British Journal of Ophthalmology 1994; 78: 486–487

Ophthalmic manifestations of neonatal protein C deficiency

A Cassels-Brown, A M B Minford, S L Chatfield, J A Bradbury

Protein C is a vitamin K dependent plasma zymogen which acts by regulating coagulation by its specific inactivation of factors V and VII, and facilitates fibrinolysis by elevating circulating plasminogen activator levels. Protein C deficiency is a rare condition which predisposes to episodes of potentially blinding and lethal thromboembolism. In the newborn period, congenital protein C deficiency occurs as an autosomal recessively inherited condition; homozygotes have very low or undetectable protein C activity (usually less than 1%, normal 70–140%)[1] and present within the first few days of life. Heterozygotes have levels of around 50% and usually remain asymptomatic until adolescence or adult life. Neonatal protein C deficiency may also be acquired and transient, occurring particularly in ill preterm babies[2] with the resultant thromboses being as profound as in the homozygous state.

We present two cases of neonatal protein C deficiency, one with the classic homozygous state and the other a premature neonate with a probable acquired state. Both cases developed the typical systemic manifestation of purpura fulminans (necrotic skin lesions).

Case 1

A healthy Asian female, born at 39 weeks' gestation, presented on her sixth day of life with an area of purpura fulminans on her left calf (Fig 1). A very low protein C activity (less than 12%) and family history led to the diagnosis of homozygous protein C deficiency. She was initially treated with heparin anticoagulation for less than 24 hours and was then commenced on intravenous protein C therapy (Immuno AG).

On day 11 ophthalmic review confirmed non-reactive pupils and that she did not respond to bright light with either eye. She had a small left sided subconjunctival haemorrhage, a right sided retinal arterial occlusion and bilateral florid retinal haemorrhages with swollen haemorrhagic optic discs secondary to retinal venous occlusions.

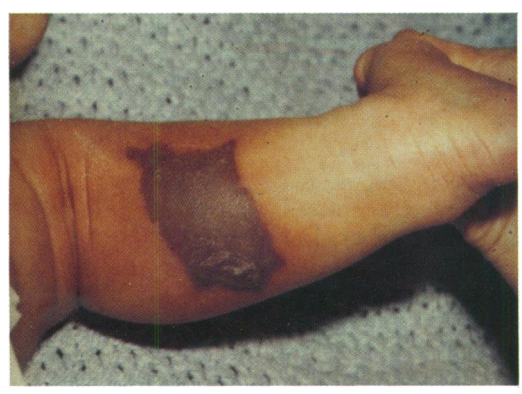

Figure 1 Case 1. Area of purpura fulminans on the back of left calf.

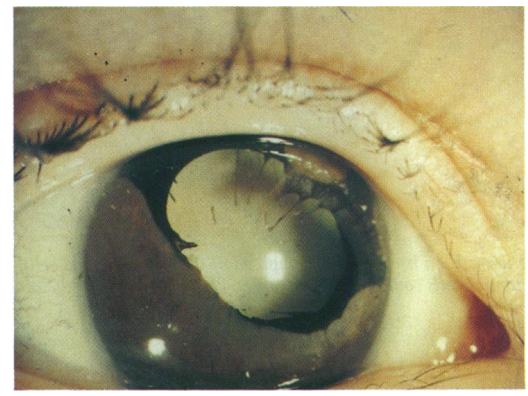

Figure 2 Case 1. Right eye with distorted pupil, ectropion uveae, posterior synechiae, posterior embryotoxon, leucocoria but clear cornea and lens.

At 12 weeks of age she had quiet white eyes with clear corneas and lenses but had bilateral posterior embryotoxon, shallow anterior chambers, ectropion uveae, and posterior synechiae (Fig 2). She also had bilateral leucocoria as a result of vitreous haemorrhages confirmed by B scan ultrasonography. By 20 weeks of age she had roving eye movements and convergent strabismus. Ultrasonography revealed bilateral dense retrolental opacities, right sided open funnel retinal detachment, the left retina appeared fully attached. Electroretinogram and visually evoked responses were absent. Around that time her right eye became injected and uncomfortable with lacrimation and lid oedema, fortunately controlled by continued topical steroid.

The child is otherwise developing normally with twice daily protein C injections via a central cannula. Her parents, who are first cousins, are both healthy but have reduced levels of protein C activity (50%). Her mother has had two previous miscarriages, one normal child and one which had undetectable protein C levels died at the age of 4 weeks from severe purpura fulminans and cerebral involvement.

Case 2

A 25 week gestation, 750 g Asian female baby was in poor condition at birth (Apgar score of 1 at 1 minute) and required intensive resuscitation and support. She had a patent ductus arteriosus, and was very bruised. After some recovery she developed transient ischaemia in her toes related to an umbilical arterial catheter. Subsequent peripheral arterial catheters had to be removed because of persistent distal cyanosis which recovered spontaneously within 48 hours. At 3 weeks of age she required reventilation after developing

Department of Ophthalmology, Bradford Royal Infirmary, Bradford, West Yorkshire
A Cassels-Brown
J A Bradbury

Department of Paediatrics, St Luke's Hospital, Bradford, West Yorkshire
A M B Minford

Special Care Baby Unit, Bradford Royal Infirmary, West Yorkshire
S L Chatfield

Correspondence to:
Mr J A Bradbury.

Accepted for publication
10 January 1994

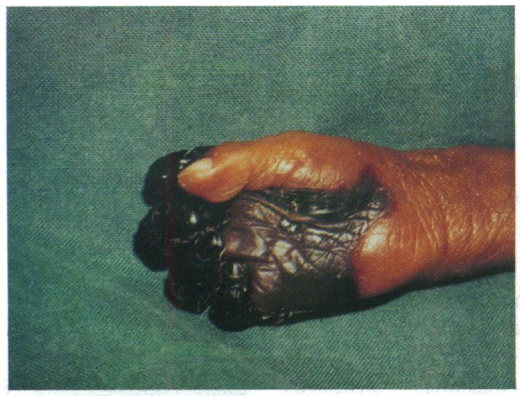

Figure 3 Case 2. Extensive infarction of right hand distal to infusion site.

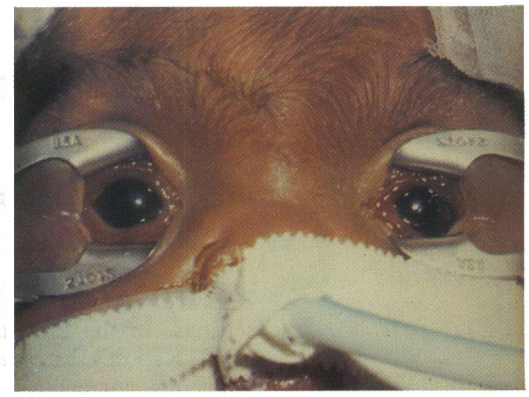

Figure 4 Case 2. Bilateral periorbital oedema and haemorrhagic chemosis.

suspected septicaemia and necrotising enterocolitis. Repeat cranial ultrasound showed fresh subependymal and ventricular haemorrhage bilaterally. Following surgical ligation of her patent ductus arteriosus she was noted to have extensive infarction of her right hand (Fig 3) related to an infusion site, and areas of purpura fulminans on her her left arm and right leg. Her protein C activity was found to be extremely low (less than 1%), and she was commenced on therapeutic doses of manufactured protein C (Immuno AG).

Ophthalmic examination was requested because the child developed marked periorbital oedema and haemorrhagic conjunctival chemosis (Fig 4). Examination also revealed hazy media, minor bilateral vitreous haemorrhages, and minor right sided retinal haemorrhage. Repeat cranial ultrasound suggested some subarachnoid haemorrhage and with worsening lung function she died at 23 days of age. The child's parents were first cousins but both had normal protein C activity with no known family history of thrombotic tendency.

Comment

As well as the ophthalmic manifestations, homozygous protein C deficiency can lead to thrombosis of the cavernous sinus and other cranial vessels, renal and deep vein thrombosis with pulmonary embolism, and thrombotic haemorrhagic gastrointestinal and genitourinary mucosal infarcts. These lesions usually cause death if not treated.

In the ophthalmic literature there are two reports of ocular involvement in homozygous protein C deficiency, both were in full term neonates.[3,4] The clinical and echographic details of case 1 very closely resemble previous reports. Hermsen *et al*[4] undertook pars plana vitrectomy and lensectomy on one eye to reveal a normal fundus. They believed the findings substantiated a diagnosis of persistent hyperplastic primary vitreous. We were, however, able to visualise the fundi of both cases presented in this paper and neither showed any evidence of persistent hyperplastic primary vitreous.

Neonates can have life threatening thromboses resulting from severe protein C deficiency but as an acquired and transient condition.[2] Case 2 is the first report of ophthalmic involvement in both a premature neonate and in what we believe to be an acquired state. Premature delivery and respiratory distress syndrome are known to activate coagulation and consumption of clotting factors. Protein C levels rise slowly over the first year of life and may not reach the normal adult range until after 1 year.[5] This acquired form of deficiency has also been reported in older paediatric cases and adults with anticoagulant therapy, liver disease, disseminated intravascular coagulopathy, and in patients postoperatively.

Individuals heterozygous for protein C deficiency have concentrations of around 50% of normal,[1] tend to have a family history of thromboses, and can present with thromboses as early as adolescence. Heterozygotes can develop retinal vascular occlusions much later in life.[6] Both parents of case 2 had normal levels of protein C activity and no known family history of thromboembolism. We are not, however, able to fully exclude the possibility that case 2 was a heterozygote presenting unusually early.

Therapy for protein C deficiency related thromboses has included fresh frozen plasma, prothrombin complex concentrate, anticoagulation, and hepatic transplantation. A manufactured purified protein C replacement preparation (Immuno AG, Industriestrasse 67, A-1220, Vienna, Austria) is currently being evaluated by a clinical trial on a named doctor/patient basis. With increasing survival and screening of premature babies ophthalmologists should be aware of this treatable cause of haemorrhagic and thrombotic ophthalmic lesions, particularly in areas of high consanguinity.

We thank Dr E Johnson, Bradford Royal Infirmary, for haematological assistance and the medical photographers at St Luke's Hospital, Bradford and the General Infirmary at Leeds.

1 Marlar RA, Montgomery RR, Broekmans AW. Diagnosis and treatment of homozygous protein C deficiency. *J Paediatr* 1989; **114**: 528–34.
2 Manco-Johnson MJ, Marlar RA, Jacobson LJ, Hays T, Warady BA. Severe protein C deficiency in newborn infants. *J Pediatr* 1988; **113**: 359–63.
3 Pulido JS, Lingua RM, Cristol S, Byrne SF. Protein C deficiency associated with vitreous haemorrhage in a neonate. *Am J Ophthalmol* 1987; **104**: 546–7.
4 Hermsen VM, Conahan JB, Koops BL, Cunningham RD. Persistent hyperplastic primary vitreous associated with protein C deficiency. *Am J Ophthalmol* 1990; **109**: 608–9.
5 Nardi M, Karparkin M. Prothrombin and protein C in early childhood: normal adult levels are not achieved until the fourth year of life. *J Pediatr* 1986; **109**: 843–5.
6 Nelson ME, Talbot JF, Preston FE. Recurrent multiple-branch retinal arteriolar occlusions in a patient with protein C deficiency. *Graefes Arch Clin Exp Ophthalmol* 1989; **227**: 443–7.