

Vitreoretinal Findings Similar to Retinopathy of Prematurity in Infants with Compound Heterozygous Protein S Deficiency

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Objective: To present previously undescribed vitreoretinal findings similar to severe retinopathy of prematurity (ROP) in two siblings (daughter and son) with a thrombophilic disorder, compound heterozygous protein S (PS) deficiency.

Design: Family genotype study and literature review.

Participants: Two unrelated heterozygous PS-deficient parents and their two children with compound heterozygous PS deficiency were studied. The gestational age and birth weight of the daughter were 40 weeks and 3200 g, respectively, and those of the son were 34 weeks and 2150 g, respectively. Three other neonates with homozygous or compound heterozygous PS deficiency and ophthalmologic findings were identified in the literature.

Intervention: The daughter underwent lensectomy-vitreotomy at 48 weeks adjusted age bilaterally. The son underwent therapy developed for severe ROP: laser therapy of the peripheral avascular retina at 39 weeks adjusted age, and bilateral lensectomy-vitreotomy with membrane peel of intravitreal proliferation from the optic disc at 42 weeks adjusted age.

Main Outcome Measures: The main clinical outcome measures were retinal appearance and functional vision. Genotypes of the family members were determined.

Results: One of the four eyes retained functional vision. A normal-appearing posterior retina, normal scotopic and photopic flash electroretinograms, and a normal flash visual-evoked response were documented from the left eye of the son at 62 weeks adjusted age. The other three eyes had inoperable retinal detachments and no functional vision. The mother had type I PS deficiency and the father had type II PS deficiency. Compound heterozygous PS deficiency was confirmed in both children.

Conclusion: In both children, normal vasculogenesis was interrupted. At 39 weeks adjusted age, the retinal examination of the son revealed extraretinal fibrovascular proliferation at the optic disc (reactivation of the hyaloid system) and in the peripheral retina (interruption of inner retinal vascularization). Patients with homozygous or compound heterozygous PS deficiency may present as infants with severe ROP. The authors' experience suggests that appropriately timed surgical procedures, which are efficacious for ROP, can preserve vision in infants with thrombophilic disorders. *Ophthalmology* 1999;106:1525-1530

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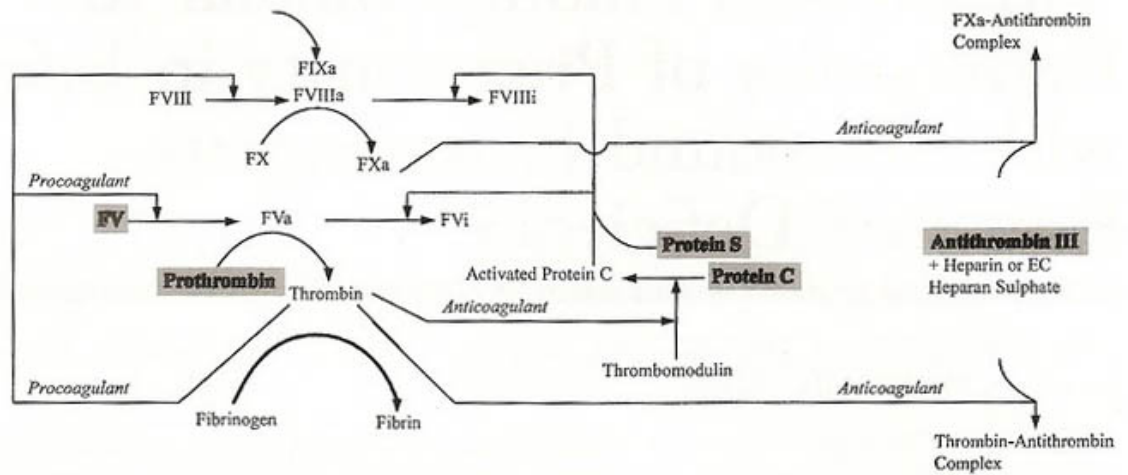
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Hereditary thrombophilic diseases include five genetic disorders of hemostasis that are established as risk factors for thrombin generation and venous thrombosis (Fig 1 and Table 1).¹⁻¹⁷ Two defects (resistance to activated protein C [APC-R] associated with the factor V Leiden [FV R506Q] mutation and increased prothrombin associated with the prothrombin [FII G20210A] mutation) are always associated with the same genetic defect, involve the procoagulant factors, and are present in 63% of families with inherited thrombophilia. Even in the homozygous state, these defects do not usually cause abnormalities in the neonatal period unless other risk factors are present: genetic (other thrombophilic disorders) or environmental (e.g., sepsis, trauma, surgery). In contrast, three defects (protein C [PC] deficiency, protein S [PS] deficiency, and antithrombin [ATIII] deficiency) are heterogeneous, involve the anticoagulant pathways, and are present in 16% of families with inherited

Figure 1. Representation of the anticoagulant pathways, which are involved in the regulation of coagulation proteinase activity, and of the procoagulant feedback pathways, which are involved in the activation of factors V and VIII. The three genetic defects involved in anticoagulant pathways (protein S deficiency, protein C deficiency, and antithrombin deficiency) and the two genetic defects involved in procoagulant pathways (activated PC resistance, FV R506Q, or factor V Leiden mutation; and FII G20210A or prothrombin mutation) are highlighted.



thrombophilia. In the homozygous state, these defects do affect neonates without any other concurrent risk factors.

Heterozygous PS deficiency is an autosomal-dominant disorder first described in 1984.¹⁸ The gene for PS is located near the centromere of chromosome 3.¹⁹ The disorder usually presents initially between the ages of 15 and 50 years and includes deep vein thromboses, pulmonary emboli, superficial phlebitis, and other venous thromboses including axillary, subclavian, mesenteric, and cerebral veins. Ophthalmologic findings reported in association with heterozygous PS deficiency include cen-

tral and branch retinal artery occlusions, Behçet syndrome, and ischemic optic neuropathy.

Homozygous and compound heterozygous PS deficiencies,¹³⁻¹⁷ although extremely rare, are associated in the very early neonatal period with purpura fulminans, disseminated intravascular coagulation, and, rarely, massive thrombosis.¹² Ophthalmologic manifestations in these severely affected patients have been variously described as retinal thromboses, retinal hemorrhages, vitreous hemorrhages, angle closure glaucoma, retinal detachments, and choroidal detachments, but all have resulted in profound visual loss,

Table 1. Hereditary Thrombotic Diseases

Genetic Disorder	FV R506Q	FII G20210A	AT III Deficiency	PC Deficiency	PS Deficiency
Pathway ¹	Procoagulant	Procoagulant	Anticoagulant	Anticoagulant	Anticoagulant
Prevalence (%)* ¹	45	18	4.3	5.7	5.7
Mutations ¹	1	1	>79	>160	>69
Chromosome ²	1q23	11p11-q12	1q23-q25	2q13-q14	3p11.1-q11.2
Ocular findings in patients with heterozygous deficiency	Central retinal vein thrombosis, and peripheral retinal neovascularization	None reported	None reported	Branch retinal artery occlusion	Central and branch retinal artery occlusion, Behçet syndrome, and ischemic optic neuropathy
Ocular findings in neonates with homozygous or compound heterozygous deficiency	None reported	None reported	None reported	Vitreous hemorrhage and retinal detachment ⁴⁻¹¹	Vitreous hemorrhage and retinal detachment ¹³⁻¹⁷
Systemic findings in neonates with homozygous or compound heterozygous deficiency	None reported	None reported	Cerebral and femoral arterial thrombosis, intracardiac, inferior vena cava, femoral, and iliac veins ³	Purpura fulminans, cerebral and renal thrombosis ¹²	Purpura fulminans, cerebral and renal thrombosis ¹²

FV R506Q = Factor V mutation; FII G20210A = prothrombin, factor II mutation; ATIII = antithrombin; PC = protein C; PS = protein S.

* Prevalence in families with inherited thrombophilia.

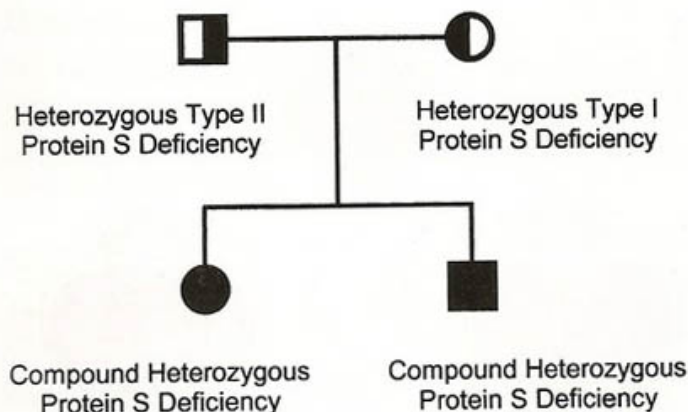


Figure 2. Pedigree of nonconsanguineous family.

usually total blindness. This article reports on a family with two compound heterozygous PS-deficient infants and is especially informative regarding the natural history and therapeutic implications of these ocular abnormalities.

Patients and Methods

Family Report

The family consisted of nonconsanguineous parents and two offspring (a daughter and a son) (Fig 2).

Case Report of Mother

The mother, a 25-year-old black woman, had no visual complaints and no history of venous thrombosis. Ophthalmologic examination revealed bilateral avascularity of the extreme peripheral retinas, but no other abnormalities were recognized.

Case Report of Father

The father, a 26-year-old black man, had no visual complaints and no history of venous thrombosis. Ophthalmologic examination revealed bilateral avascularity of the extreme peripheral retinas and temporal pallor of the optic nerves.

Case Report of Daughter

The first child, a daughter, was born at 40 weeks gestational age and weighed 3200 g. On the second day of life, she developed purpura fulminans confirmed by skin biopsy. The functional PS level was less than 1%, and the diagnosis of compound heterozygous PS deficiency was made. A magnetic resonance imaging (MRI) study of the brain on the fifth day of life revealed hemorrhages in the cerebral cortex and pituitary gland, prompting fresh frozen plasma (FFP) transfusions. The initial ophthalmologic examination at 41 weeks adjusted age revealed bilateral persistent hyperplastic primary vitreous with retinal detachments. At 48 weeks adjusted age, the right eye underwent lensectomy-vitreotomy, membrane peel, and silicone oil injection. The left eye underwent lensectomy-vitreotomy, membrane peel, and air-fluid exchange. These and multiple other surgeries were performed at another surgical facility. The retinas developed inoperable detachments, and visual outcome was no light perception bilaterally. At 2 years of age, the patient's MRI demonstrated delayed myelina-

tion and abnormalities in the perifrontal horn region (right worse than left) and in the periventricular region.

Case Report of Son

The second child, a son, had the same heterozygous PS deficient parents and had the diagnosis of compound heterozygous PS deficiency made in utero. He was born at 34 weeks gestational age and weighed 2150 g. The functional PS level was less than 1% at birth. On the second day of life, the patient's FFP transfusions were begun. At 35 weeks adjusted age, the patient was doing well and an ophthalmologic examination was normal except for persistent hyaloid arteries. The FFP transfusions were then discontinued. The next week, the patient had bloody stools and was diagnosed with thrombotic necrotizing enterocolitis. He underwent a resection of the necrotic bowel, and FFP transfusions were restarted. At 38 weeks adjusted age, the FFP transfusions were again discontinued. At 39 weeks adjusted age, purpura fulminans developed, and ophthalmologic examination revealed vascular abnormalities from two locations:

1. From the hyaloid artery remnants extending from the optic disc into the vitreous, extraretinal fibrovascular proliferation was identified with tractional retinal folds distorting the posterior retina in the right eye (Fig 3).
2. At the interface between the vascular and avascular retina, arteriovenous shunting of blood in a demarcating ridge was noted in addition to dilation of the retinal veins with segmental beading in the posterior retina in the left eye (Fig 4).

The patient underwent peripheral diode laser bilaterally and, after surgery, developed bilateral anterior chamber and vitreous hemorrhages. As the hemorrhages slowly cleared, bilateral opacification of the lenses was observed. By 40 weeks adjusted age, the FFP transfusions were restarted and at 42 weeks adjusted age, b-scan ultrasonography demonstrated bilateral proliferation of membranes from the optic nerves into the vitreous (right eye worse than left eye). The right eye underwent lensectomy-vitreotomy with an extensive membrane peel and air-fluid exchange, and the left eye underwent lensectomy-vitreotomy with a minimal membrane peel at the optic disc, as described for retinopathy of prematurity (ROP).²⁰ At 6 months of age, an MRI of the abdomen demonstrated small, nonoccluding thrombi within the right renal vein and subhepatic inferior vena cava. An MRI of the brain revealed delayed myelination and hypoplasia of the right posterior inferior cerebellum, possibly representing in utero occlusion of the right posterior inferior cerebellar artery.

Results

Mother

The PS total antigen was 23 $\mu\text{g/ml}$ (normal range, 17–47 $\mu\text{g/ml}$), the PS free antigen was 6 $\mu\text{g/ml}$ (normal range, 6–14 $\mu\text{g/ml}$), and the C4b binding protein antigen was 61% (normal range, 60%–145%). The PS activity was low at 31% (normal range, 70%–130%). These values are consistent with type I heterozygous PS deficiency.

Father

The PS total antigen was 27 $\mu\text{g/ml}$, and the PS free antigen was 8 $\mu\text{g/ml}$. The C4b binding protein antigen was 167% (high), and the PS activity was 56% (low). These values are consistent with type II heterozygous PS deficiency.

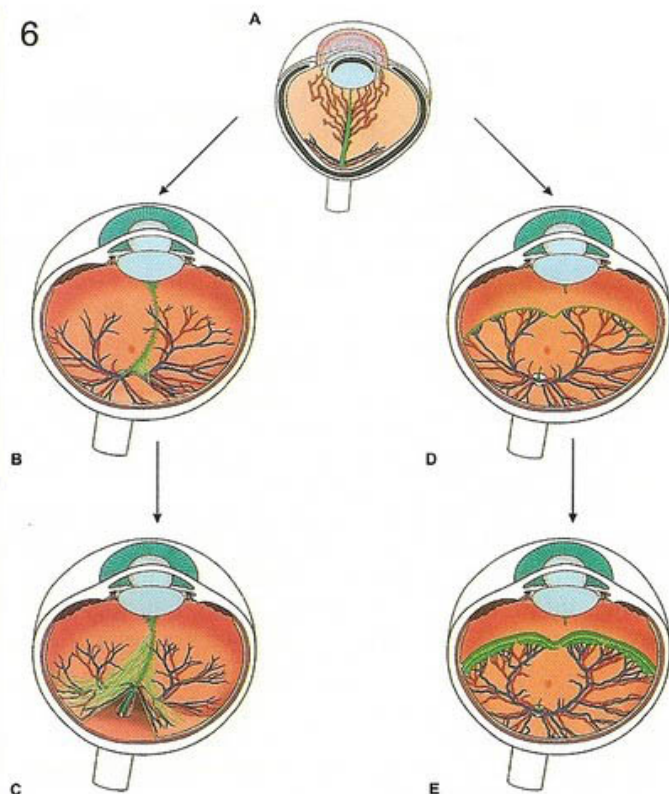
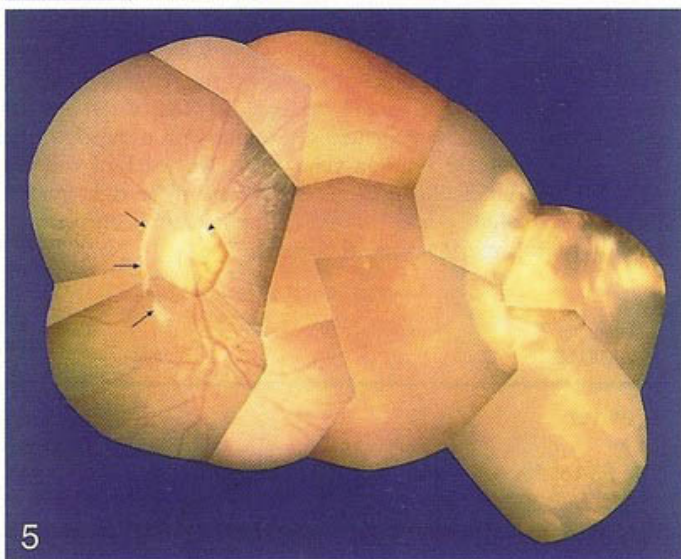
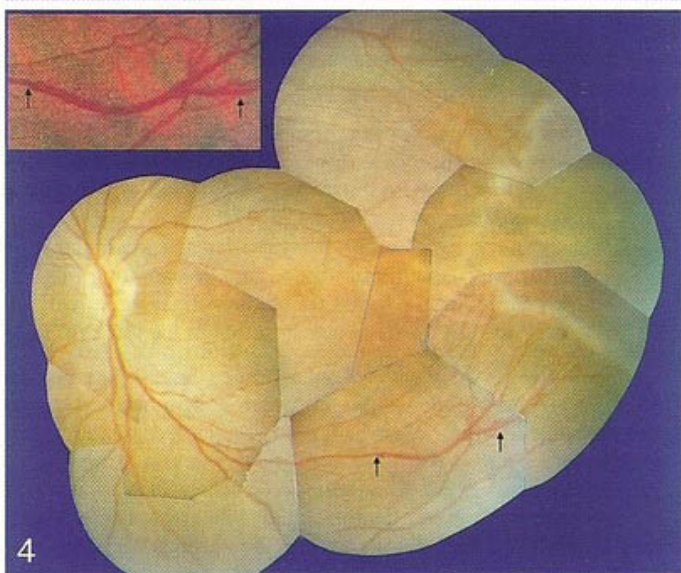
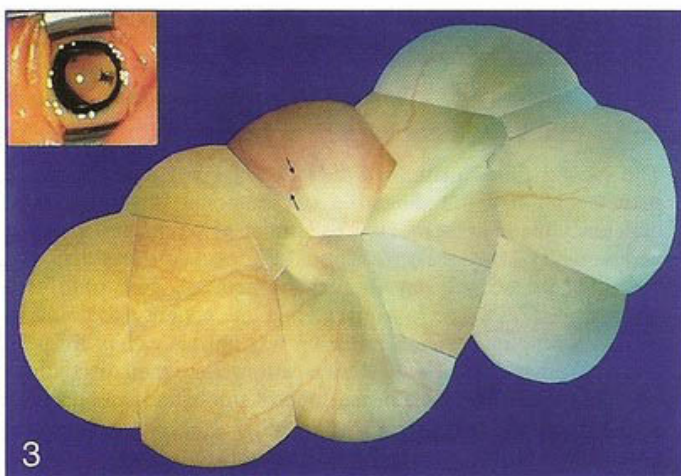


Figure 3. Retinal montage of right eye of son immediately before initial diode laser therapy. (Inset) Extraretinal fibrovascular proliferation from the optic disc toward the posterior aspect of the lens.

Figure 4. Retinal montage of left eye of son immediately before initial diode laser therapy. (Inset) Venous beading and unusual arterial anastomoses.

Figure 5. Retinal montage of left eye of son at 8.5 months of age showing attached retina with remnants of the peripapillary preretinal membrane (small arrows) and of the papillary stalk simulating a Bergmeister's papilla (arrowhead).

Figure 6. Schematic representation of the normal embryonic vascular development (hyaloid and inner retinal) and the disequilibrium leading to various clinical disorders. **A**, embryologic stage with hyaloid vascular system regression and inner retinal vascular system progression. **B,C**, progressive posterior to anterior proliferation of myofibroblasts causing retinal detachment beginning at the optic disc. **D,E**, progressive centripetal proliferation of myofibroblasts causing retinal detachment beginning at the vascular-avascular interface.

Daughter

The PS total antigen was 29 $\mu\text{g/ml}$, the PS free antigen was 6 $\mu\text{g/ml}$, and the C4b binding protein antigen was 116%. The PS activity was 19% (low). This significant decrease of PS activity is consistent with compound heterozygous PS deficiency for a patient receiving FFP transfusions.

Son

The PS total antigen was 28 $\mu\text{g/ml}$, the PS free antigen was 7 $\mu\text{g/ml}$, and the C4b binding protein antigen was 126%. The PS activity was 17% (low). This significant decrease of PS activity is consistent with compound heterozygous PS deficiency for a patient receiving FFP transfusions.

At 8.5 months of age (62 weeks adjusted age), the right eye had no light perception with an inoperable retinal detachment and phthisis, but the left eye had central fixation with a +30.00 diopter contact lens and an attached retina (Fig 5). Normal scotopic and photopic flash electroretinograms and normal flash visual-evoked responses were documented from the left eye.

Discussion

The known components of the protein C (PC) anticoagulant pathway are thrombomodulin (TM), an endothelial cell thrombin receptor, which, in complex with thrombin, activates the plasma zymogen, PC, to the anticoagulant, activated PC (APC). The APC, in turn, forms a complex with plasma PS that assembles on endothelial cell PC receptor (EPCR) to inactivate factors Va and VIIIa. The APC resistance due to a polymorphism in factor V (FV R506Q) and a failure to form thrombin due to a polymorphism in factor II (prothrombin) (FII G20210A) are additional risk factors for thrombosis. The potential risk of deficiencies of TM and EPCR is currently not measurable.²¹ Antithrombin (ATIII) deficiency is another risk factor for thrombosis since the ATIII anticoagulant pathway, which works in concert with the PC pathway to reduce thrombin generation, also keeps the coagulation and anticoagulation systems in a finely tuned balance²² (Fig 1). Specialized hemostasis and thrombosis clinics will screen for these five genetic defects of inherited thrombophilia. Additionally, the metabolic disorder, homocysteinemia, resulting from deficiency of cystathionine β -synthetase (CBS) or methylenetetrahydrofolate reductase (MTHFR), should be included in screening for inherited thrombophilia.²³

The early natural history of ocular abnormalities in infants affected by homozygous and compound heterozygous deficiencies of hemostatic factors has not been documented previously because most eyes have been diagnosed at a rather advanced stage. The daughter reported in this article is typical of the relatively late ocular diagnosis made in compound heterozygous PS-deficient children. She presented with bilateral persistent hyperplastic primary vitreous with retinal detachments that could not be rescued surgically.

In contrast, the son (6 weeks premature) reported in this article is informative with regard to natural history. This child benefited from prenatal diagnosis of PS deficiency and from early ocular examinations. Initial ocular examination

revealed a normally regressing hyaloid vascular system and a normally progressing inner retinal vascular system. Subsequently, however, when medical therapy was interrupted, neovascular and fibrovascular proliferations were observed in both possible locations: (1) *from the optic disc* (reactivating the hyaloid system; diagrammatic representation shown in Figs 6B and C) and (2) *at the vascular-avascular interface* (interrupting inner retinal vascularization; diagrammatic representation shown in Figs 6D and E). The clinical appearance of marked extraretinal fibrovascular proliferation from the hyaloid remnants extending *from the optic disc* into the vitreous with tractional retinal folds is shown in the unsuccessfully treated right eye (Fig 3). Dilation of the retinal veins with segmental beading in the posterior retina and arteriovenous shunting of blood in a demarcating ridge *at the vascular-avascular interface* is shown in the successfully treated left eye (Fig 4).

Normal vasculogenesis is initiated as the hyaloid vascular system that first progresses and then regresses and is completed as the inner retinal vascular system that progresses to the ora serrata. An integrated interpretation of signs and symptoms associated with persistent fetal vasculature (the hyaloid vascular system)²⁴ and with abnormal vasculogenesis (the inner retinal vascular system)²⁵ recognizes that these processes are in equilibrium until normal ocular vasculogenesis is irreversibly completed. That is, these processes are highly inter-related and can advance normally or reverse unexpectedly (Fig 6). Thus, apparently completed processes can be reactivated with the ultimate complete destruction of the vascularized and differentiated retina. This type of abnormal vasculogenesis interrupting the inner retinal vascular system and reactivating the hyaloid vascular system has been well documented in ROP. In premature infants, relative hyperoxia followed by hypoxia stimulates the overproduction of vascular endothelial growth factor.²⁶ Although no pathologic studies are available, it is possible that inner retinal vascular thromboses in this thrombophilic disorder (perhaps reflected by venous beading) result in hypoxia that triggers the overproduction of vascular endothelial growth factor.

The ocular findings of homozygous and compound heterozygous anticoagulant thrombophilic genetic disorders are severe if untreated. These abnormalities have been described in homozygous and compound heterozygous PC deficiency and PS deficiency and, by this report, have been incorporated into the known sequence of ocular vasculogenesis (Fig 6). Homozygous and compound heterozygous ATIII deficiencies are usually incompatible with life.³ The glimpse of the natural history of ocular destruction by homozygous and compound heterozygous hereditary thrombophilic disorders afforded by this family study emphasizes that this group of diseases must be included in the differential diagnosis of infants with early bilateral retinal detachments. A recent report described heterozygous thrombophilic disorders associated with porencephaly and blindness.²⁷ Similarly, previously reported term anencephalic infants with ROP²⁸⁻³¹ may well represent heterozygous, homozygous, or compound heterozygous thrombophilic disorders.

Thus, in *preterm* infants with unexpectedly severe ROP (relatively mild prematurity with minimal risk factors) and in *term* infants with retinal detachments manifested by

persistent fetal vasculature or abnormal inner retinal vasculogenesis, mutations should be considered in the genes for Norrie disease (Xp11.3)³²; MTHFR (1p36.3); CBS (21q22.3); PS (3p11.1-q11.2); PC (2q13-q14); ATIII (1q23-q25); factor V (1q23); and factor II (11p11-q12). As genetic information becomes available, mutations might be considered in the genes for Walker-Warburg disease (9q31); familial exudative vitreoretinopathy (11p12); incontinentia pigmenti (Xq28); TM gene (20p11); EPCR gene (unknown); and other disorders. Additionally, pregnancies may be monitored in families with known heterozygous thrombophilic disorders or in families with the disorders listed above. Early identification of affected children could allow early induction of labor and aggressive surgical intervention (peripheral retinal photocoagulation) and/or early institution of medical therapies (replacement therapies) until normal ocular vasculogenesis is irreversibly completed.

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