

Bilateral leukocoria in a patient with homozygous protein C deficiency

Nasrat M. Khan, MD, Noura D. Al-Dohayan, FRCS, Fatima S. Al-Batiniji, MD.

ABSTRACT

We describe a bilateral leukocoria and neonatal purpura fulminans in a male infant, born at full term after an unremarkable pregnancy to a healthy consanguineous married couple. Multiple hemorrhagic skin bullae were found at birth on various parts of the body with bilateral leukocoria, organized vitreous hemorrhage, retinal detachment, and intracranial hemorrhage with undetectable levels of protein C activity. We report a clinical case of homozygous protein-C deficiency with severe purpura fulminans and bilateral leukocoria.

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From the Department of Ophthalmology, Strabismus and Pediatric Ophthalmology Service, Riyadh Armed Forces Hospital, Riyadh, Kingdom of Saudi Arabia

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Address correspondence and reprint request to: Dr. Nourah D. Al-Dohayan, Department of Ophthalmology, Strabismus and Pediatric Ophthalmology Service, Riyadh Armed Forces Hospital, Riyadh, Kingdom of Saudi Arabia. Tel. +966 (1) 4777714 Ext. 23878 / 25702. Fax. +966 (1) 4760853. E-mail: naldohayan@hotmail.com

Protein C is a 62-kD glycoprotein, which is synthesized in the liver as a vitamin K dependent zymogen.¹⁻¹⁵ Its normal blood concentration is 4 mcg/ml.¹ Protein C is a plasma inhibitor protein that once activated, will inhibit clot formation and enhance fibrinolysis by elevating plasminogen activator levels. Protein C plays profibrinolytic, anti-inflammatory, and anti-ischaemic roles.¹ Protein C deficiency is a rare autosomal recessive condition, first described in 1981. The incidence of symptomatic protein C deficiency is 1 in 16,000 to 1 in 32,000 while that of severe protein C deficiency is approximately 1 in 500,000 to 1 in 750,000 live births.¹⁻³ The condition is inherited

in homozygous and heterozygous forms. The homozygotes have very low or undetectable protein C activity (usually less than 1%, normal level 70-140%).¹⁻³ The homozygous state is usually not compatible with long-term survival, death results from life threatening neonatal purpura fulminans or massive venous thrombosis.¹⁻¹⁵ Compound heterozygotes have approximately 50% levels of protein C and usually remain asymptomatic until adolescent or adult life thereafter they may develop manifestations of deep venous thrombosis.¹⁻⁸ In this report, we present a rare case of bilateral leukocoria in a neonate associated with other systemic manifestations, early diagnosis and treatment could be life saving.

Case Report. A one-day-old male baby, admitted to the Neonatal Intensive Care Unit was referred for ophthalmic assessment due to bilateral leukocoria and irregular pupils. He was a product of a full term uneventful pregnancy. Birth weight was 2.650 kg. He was the first born to a healthy consanguineous married couple. Upon delivery, he was found to have multiple hemorrhagic skin bullae on the left cheek, right arm, scalp, lumbar and genital area, which burst upon delivery, and turned blackish in color the next day (**Figure 1**). He did not show any dysmorphic features, and the rest of the systemic examination was normal. Ophthalmic examination showed that he had bilateral leukocoria with vitreous hemorrhage (**Figure 2**). Intraocular tension by Schiottz tonometer was 14.6 mm Hg in the right, and 8.5 mm Hg in the left eye. Axial lengths were 15.43 mm in the right and 16.4 mm in the left eye. Slit lamp biomicroscopy showed bilateral posterior embryotoxon, bilateral ectropion uveae, and right iris stromal atrophy with poor pupillary dilatation with posterior synechiae. The lenses were clear. Fundus examination revealed bilateral organized vitreous hemorrhage, no retinal details were seen. A B-scan showed bilateral dense vitreous hemorrhage with funnel shaped retinal detachment. A CT scan on the 2 day of life showed bilateral vitreous hemorrhage and bilateral retinal detachment. An MRI showed bilateral retinal detachment (**Figure 3**) with extensive hemorrhages in the frontal, parietal, and occipital regions. His protein C activity level was only 0.05% while both parents showed low levels of protein C, father 66% and mother 69%. His renal and liver profiles were normal.

He was diagnosed with severe homozygous protein C deficiency. He was started on fresh frozen plasma (FFP) 15 ml/kg body weight 6 hourly for 2 months until all the lesions healed with large scars. His FFP was gradually tapered to once daily and the patient was discharged on warfarin. Protein C concentrate, which is the treatment

of choice, was not available at the time. He was considered inoperable for visual rehabilitation, however at age of 9 months, he was sent to Germany for further treatment of his general condition where he underwent unsuccessful attempt for retinal detachment repair. Ventriculo peritoneal shunt placement was carried out

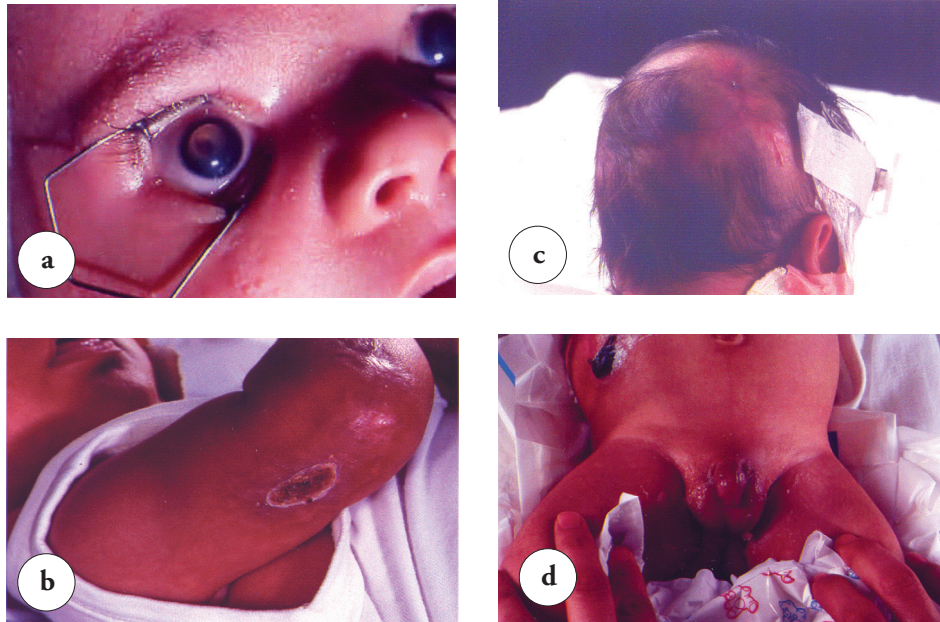


Figure 1 - a) right eye leukocoria. Hemorrhagic skin bullae of the b) arm, c) scalp, d) genital area.



Figure 2 - Bilateral leukocoria.



Figure 3 - Magnetic resonance imaging result. The 2 arrows showed bilateral retinal detachment.

under protein C concentrate coverage. He is now 5 years old with sequelae of protein C related complications of bilateral blindness, seizures, developmental delay and hydrocephalus. He is being maintained on warfarin to keep the International Normalized Ratio (INR) between 2.5-4, FFP or Protein C is given whenever he develops any new lesion. He has 2 female siblings who are heterozygote and asymptomatic like their parents.

Discussion. Protein C is a rare genetic disorder; its major sites of involvement are skin, eyes, central nervous system, and kidneys. Ocular manifestation of homozygous protein C deficiency includes vitreous hemorrhage, retinal and sub-retinal hemorrhages, venous and arterial occlusion, microphthalmos, and leukocoria secondary to retinal detachment or persistent hyperplastic primary vitreous.¹⁰ Systemic manifestation includes thrombosis of cavernous sinus and other cranial vessels, renal and deep vein thrombosis with pulmonary embolism, and thrombotic hemorrhagic gastrointestinal and genitourinary mucosal infarct. These lesions usually cause death if not treated.¹ The clinical signs of protein C deficiency may manifest within 2 hours to 2 weeks after birth.^{2,3,10} On the first day of life our patient showed purpura fulminans, intracranial hemorrhage, and bilateral leukocoria secondary to dense organized vitreous hemorrhage with funnel shaped retinal detachment, most likely indicating intrauterine occurrence. Ergenekon et al¹⁰ also described a 2-day old neonate with unilateral leukocoria and purpura fulminans stressing the fact that the infant suffered from protein C deficiency in utero and leukocoria could be the first manifestation of homozygous protein C deficiency. Our patient has bilateral leukocoria as first manifestation in day one, which supports Ergenekon's findings. Churchill et al,³ described a spectrum of protein C deficiency within one family, the heterozygote parents had no thromboembolic episodes though the mother had several miscarriages and had one neonatal death from severe purpura fulminans with undetectable protein C levels. Ocular manifestations were bilateral central retinal vein occlusion, vitreous hemorrhages, and a right central retinal artery occlusion. The youngest child was prenatally diagnosed as homozygous protein C deficient. Ocular examination showed right leukocoria with underlying total retinal detachment and left macular hemorrhage. Churchill et al³ thus challenges the hypothesis by Hattenbach et al,² that a thrombotic event occurs only postnatally.

Vitreous hemorrhage has been attributed to retinal vein occlusion, as it appears to be the most likely cause. Though both retinal artery and retinal vein occlusion have been reported in patients with heterozygous protein C deficiency. It is not clear whether ophthalmic and skin

lesions of protein C deficiency develop simultaneously, or retinal vessels occlusion are a result of intrauterine hypercoagulability.⁴ Cassels-Brown et al,⁴ reported bilateral retinal hemorrhages with swollen hemorrhagic optic discs resulting from retinal vein occlusion, while noting a retinal artery occlusion in the second eye. Hattenbach et al,² also reported similar clinical findings in a full term neonate unilaterally.

The definite diagnosis of homozygous protein C is difficult in neonates as protein C levels rise slowly over the first year of life, and may not reach the normal adult levels until beyond the age of one year, but characteristic patchy necrotic lesions of neonatal purpura fulminans or disseminated intravascular coagulation (DIC) are typical of homozygous protein C deficiency and should alert the clinician to the diagnosis. Also, testing the parent's levels of protein C levels will aid in the diagnosis.¹²

The DNA sequence and the chromosomal location of Protein C is 2q13-q14. Abu-Amero et al,¹⁴ performed the molecular analysis on our patient and his parents. Genomic DNA was extracted from peripheral blood; exons of protein C were amplified by polymerase chain reaction and sequenced. Sequencing revealed the presence of a novel CCTG duplicate nucleotide (effective insertion) after nucleotide 8826 in exon 9 of the protein C gene. This insertion is found in the homozygous state in patient and in the heterozygous state in both parents. It results in a frame-shift mutation, which introduces a stop-codon, thereby generating a prematurely truncated protein. These molecular findings agree with the presence of extremely low levels of protein C activity in our patient (homozygous state) and both his parents (heterozygous state), thereby indicating that this effective insertion was inherited as an autosomal recessive trait.

Treatment of protein C deficiency related thrombosis, in homozygous and compound heterozygous must be rigorously treated. The initial treatment is with FFP 8-12 ml/kg every 12 hours until all lesions are healed.^{4,8,12} For long term treatment of this condition, protein C concentrate could be administered either intravenously or subcutaneously on a weekly basis or more frequently.^{5,12} A vitamin K antagonist (warfarin) could be given to keep the plasma thromboplastin in the range of 1.5-2 times of the control values or the INR should be between 2.5 and 4.4.^{1,8} Liver transplantation may be considered in life threatening disease; it has been attempted in one case with success,⁸ though the long-term complications are not known. Currently, in utero treatment is not possible in suspected cases as maternal supplements do not cross the placenta and the biological half life of protein C is short (<8 hours) so direct fetal replacement is not practical.³

Other possible causes of vitreous hemorrhage may be observed in cases of birth trauma, retinopathy of prematurity, persistent hyperplastic primary vitreous, retinoblastoma (may be a presenting sign), galactosemia, retinal dysplasia, optic disc hamartomas, drugs (for example, aspirin, anticoagulants), hypercapnia, and coagulation defects.¹³

In conclusion, leukocoria in a neonate, when associated with other signs of reduced clotting ability, should alert the clinician to test for Protein C deficiency. Although the syndrome is rare, the timely identification of such patients may be life saving and may permit the clinician the opportunity to initiate timely therapeutic intervention. Ophthalmologists should be aware of this treatable cause of hemorrhagic and thrombotic ophthalmic lesions, particularly in areas of high consanguinity.

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