Persistent Fetal Vasculature and Severe Protein C Deficiency

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Key Words

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Abstract

Persistent fetal vasculature (PFV) is most often a condition of unknown cause. It represents persisting elements of fetal ocular vessels including the hyaloid arterial network. Protein C is a vitamin K-dependent serine protease, which regulates coagulation. Deficiency of protein C leads to a prothrombotic state. We report the case of a male infant born at 34 weeks gestation to non-consanguineous parents. Ophthalmic examination found bilateral PFV, microphthalmia and vitreoretinal dysplasia. He also suffered bilateral renal vein thrombosis and purpura fulminans and was diagnosed with severe protein C deficiency. Genetic analysis of the *PROC* gene revealed two separate pathogenic mutations, confirming compound heterozygote status. Both parents were found to be heterozygous. While ocular manifestations (commonly haemorrhages) are often seen in protein C-deficient patients, a search of the literature reveals very few recorded cases of PFV in severe protein C deficiency. We hypothesise that protein C deficiency was the cause of PFV in

this patient. Intraocular thrombotic events in utero could affect the normal development of ocular vessels and lead to persistent elements of fetal vasculature in the eye. Consideration should be given to the possibility of protein C deficiency in patients presenting with PFV, particularly if bilateral.

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The term persistent fetal vasculature (PFV) is used to describe a range of congenital abnormalities of the eye. This includes, anteriorly, a retrolental plaque with a clear lens, a shallow anterior chamber and elongated ciliary processes. The front part of the posterior segment of the eye can also be involved with contraction of the plaque and traction on the vitreous base and retina. In the posterior segment, fibrous tissue from the hyaloid system may fail to regress resulting in posterior peripapillary traction on the retina and detachment, although these changes are usually unilateral (90%). This appearance can mimic retinoblastoma, retinopathy of prematurity, retinal dysplasia, posterior uveitis and even congenital cataracts. This posterior form of PFV (previously known as persistent hyperplastic primary vitreous, PHPV) may present with leukocoria [Traboulsi, 1993]. Ultrasound and CT scan of the eye looking for calcium deposition can help distinguish between PFV and retinoblastoma.

Table 1. Details of cases reported in the literature of severe protein C deficiency and ocular findings suggestive of PFV; the current case is listed for comparison

Report	Ocular features
Hermesen et al. [1990]	Bilateral PHPV with microphthalmos, vascularised lens with funnel-shaped retrolental masses, non-existent anterior chambers, normal retina and optic nerve
Estelles et al. [1984]	Bilateral vitreous haemorrhages and intravitreal fibrin masses
Pulido et al. [1987]	Bilateral vitreal haemorrhages, prominent iris vessels, shallow anterior chamber, synechiae, cataract, retrolental membrane and funnel-shaped retinal detachment in both eyes
Park et al. [2005]	Bilateral corneal opacity, microphthalmia, posterior synechiae, pupillary membrane, shallow anterior chamber, vitreoretinopathy suggesting PHPV, intravitreal masses, funnel-shaped retinal detachment with bilateral retinal dysplasia
Auletta and Headington [1988]	Bilateral leukocoria, raised intraocular pressure, flattened anterior chambers, iris atrophy, lens adhesions, bilateral retinal detachment
Paysse et al. [2002]	Bilateral retinal detachment, flat anterior chamber, fibrotic hyaloid arteries
Soria et al. [1994]	Microphthalmia, irregular globe, persistence of primary vitreous
Rappaport et al. [1987]	Hyperplastic vitreous bilaterally
Marciniak et al. [1985]	Microphthalmia, anteriorly displaced spherical lens, fibrovascular stalk extending from lens to optic nerve
Cassels-Brown et al. [1994]	Right retinal artery occlusion, bilateral retinal haemorrhage, retinal venous occlusions, posterior embryotoxon, shallow anterior chambers, ectropion uveae, posterior synechiae, vitreous haemorrhages, strabismus, retrolental opacities, right open funnel retinal detachment
Hattenbach et al. [1999], case 1	Strabismus, left retrolental opacities, funnel retinal detachment and microphthalmos, shallow anterior chamber, vitreous haemorrhage
Hattenbach et al. [1999], case 2	Right vitreous haemorrhage, shallow anterior chamber, posterior synechiae, funnel retinal detachment, microphthalmos
Current case	Bilateral microphthalmia and PFV, vitreoretinal dysplasia

In vitreoretinal dysplasia, where the retina and vitreous are maldeveloped, PFV can be an isolated abnormality [Fulton, 1978]. However, it may be associated with systemic problems such as Norrie's disease [Warburg, 1963], incontinentia pigmenti [Francois, 1984] and Warburg syndrome [Warburg, 1971]. It also occurs in trisomy 13, trisomy 18 and triploidy.

Protein C is a vitamin K-dependent serine protease enzyme, synthesised in the liver. It circulates in the blood as an inactive protein, and is activated by thrombin when it is bound to thrombomodulin. It functions in conjunction with its cofactor, protein S. The normal function of activated protein C is to inactivate coagulation factors Va and VIIIa. Thus, deficiency of the protein leads to a proco-

agulant state [Handin, 1994]. The gene encoding protein C (*PROC*) is located on chromosome 2 at position 2q13–q14 and to date nearly 200 pathogenic mutations have been found [D'Ursi et al., 2007]. Patients with heterozygous mutations have a reduced level of protein C and are at increased risk of thromboembolic events. However, many such patients may never exhibit any clinical manifestations of the disorder [Bovill et al. 1989]. Conversely, homozygous or compound heterozygous patients often suffer severe, life-threatening complications from birth. The most common presentation is purpura fulminans, a rapidly progressing haemorrhagic necrosis of the skin, which can occur within the first few hours of birth. Cerebral and/or ophthalmic damage can occur in utero and

children are often born with visual impairment [Marlar et al., 1989; Monagle et al., 2008]. In addition, patients may suffer venous thromboembolism. Severe homozygous deficiency is rare with an incidence estimated between 1 in 160,000 to 1 in 360,000 [De Stefano et al., 1996].

A small number of cases of homozygous or compound heterozygous protein C deficiency have previously been reported in association with findings suggestive of PFV. Four reports mention PFV in particular (see table 1). Here we report another case of bilateral PFV with severe protein C deficiency, drawing attention to this association.

Case Report

A male infant was born prematurely at 34 weeks' gestation by Caesarian section owing to a sudden deterioration in maternal health from Crohn's disease with development of an abdominal abscess. He had a birth weight of 2,300 g (50th–75th centile). He is the only child of non-consanguineous parents, who were healthy except for maternal Crohn's disease. He was pale and floppy at birth and required intubation and ventilation but was weaned onto continuous positive airway pressure and then managed on air by 24 hours of age. However, he subsequently became hypertensive and anuric and developed frank haematuria 72 hours postnatally. His renal failure was found to be secondary to bilateral renal vein thrombosis and he required dialysis for two months. Within the first two days of life he was noted to have left-sided leukocoria. Ophthalmic examination at 4 months of age showed bilateral microphthalmia and appearances consistent with bilateral PFV. The retina was obscured on the left but on the right there was also evidence of retinal dysplasia, confirming a congenital aetiology. This was confirmed on examination under anaesthetic at 8 months of age, by which time there was absence of the red reflex in both eyes and evidence of bilateral vitreoretinal dysplasia. Severe bilateral retinal dysfunction was found on electrodiagnostic studies, which showed that flash occipital visual evoked potentials were severely degraded.

He was noted to have unusual bruising at 1 month of age, when he developed a large necrotic area over his right thigh, which resolved. His development at 7.5 months of age was assessed to be within normal parameters given his visual impairment. However, at the age of 8 months he presented with purpura fulminans particularly affecting his left arm and groin where there were large confluent areas of purpura (fig. 1). On examination at 10 months

Fig. 1. Purpura fulminans of the left arm.

he had poor growth, a length of 64.2 cm (0.4th centile), weight of 7.56 kg (2nd centile) and a head circumference of 41.1 cm (<0.4th centile). He had poor vision with roving eye movements.

Investigations found protein C levels to be below the limit of detection. He had a normal male karyotype (46, XY). Genetic testing for Norrie's disease was negative. Sequencing of the *PROC* gene showed compound heterozygous mutations with a C>T substitution at nucleotide c.1019 (p.Thr340Met) and a G>A substitution at c.1201 (p.Asp401Asn). Both mutations are located in exon 9 and both have been previously reported as being pathogenic. The c.1019C>T variant results in a type I protein C deficiency, with a concordant reduction in protein C antigen and activity, while the c.1201G>A mutation is associated with type II deficiency, where normal amounts of dysfunctional protein are produced. Both parents have been found to have decreased levels of protein C (mother 46 U/dl, father 61 U/dl, normal range 75–125 U/dl), consistent with heterozygous deficiency, and each has been found to carry one of these mutations.

Discussion

This report of bilateral PFV and severe protein C deficiency provides further evidence that there may be a causal relationship between these two conditions and highlights the possibility that this developmental eye abnormality could be secondary to abnormal coagulation in the fetus. Coagulation proteins are not thought to cross the placenta from mother to fetus [Bleyer et al., 1971]. This is further evidenced by reports of antenatal findings described in fetuses subsequently found to have severe protein C deficiency [Kirkinen et al., 2000].

A review of the literature identified some 12 cases where severe protein C deficiency was associated with ophthalmic signs compatible with a diagnosis of PFV. The spectrum is quite varied but is very dependent on variation in descriptions and the detail provided (see table 1). Occasional patients with retinal and vitreal dysplasia have been reported with severe autosomal recessive protein S deficiency. Two patients with severe compound heterozygous protein S deficiency were reported by Mintz-Hittner et al. [1999]. The female infant was diagnosed with bilateral PHPV and her male sibling presented with persistent hyaloid arteries and extraretinal fibrovascular proliferation with retinal folds.

PFV is in most cases thought of as an idiopathic disorder and the cause is unknown. Goldberg [1997] has suggested that intraocular ischaemia in utero could lead to the compensatory upregulation of angiogenic stimuli and hence persistence of fetal vascular structures. Occasionally PFV has been reported as an isolated finding in a small number of families [Waardenburg, 1961; Wang and Phillips, 1973; Lin et al., 1990]. The inheritance pattern has not been consistent and a genetic cause, although postulated, has not been identified. However, in these reports, fetal coagulation disorders have not been considered or investigated.

Given that PFV can occasionally be diagnosed in patients as part of a more complex developmental disorder, we suggest that it would be prudent to consider a defect of coagulation, specifically deficiency of protein C or S,

in the differential diagnosis of such patients. We hypothesise that the developing fetus in our report had a prothrombotic tendency in utero and that this may have been responsible for his bilateral congenital eye findings. It is reasonable to assume that thrombosis of the fetal hyaloid arterial system at a crucial developmental stage may underlie the developmental eye pathology. However, the role of protein C is not solely confined to coagulation but includes an additional cytoprotective pathway mediated by a separate mechanism [Mosnier et al., 2007]. This pathway has a number of effects including alteration of gene expression profiles, anti-inflammatory and anti-apoptotic activity and maintenance of the endothelial barrier. It is possible that disruption of this pathway may play a role in the pathogenesis of PFV in our case. Further evidence will be required to help elucidate the relative contributions of each pathway to this pathology. Notwithstanding this, however, we conclude that PFV may be a presentation of protein C deficiency, particularly if it is bilateral, and this should be considered in the differential diagnosis.

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