

## Case Report

# Homozygous Severe Protein C Deficiency Type I: Long-term Prophylactic Intermittent Therapy with Subcutaneous Purified Protein C Concentrate: First Case Report from Kuwait

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### ABSTRACT

We describe here, with review of the relevant literature, our experience with subcutaneous protein C concentrate on a long-term basis for the prophylaxis of thrombotic episodes in a Kuwaiti girl with homozygous severe

protein C deficiency – Type 1, causing neonatal purpura fulminans and blindness in left eye due to retinal vessel coagulopathy. To the best of our knowledge, this is the first such case report of this genetic disorder from Kuwait.

KEYWORDS: protein C concentrate, protein C deficiency, intermittent prophylactic therapy

### INTRODUCTION

Protein C (Pr C) is a vitamin K dependent natural anticoagulant glycoprotein, which is synthesized in the liver and then circulates in the blood as an inactive zymogen<sup>[1]</sup>. It is activated on the vascular endothelial cell wall by a complex of thrombin and thrombomodulin forming activated Protein C (APC) which then inhibits activated factors V and VIII and stimulates fibrinolysis<sup>[2-4]</sup>. Homozygous protein C deficiency is inherited in an autosomal recessive fashion and is of two types<sup>[5]</sup>. The most common is Type I in which both functional protein C [Pr C (f)] and antigenic protein C [Pr C (a)] are equally reduced or undetectable in the blood. In the less common type II protein C deficiency, the patients have reduced protein C (f) concentration in the blood while protein C (a) being normal or slightly low. Homozygous severe protein C deficiency is a rare but serious disease which presents with life-threatening neonatal thrombosis and purpura fulminans with frequent association with disseminated intravascular coagulation<sup>[6]</sup>. Thrombotic events involving the central nervous system and the eyes may lead to neuro-developmental problems and blindness<sup>[5,7]</sup>. Various therapeutic options have been described for long-term management of severe congenital protein C deficiency, oral anticoagulant therapy being the standard therapy<sup>[8-10]</sup>. In recent years, a small number of children with this condition have been successfully treated with protein C concentrate intravenously or subcutaneously<sup>[11-15]</sup>.

We describe here, with a review of the relevant literature, our experience with subcutaneous

protein C concentrates on a long-term basis for prophylaxis of thrombotic episodes in a Kuwaiti girl with homozygous severe protein C deficiency – Type 1 presenting with neonatal purpura fulminans and blindness in left eye due to retinal vessel thrombosis.

### CASE REPORT

A full term female Kuwaiti infant was born with a birth weight of 3.25 kg on 5.6.2000 in Saudi Arabia by normal delivery after an uneventful pregnancy. This was the first child of consanguineous Kuwaiti father and Saudi mother. She was well until four weeks of age when she was presented to a hospital in Saudi Arabia, with spontaneous painful swelling over the calf muscles of the left leg and was treated with antibiotics. At the age of two months, she was seen at a specialist hospital with an erythematous swelling of 8 cm x 3 cm size, which soon became blackish and necrotic at the site of her first dose of DPT and hepatitis vaccines in the left thigh. The investigations then revealed absent protein C antigen and activity but normal protein S and anti thrombin III. The Protein C assay in the parents showed both parents heterozygous for Protein C deficiency, father having Protein C level 0.32 IU/ml (normal value, 0.64 to 1.13) immunologically and 0.36 IU/ml (normal value, 0.50 to 1.24) functionally and mother having 0.28 IU/ml immunologically and 0.31 IU/ml functionally. She was diagnosed to have homozygous severe protein C deficiency with both parents being carriers of the disease. She was treated with I.V. fresh frozen plasma (FFP) and

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Fig. 1: Scar of thrombotic skin necrosis in left upper thigh at the site of first dose of DPT and hepatitis B vaccines.

antibiotic and subsequently with oral Warfarin therapy keeping INR between 2.5 to three. On her return to Kuwait in January 2001 she developed an episode of purpura fulminans and was admitted to a regional hospital where she received I.V. FFP and antibiotics. As her condition deteriorated with further episodes of thrombotic lesions in the limbs, she was sent for further management to our Unit where she was found to have blackish necrotic lesions over left and right thighs, small and blind left eye and an old scar of 12 cm X 6 cm size over left upper thigh at the site of her previous thrombotic lesions (Fig. 1). Further Protein C assay in the infant and her parents in our unit confirmed the diagnosis of homozygous severe congenital protein C deficiency both immunologically and functionally. She was managed with I.V. FFP and heparin. Her lesions healed with no further new ones. She was discharged home on oral Warfarin. Subsequently she had several attacks of purpura fulminans requiring admission for FFP, heparin and adjustment of dose of Warfarin causing great deal of distress to the child and family. It was increasingly difficult to find a good venous access in this infant for I.V. medications and INR measurements. We then decided to use protein C concentrate (Ceprotein, Human, Dried, Vapor heated, Baxter AG, Vienna). Initially she was given protein C concentrate 50 IU/kg per dose by two hours subcutaneous infusion using a syringe pump every 12 hours daily along with daily oral Warfarin. This dose maintained her protein C activity around 10% (trough level) (normal value, 66-129%) and reduced dramatically the episodes of purpura fulminans. While on this regimen, she was evaluated by an ophthalmologist. Lensectomy and vitrectomy were done under general anesthesia and she was found to have irreversible total retinal detachment with a lot of peripheral tractions in the

left eye causing blindness. She tolerated the surgical procedure without any thrombotic complications. As the protein C concentrate is very expensive and not easily available in Kuwait, we gradually reduced the dose of protein C concentrate to 50 IU/Kg/day by two hours subcutaneous infusion twice weekly as maintenance dose along with daily oral Warfarin maintaining the INR between two to three. This intermittent prophylactic dose of protein C concentrate subcutaneously in conjunction with daily oral Warfarin had reduced the troublesome thrombotic episodes and had indeed improved her quality of life considerably, while maintaining her protein C activity around two to 3% (trough level). She has no adverse effects from the subcutaneous protein C concentrate infusion and her virology screening for HBV, HCV and HIV had been negative consistently. She is now two years of age and developing normally with normal growth parameters except for the blindness in the left eye.

## DISCUSSION

Homozygous protein C deficiency is a rare genetic disorder which usually presents with fatal purpura fulminans or thrombotic complications during neonatal period. There are only about 20 previous case reports of this condition<sup>[12]</sup>. Until recently, the only available treatment has been with either FFP or prothrombin complex concentrate (PCC) during the acute phase followed by anticoagulation with Warfarin maintaining the INR at 2.5 to 4.4 in order to strike a more even balance between coagulation and anticoagulation<sup>[6,8,9,10]</sup>. Both PCC and FFP carry a theoretical risk of transmitting virus infection, particularly if used for a long time, though this risk is now minimized via viricidal treatment<sup>[12]</sup>. Recently protein C concentrate has been used intravenously as well as subcutaneously in the management of severe protein C deficiency<sup>[1,5]</sup>. As protein C is very expensive and not readily available in Kuwait, we decided to use this medication for long-term prophylaxis with a moderate maintenance dose (50 iu/kg subcutaneous infusion over two hours twice weekly) along with daily oral Warfarin after stabilizing her condition with twice daily subcutaneous infusion of protein C. This combination therapy with intermittent prophylactic protein C and daily oral Warfarin has indeed made the life style of this child more tolerable by preventing troublesome purpura fulminans. The only handicap she has now from this disease is blindness in the left eye due to retinal vessel coagulopathy. It is difficult to ascertain, if the retinal vessel thrombosis is prenatal or postnatal. A small left eye with severe retinal damage since very

early infancy is more in favor of *in utero* vascular insult.

It appears that intermittent prophylactic use of protein C by subcutaneous route in conjunction with daily oral Warfarin is a good therapeutic tool in the long-term management of children with troublesome episodes of purpura fulminans due to homozygous severe protein C deficiency. Similar view had also been expressed by other authors<sup>[13,15]</sup>. A large scale study is needed to work out the exact dose and frequency of administration of protein C concentrate together with oral anticoagulation for long-term prophylaxis. Restoration of normal protein C levels may be achieved through liver transplant and gene therapy, which remain the treatment of choice<sup>[16-18]</sup>.

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