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Surgical treatment of traction retinal detachment associated with compound heterozygous congenital protein C deficiency

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ABSTRACT

Purpose: Congenital protein C deficiency leads to a prothrombotic state that may result in potentially sight- and life-threatening thromboembolic attacks. In this report, we report two cases of infants with compound heterozygous protein C deficiency who underwent lensectomies and vitrectomies for the treatment of traction retinal detachments (TRDs).

Observations: One two-month-old and one three-month-old female neonates with leukocoria and purpura fulminans received a diagnosis of protein C deficiency and were referred to ophthalmology. In both cases, the right eye had a total retinal detachment that was considered inoperable, while the left eye had a partial TRD for which surgery was performed. Of the two operated eyes, one resulted in a total retinal detachment, while the other eye has remained stable with no retinal detachment progression three months after surgery.

Conclusions: Compound heterozygous congenital protein C deficiency may lead to the rapid development of severe TRDs with poor visual and anatomical prognoses. Early diagnosis and surgery for the treatment of partial TRDs with low disease activity may help prevent progression towards total retinal detachments in these infants.

1. Introduction

Protein C is a vitamin K-dependent serine protease and anticoagulant enzyme which plays a major role in blood coagulation through regulation of factors VIIIa and Va.[1] Congenital protein C deficiency is a rare disorder that is caused by autosomal mutations in the protein C (*PROC*) gene, resulting in blood hypercoagulability which can lead to potentially sight-threatening and fatal thromboembolic attacks.

Plasma levels of protein C activity correlate with the time to onset of thromboembolic events. The homozygotes or compound heterozygotes for *PROC* gene variants show less than 10% of plasma protein C activity and present with thromboembolism soon after birth. On the other hand, heterozygotes are difficult to diagnose in childhood due to increases in plasma protein C activity with age.[2]

Systemic risks in affected patients include purpura fulminans, deep vein thrombosis, pulmonary embolism, renal thrombosis, and central nervous system thrombosis.[2,3] Ophthalmic associations with protein C deficiency include cataracts,[4–6] corneal opacities,[6–8] shallow anterior chambers,[4,6,9–12] lens adhesions,[5,9] iris atrophy,[9] microphthalmia,[7] Peter's anomaly,[8,13] persistent fetal vasculature (PFV),[3,7,14,15] vitreous hemorrhage,[4,6,11,16–19] retinal artery occlusions,[17,18,20] retinal vein occlusions,[17,18,20] ischemic optic neuropathy,[21] macular hemorrhage[22]

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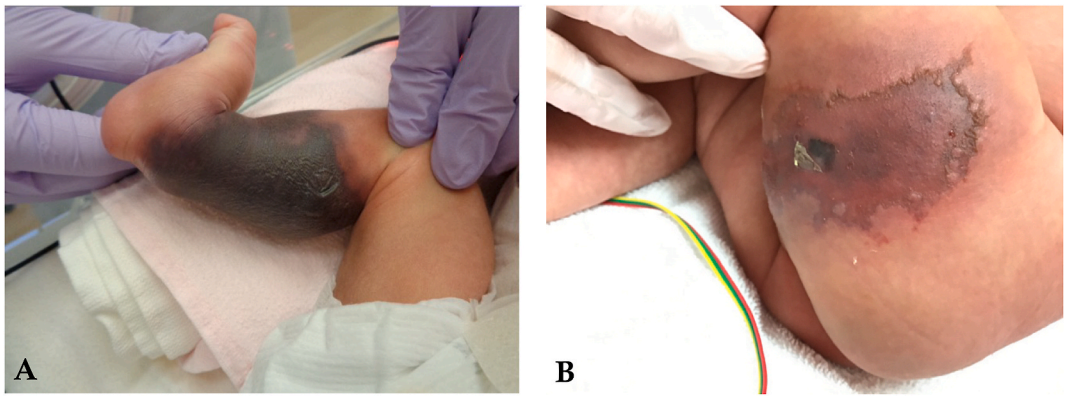

Fig. 1. Skin necrosis with central bullae and peripheral erythema due to purpura fulminans. (A) Case 1; right leg photographed on the first day of life. (B) Case 2; left leg photographed on the third day of life.

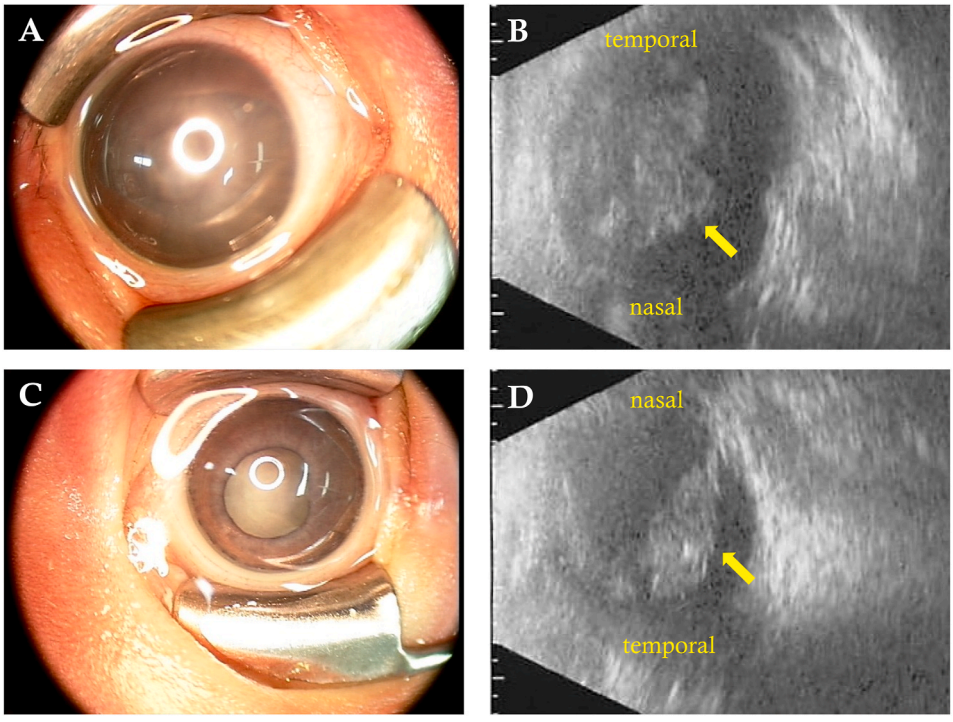

Fig. 2. Case 1: pre-operative findings. The right eye had a significant corneal opacity and a flat anterior chamber with iris adhesions to the cornea (A). B-scan ultrasonography revealed a total retinal detachment (arrow) (B). The left eye presented with rubeosis iridis (C), a fibrovascular stalk, and a total retinal detachment (arrow) (D).

and retinal detachments.[4–7,11,12,17,18,23] While the pathophysiology underlying retinal detachments has not been fully elucidated, previous studies suggest that ischemia may underlie this condition.[1,5]

Here we report two cases of infants with compound heterozygous protein C deficiency who underwent lensectomies and vitrectomies for the treatment of traction retinal detachments (TRDs).

2. Case report

2.1. Case 1

A Japanese female neonate was born at 36 weeks' gestation (2402g, APGAR score 9/10) via natural labor to a 31-year-old mother (gravida 2 para 1). On the first day after birth, the infant presented with purpura fulminans on her right lower leg (Fig. 1A). Laboratory tests revealed 3% protein C activity (adult reference range: 64–146%), leading to a diagnosis of protein C deficiency. She was started on anti-coagulant therapy (low molecular weight heparin and warfarin) and fresh frozen plasma (FFP).

The infant underwent next-generation sequencing (NGS) that revealed two heterozygous variants in the *PROC* gene (NM_000312.4): ex9: c.1218G>A, p.M406I/ex9: c.1015G>A, p.V339M that were confirmed by Sanger sequencing. The parent was the heterozygote for each variant. The two variants were very rare in gnomAD (allele frequencies of 0.000007 [M406I] and 0.000026 [V339M]). The ex9: c.1218G>A, p.M406I variant was predicted to be likely pathogenic (PM3) and the ex9: c.1015G>A, p.V339M variant pathogenic (PS1) according to ACMG-AMP criteria.

On the second day after birth, leukocoria was detected and she was referred to the ophthalmology department. While visibility was poor, retinal folds due to PFV were suspected. One week after birth, the right eye presented with a total retinal detachment, while the left eye had a retinal fold and partial TRD nasally with the temporal retina attached. One month after birth, both eyes had rubeosis iridis and vitreous

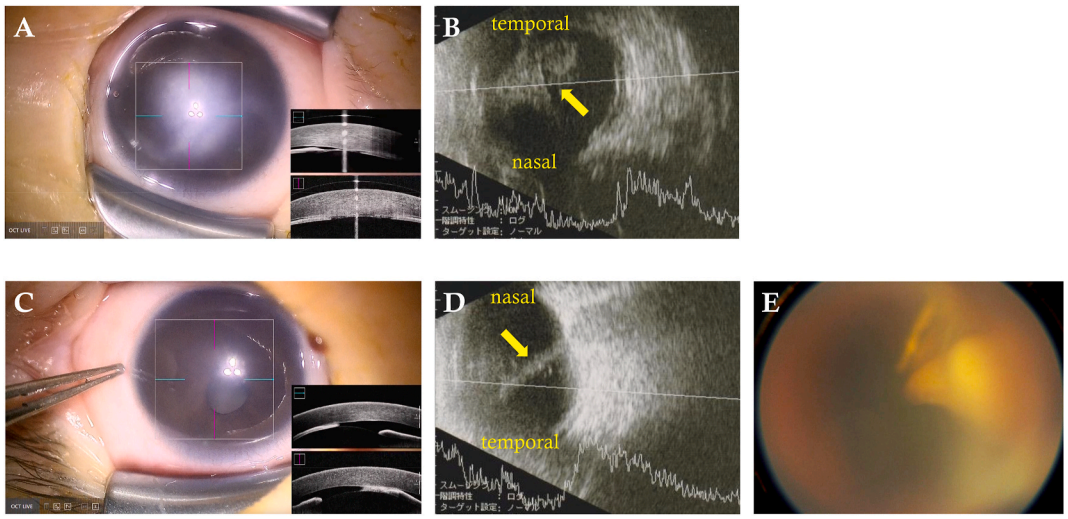

Fig. 3. Case 2: peri-operative findings. Both eyes had flat anterior chambers with iris adhesions to the cornea (A, C). The right eye had a significant corneal opacity which prevented visualization of the posterior pole (A), while the left eye had poor mydriasis due to posterior synechiae (C). On B-scan ultrasonography, the right eye had a total retinal detachment (arrow) (B) and the left eye had a fibrovascular stalk with a partial TRD superotemporally (arrow) (D). The retinal stalk and TRD were confirmed by RetCam imaging (E).

hemorrhage, indicating high disease activity. The right eye had additionally developed flattening of the anterior chamber and, given the extensive vitreoretinal membranes and the retina having been totally detached for more than one month, the eye was considered inoperable (Fig. 2A–B). The left eye had also progressed to a total detachment (Fig. 2C–D).

On day 45 after birth, the patient's general condition improved sufficiently to undergo general anesthesia, and she was operated on for treatment of the left eye using a 23-gauge system (the only available system at this hospital) and a 23-gauge infusion cannula (ME Technica, Tokyo, Japan) to enable limbal infusion. Due to poor mydriasis, iris retractors were used to aid with the surgery. Retrolenticular fibrotic membranes were then removed via bimanual surgery. Prominent neovascular vessels were present, and intraoperative hemorrhage occurred during excision of proliferative vitreoretinal membranes with scissors and a vitrector. While the hemorrhage was persistent, likely due to ischemia-induced neovascularization and the use of systemic antiplatelet and anti-coagulation therapy, retinal traction was released in all four quadrants, but a total retinal detachment remained (Fig. 4A and C). All incisions were closed with sutures and no tamponade was used.

Three months postoperatively, the retina in the left eye remained completely detached. Eight months postoperatively, phthisis bulbi was noted, along with rubeosis iridis and fibrovascular membrane formation.

2.2. Case 2

A Japanese female neonate was born at 40 weeks' gestation (2982g,

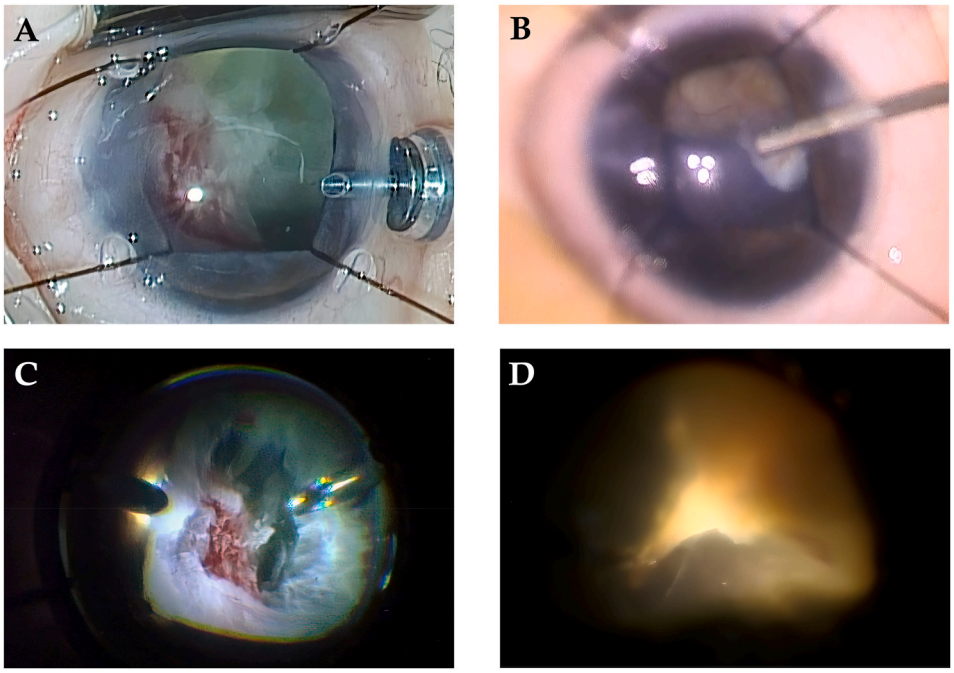

Fig. 4. Intra-operative findings. At the end of the surgery, a total retinal detachment remained in the left eye of Case 1 (A, C), while the inferior and nasal quadrants of the retina remained attached in the left eye of Case 2 (B, D).

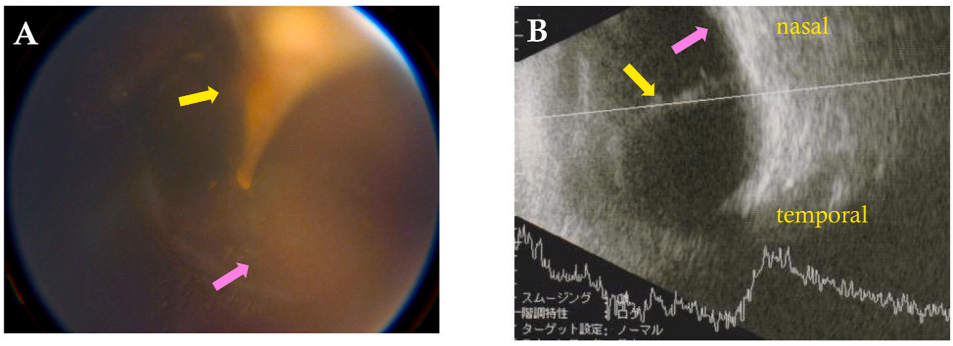

Fig. 5. Post-operative findings. 3 months after surgery, RetCam imaging (A) and B-scan ultrasonography (B) confirmed that a TRD remained superotemporally (yellow arrow) while the nasal and inferior retina remained attached (purple arrow) in the left eye of Case 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

APGAR score 8/9) via natural labor to a 31-year-old mother (gravida 3 para 1). On the third day after birth, the infant presented with purpura fulminans on her left leg (Fig. 1B). Laboratory tests revealed less than 10% protein C activity (adult reference range: 64–146%), leading to a diagnosis of protein C deficiency, and she was treated with low molecular weight heparin, warfarin, FFP, and activated protein C (APC).

An older sibling of this infant was a protein C deficient patient with neonatal purpura fulminans. Rapid Sanger sequencing of this infant identified compound heterozygous variants in the *PROC* gene (NM_000312.4): ex7: c.545C>T, p.P182L/ex9: c.1015G>A, p.V339M that were identical to those of the sibling. The parent was the heterozygote for each variant. These variants were very rare in gnomAD (allele frequencies of unknown [P182L] and 0.000026 [V339M]) and pathogenic (PS1) according to ACMG-AMP criteria.

Two months after birth, leukocoria was detected and she was referred to the ophthalmology department. As vitreous hemorrhage and suspected retinal detachments were present in both eyes, the patient was referred to Kindai University Hospital for further assessment.

Three months after birth, examination under anesthesia revealed flat anterior chambers in both eyes (Fig. 3A–C). The right eye had a significant central corneal opacity that prevented direct visualization of the posterior pole, and B-scan ultrasonography revealed a total retinal detachment (Fig. 3A–B). The left eye had a clear cornea but displayed a distorted pupil and poor mydriasis due to posterior synechia formation (Fig. 3C). Examination of the posterior pole revealed a retinal fold and a partial TRD temporally (Fig. 3D–E).

The patient subsequently underwent surgery using a 25-gauge system in both eyes. The right eye displayed a flat anterior chamber and localized areas of iris adhesion to the cornea, as confirmed by intraoperative optical coherence tomography (OCT) (Fig. 3A). Anterior chamber paracentesis and ophthalmic viscosurgical device (OVD) injection enabled separation of the iris from the cornea, after which the lens was removed using a 23-gauge limbal infusion cannula (ME Technica, Tokyo, Japan) and a vitrector. As the corneal opacity prevented visualization of the posterior pole, vitrectomy was not performed in this eye.

The left eye similarly displayed a flat anterior chamber (Fig. 3B), and the lens was removed in the same manner as with the right eye. Since removal of the posterior synechiae did not result in improved mydriasis, iris retractors were used to aid with visualization of the posterior pole. A 25-gauge vitrectomy system and limbal infusion were used to remove vitreoretinal traction. At the end of the surgery, a retinal fold and partial TRD remained superiorly and temporally, while the inferior and nasal retina remained attached (Fig. 4B and D). All incisions were closed with sutures and no tamponade was used. Three months post-operatively, while a retinal fold remained in the superotemporal quadrant, there was no apparent progression of the TRD on RetCam imaging (Fig. 5A) and B-scan ultrasonography (Fig. 5B).

3. Discussion

In the current study, both cases were compound heterozygous infants with less than 10% protein C activity, and they presented with episodes of purpura fulminans within the first three days after birth. Ophthalmic findings included leukocoria, corneal opacities, shallow anterior chambers, lens adhesions, vitreous hemorrhage, and TRDs. In addition, asymmetry in ocular pathology was noted: in both cases, the right eye had a severe total TRD that was deemed inoperable, while the left eye had a partial TRD with some limited visual potential.

While the pathophysiology underlying TRDs associated with protein C deficiency has not been fully elucidated, previous studies suggest that vascular occlusion and subsequent ischemia underlie this pathology, similar to other pediatric vitreoretinal diseases such as retinopathy of prematurity (ROP) and familial exudative vitreoretinopathy (FEVR). Fluorescein angiography performed by Ghassemi et al.[5] on an eye with an attached retina showed the presence of avascular areas and leakage, and laser photocoagulation led to the stabilization of the treated eye for 28 months.[5] In the current study, poor mydriasis, corneal opacities, and extensive retinal detachment did not allow angiography to be performed, but fading arterioles and venules were observed in the peripheral retina intraoperatively. Given the ischemia underlying this pathology, anti-VEGF therapy may be a viable option for the prevention of retinal detachment progression. In advanced stages of the disease with significant TRDs, however, surgical intervention becomes

Table 1
Genotypes of the Japanese infants with double mutations of the protein C gene.

Patient No.	Sex	Age of onset	PC Activity (%)	Mutation	Pathogenicity	Genotype	Estimated origin	References
1	F	1 d	3	**ex9: c.1218G>A, p.M406I/ex9: c.1015G>A, p.V339M**	likely pathogenic (PM3)/ pathogenic (PS1)	compound heterozygous	m/f	29-32/26-28
2	F	3 d	<10	ex7: c.545C>T, p.P182L/**ex9: c.1015G>A, p.V339M**	pathogenic (PS1)/pathogenic (PS1)	compound heterozygous	m/f	33/26-28

The bold mutations are one of five major mutations in Japanese protein C deficiency. Variants were validated using direct Sanger sequencing (NGS) at Kazusa DNA Research Institute (Chiba, Japan; no CLIA certification). d, day; m, mother; f, father; ex, exon; PC, protein C; PM, pathogenic moderate; PS, pathogenic strong.

necessary to relieve the tractional forces on the retina.

Surgical treatment of patients with pathologies associated with protein C deficiency has previously been reported. Vitrectomy has been performed for the treatment of anterior PFV[10] and lensectomy has been performed to prevent progression of secondary glaucoma.[7] To the best of our knowledge, surgery for a retinal detachment associated with protein C deficiency has previously been reported only once.[24] In this report, a Caucasian infant underwent vitrectomy for a vitreous hemorrhage and retinal detachment, but lost vision in the operated eye. In the current study, Case 1 resulted in a total retinal detachment. Case 2 has remained stable three months after surgery with no apparent exacerbation of the TRD, and the retina devoid of traction remained attached, similar to cases of FEVR[25,26] or PFV.[27]

Of note, Case 1 could not be treated with APC due to the timing of diagnosis and unavailability of this specialized treatment modality. On the other hand, Case 2 received prompt administration of APC since her older sibling had also been diagnosed with protein C deficiency; this family history allowed neonatologists to start elective observation for early treatment just after birth. This difference in treatment modality may have contributed to the higher disease activity (extensive membranes, vitreous hemorrhage, rubeosis iridis) and poorer surgical outcome in Case 1.

Additionally, the genetic background of the two infants may have influenced the outcome of the surgical interventions (Table 1). Case 1 had inherited two of the five major mutations in Japanese protein C deficiency[28]: the c.1015G>A mutation, a pathogenic variant (PS1) which has been reported to cause intracranial thrombosis and purpura fulminans,[29–31] and the c. 1218G>A mutation, a likely pathogenic variant (PM3) which has been associated with deep vein thromboses.[32–35] Case 2 inherited one of the five major mutations (c.1015G>A) and the c. 545C>T mutation, a variant which has been reported in the Human Gene Mutation Database (HGMD) and in a previous report[36] but is not one of the major mutations.

While longer-term observation is required, the current study suggests that early diagnosis of protein C deficiency and surgical intervention for the removal of vitreoretinal traction in eyes with low disease activity and partial TRDs may potentially help prevent progression towards total retinal detachments.

4. Conclusion

Neonatal ophthalmic findings such as leukocoria and retinal detachments may be the first manifestations of protein C deficiency. In compound heterozygous cases, congenital protein C deficiency may lead to the rapid development of severe TRDs with poor visual and anatomical prognoses. Early diagnosis and vitrectomy for the treatment of partial TRDs with low disease activity may help prevent progression to total retinal detachments in these infants.

Patient consent

Written consent to publish this case has been obtained. This report does not contain any personal identifying information.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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