with inherited thrombophilia not on long-term anticoagulation is 48 percent.22 Risk of recurrence is certainly higher if anticoagulation therapy is discontinued: 51 percent of patients had a recurrent VTE within one year, and 87 percent experienced a recurrence within seven years.24 Thus, the conclusion can be drawn that continued anticoagulation seems to be the best course for patients with PC deficiency.

Mental outcomes vary widely for these patients and depend on the severity of the intracranial insult. Infants who have suffered neonatal strokes may have normal outcomes, but they may also develop cerebral palsy, cognitive or visual impairment, as well as seizure disorders.25 Seizures should be treated to avoid further interference with brain growth and overall development.

Protein C deficiency is a rare but life-threatening disorder of coagulation. Some complications may be inevitable, but prompt recognition and treatment of the underlying disease can optimize outcomes for these unique patients.

REFERENCES

About the Authors
Alicia Kelly has worked in the NICU at the Nationwide Children’s Hospital for six years. She recently completed the Neonatal Nurse Practitioner program at the Ohio State University and has begun working in her unit as an NNP. This article came about during required professional development during her transition from RN to NNP.

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