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Invited Review

Avascular Peripheral Retina in Infants

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Abstract

Avascular peripheral retina in an infant is a common characteristic of numerous pediatric retinal vascular disorders and often presents a diagnostic challenge to the clinician. In this review, key features of each disease in the differential diagnosis, from retinopathy of prematurity, familial exudative vitreoretinopathy, Coats disease, incontinentia pigmenti, Norrie disease, and persistent fetal vasculature, to other rare hematologic conditions and telomere disorders, will be discussed by expert ophthalmologists in the field.

Keywords: Avascular retina, retinopathy of prematurity, familial exudative vitreoretinopathy, Coats disease, incontinentia pigmenti, persistent fetal vasculature, Norrie disease

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Introduction

Pediatric retinal vascular diseases are the leading causes of childhood blindness throughout the world.[1] Therefore, correct and timely diagnosis of an infant presenting with a retinal vascular disease is of paramount importance. However, this can often be challenging.

Avascular peripheral retina is a common feature of many pediatric retinal vascular diseases. Therefore, the clinician should seek out key features that will help differentiate the various diseases that may present in such a manner. Clinical evaluation should begin with a detailed medical history, including gestational age, weight, birth history, neonatal course, and the presence of any systemic findings. Family history, including known ocular disease in the immediate family or close relatives and the presence of parental consanguinity should be questioned. A comprehensive ophthalmological examination should then be performed. Also, examination of available family members often provides important clues for an accurate diagnosis.

In this article, experienced ophthalmologists in the field will review key points of diseases included in the differential diagnosis of a pediatric patient presenting with avascular peripheral retina. The major differential diagnosis includes retinopathy of prematurity (ROP), familial exudative vitreoretinopathy (FEVR), Coats' disease, incontinentia pigmenti (IP), Norrie disease, and persistent fetal vasculature (PFV). In addition, other rare conditions that may present with avascular peripheral retina, such as hematologic and inflammatory conditions and telomere disorders, will also be discussed.

Retinopathy of Prematurity (ROP)

The studies of basic mechanisms of the development of the normal retinal vascular network dates back to Michaelson[2] in 1948 and later to Flower et al.[3] who, using ink-injected flat mounted kitten retinas, observed the presence of large portions of peripheral non-vascularized retina at birth. The seminal studies of Michaelson[2], Flower et al.,[3] Smith[4], and Chan-Ling[5] have contributed to defining the mechanisms underlying the development of the vascular network, including vasculogenesis of the posterior areas surrounding the papilla, angiogenesis of the more peripheral areas, and subsequent progression of the vascular network towards the retinal periphery. The formation of the retinal vascular network begins between 14 and 15 weeks of gestational age with the appearance of a patent superficial capillary plexus around the optic disc, and is mediated by angiogenesis. The inner vascular plexus develops rapidly and reaches its limits by 32 weeks, and a small area of avascular retina persists.[6] The deeper vascular plexus starts forming in the perifoveal zone around 24 weeks of gestation. Retinal angiogenesis of the deeper plexus is centered around the fovea and is driven by the maturation of photoreceptors and the consequent increase in metabolic demand. The deeper plexus reaches its limits by birth.[5] During normal development, the retinal vasculature is constantly remodeled by increasing capillary density in order to meet the metabolic demands of the retina.

Knowledge of retinal vascular development allows clinicians to recognize the features of delayed retinal vascularization (extension, topography, branching vessels, capillary density) after premature birth, which characterize the first phase of ROP.[4] Later, the persistent avascular retina stimulates the vascular endothelial growth factor (VEGF)-driven vasoproliferation that is the hallmark of the second phase of ROP (Figure 1).[4] Laser photoablation aims to destroy the avascular retina where the VEGF is produced. In contrast, the introduction of anti-VEGF drugs for inhibition of vasoproliferation in stage 2 leads to abnormal persistence of avascular retina (Figure 2). The persistent avascular retina can stimulate reactivation or recurrence of the vasoproliferation, as evidenced in studies of preterm infant eyes treated with bevacizumab for severe ROP.[7]

Persistent peripheral avascular retina, identified as "PAR" in the new third edition of the International Classification of ROP,[8] can correlate with the severity of ROP in the acute phase and with the risk of reactivation and recurrence of ROP after either photoablation (skip areas) or anti-VEGF injection.

Furthermore, persistent avascular retina can be observed after the acute phase in spontaneously regressed ROP or even in former premature infants without ROP or any pathologic consequences (Figure 3). This observation opens the way to the possibility that the persistence of areas of peripheral avascular

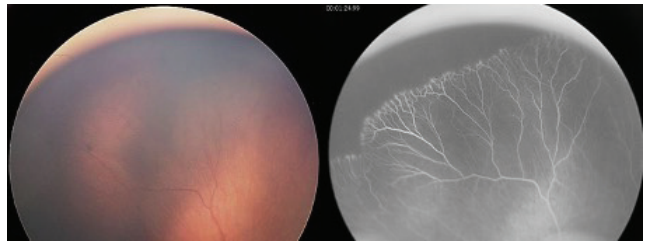

Figure 1. Color fundus image and corresponding fluorescein angiography of an avascular peripheral retina at 35 weeks of postmenstrual age in a preterm infant born at 27 weeks of gestational age with a birth weight of 890 grams (Courtesy Dr. Domenico Lepore)

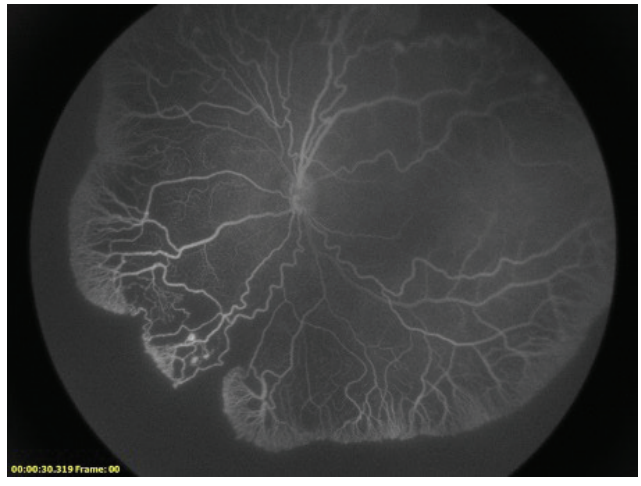

Figure 2. Fluorescein angiography showing an avascular peripheral retina in a 2-year-old child born preterm (25 weeks of gestational age, birth weight 650 g) and treated with 0.2 mg/0.02 mL of ranibizumab at 34 weeks of postmenstrual age for type 1 retinopathy of prematurity (Courtesy of Dr. Domenico Lepore)

retina is not necessarily a potentially pathogenic condition but rather a metabolically well-tolerated vascular anomaly. Further studies are needed to better understand the features that characterize this anomaly.

Familial Exudative Vitreoretinopathy

Bilateral peripheral avascular retina with associated vitreous changes is the hallmark of the rare congenital blinding retinal disorder called FEVR.[9,10] The genetic abnormality manifests as arrested retinal angiogenesis, often in the last trimester of pregnancy, that remains so for the lifetime (Figure 4, 5). The avascular retina triggers a wide array of phenotypic variations, with each component having variable severity.[9] These include retinal neovascularization, exudation, retinal folds, and subsequent vitreous hemorrhage, retinal detachment (RD) causing leukocoria, progression to iris neovascularization, neovascular glaucoma, secondary retinoschisis, macular heterotropia, and vasoproliferative tumor-like peripheral retinal lesions. Also, vitreous condensation at the edge of the arrested angiogenesis (Figure 5), epiretinal membranes, vitreoschisis, vitreomacular traction manifest variably alongside the retinal vascular pathology.

Clinical Diagnosis: Males and females are both affected. Symptoms include squint, eye poking, poor vision, leukocoria, low vision, rapid onset of visual loss, or rapid development of a cataract or glaucoma in newborns, young children, or young adults. In some patients who are asymptomatic, lesions are noticed during routine retinal examination in eyes with myopia, family screening, or in examination of the fellow eyes of RD or neovascular glaucoma of unknown cause. The more severe phenotypes present soon after birth with associated retinal dysplasia.[9] The clinical diagnosis of FEVR can be made in a full-term child in the presence of peripheral retinal avascularity with minimal vitreous condensation at the edge. These signs may be present in one or both eyes and may or may not be associated with additional retinal changes at the time of diagnosis (Figure 4). However, the association of posterior hyaloid yellow deposits seen in some of these eyes is unique to FEVR (Figure 4). In a preterm child presenting with similar characteristics but a disease tempo not consistent with ROP, the diagnosis of FEVR can be made.[9,10,11] John et al.[11] described ROPER (ROP vs FEVR) in premature babies who display retinal abnormalities more typical of FEVR than ROP, largely based on fluorescein angiography (FA) characteristics and disease course. The distinctive FA findings of ROPER include irregular vascular sprouting at the vascular-avascular junction (vs the more uniform advancing front of ROP), distinct vessel pruning, punctate hyperfluorescence, and segmental areas of vascular leakage. The diagnosis of ROPER may have implications for management because, like FEVR, these patients may manifest a more unpredictable and long-term course than those with ROP. Another clue is that vascularization does not show any forward movement into the avascular retina at any time point in FEVR. This is useful in differentiating from ROP, where the initial avascular retina always shows advancement of vascularization to a varying degree

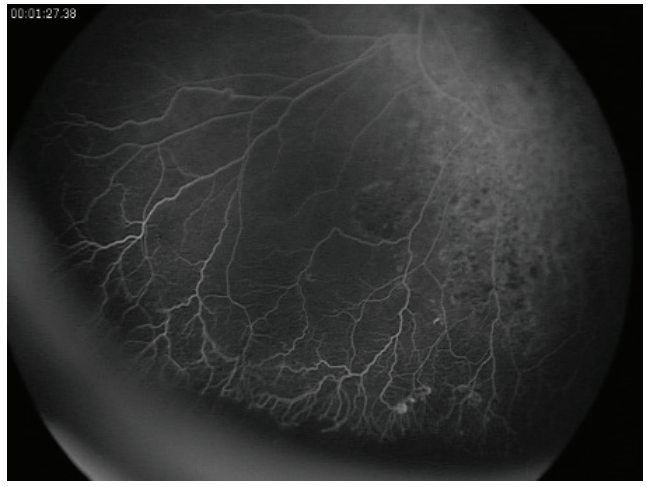

Figure 3. Fluorescein angiography of an avascular peripheral retina in a 2-year-old child who was born preterm (28 weeks of gestational age, birth weight 980 g) and had fully regressed stage 2 zone 2 retinopathy of prematurity diagnosed at 32 weeks (Courtesy of Dr. Domenico Lepore)

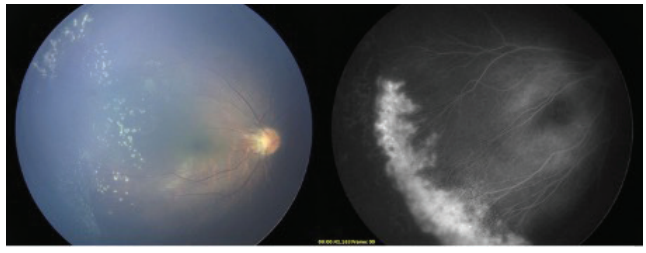

Figure 4. Avascular peripheral retina with neovascularization (NV) and typical posterior hyaloid yellow deposits in a term neonate with familial exudative vitreoretinopathy. Corresponding fluorescein angiography shows straightening of the vessels towards the periphery, avascular peripheral retina, and severe leakage from the NV at the vascular-avascular retinal junction (Courtesy of Dr. Şengül Özdek)

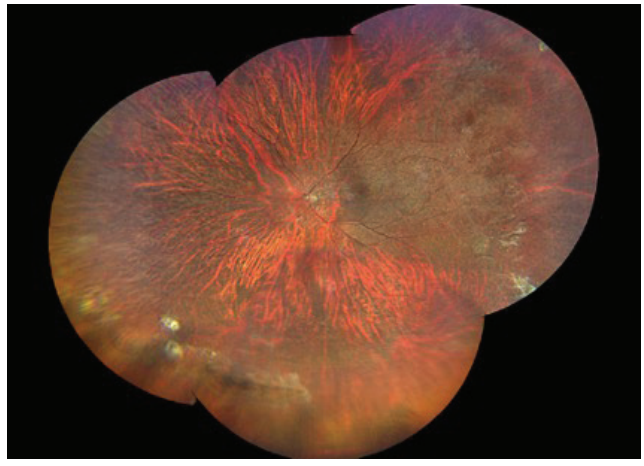

Figure 5. Fundus photo of a female patient aged 20 years. Peripheral avascular retina in familial exudative vitreoretinopathy never shows forward advancement during the lifetime, has fine but adherent vitreous condensation at the edge, and often the temporal raphe is involved more posteriorly, like a 'notch'. Avascularity is present in all quadrants but is more prominent temporally. There are no ghost vessels (Courtesy of Dr. Subhadra Jalali)

in the first few weeks and months of follow-up. Occluded/ghost vessels are hence not seen in the avascular part of the retina (Figure 4, 5). Similarly, chorioretinal scarring is typically absent in FEVR and helps to differentiate from other mimickers like vasculitis or viral retinitis. Eyes with bilaterally advanced disease have bilateral leukocoria due to retrolental fibroblastic proliferation and RD, which is not different from ROP. However, the exudative component is often more significant in FEVR than that seen in ROP.

Family Involvement: Being a hereditary retinopathy, family evaluation may reveal autosomal dominant inheritance, which is the most common, although X-linked and recessive inheritance patterns are also seen, with variable penetrance.[9,10,12] Family members can present with varying degrees of retinal problems and should always be examined in detail.[9] Probands with severe phenotypes present with RD at birth or in early infancy, resulting in bilateral blindness. They are more likely to have a mutation in the Norrie disease pseudoglioma (NDP) gene, which was previously classified as Norrie disease. However, it is now established that FEVR and Norrie are similar conditions that belong to the same spectrum of defective Wnt signal pathway mutations.[9,10,12] The next pregnancy may have similar mutations, and thus the baby may be born blind with congenital RD or develop RD very soon after birth. Early delivery and evaluation within a day or two after birth can be done to diagnose and treat the retinopathy as early as possible. Systemic associations are seen in some patients, so a thorough systemic evaluation should be performed by a neonatologist or pediatrician. Common systemic associations include hearing loss, cognitive deficits, impaired osteogenesis, muscle hypotony, microcephaly, and rarely hematological abnormalities.

Disease Classification: The severity of disease is currently described through various stages as classified by Pendergast and Trese[13] in 1998 (Table 1). With the evolution of widefield fundus FA, new insights into FEVR have emerged that led to a new classification by Kashani et al.[14] in 2014 (Table 2).

Investigations: Regular follow-up and documentation of retinal changes is essential to know the tempo of the disease and its progression, which can vary at various phases of life. Widefield fundus photography to visualize peripheral retinal changes is strongly recommended at presentation and at annual follow-ups, along with widefield FA as much as possible. Widefield optical coherence tomography (OCT) also provides insights into vitreoretinal adhesions, traction, shallow RD, retinoschisis, macular edema, or macular hole and helps guide surgical decisions. Fundus photographs/FA of the family members are also recommended whenever feasible. Genetic testing for mutations is highly desirable in the diagnosis and management of the patient and the family.

Disease Course: FEVR stages do not always progress from one to the next, but are rather phenotypes with variable presentations. Each presentation has its own natural course that can vary from no change to relentless, progressive worsening or disease reactivation after a long period of quiescence. Eyes with exudation usually have worse prognosis. RD can be seen in 21-64% of cases in FEVR and is the most common indication for surgical intervention.[13] It may be tractional, rhegmatogenous, exudative, or combined. When left untreated, eyes with early-onset FEVR with or without retinal dysplasia often develop progressive shallowing of the anterior chamber, corneo-lenticular adhesions, and ultimately corneal scarring with associated glaucoma or eventual phthisis bulbi. Infants at this stage often develop an oculodigital reflex that is very robust and difficult to stop.

Table 1. Staging of familial exudative vitreoretinopathy (FEVR) by Pendergast and Trese[13]

Stage	Features
1	Peripheral avascular retina*
2	A: Retinal neovascularization without exudates B: Retinal neovascularization with exudates
3	A: Extramacular retinal detachment without exudates B: Extramacular retinal detachment with exudates
4	A: Macula involving subtotal retinal detachment without exudates B: Macula involving subtotal retinal detachment with exudates
5	Total retinal detachment

*Peripheral avascular retina in FEVR is almost always associated with fine but adherent vitreous condensation at the edge of vascularized retina; often the temporal raphe is involved more posteriorly like a 'notch', allowing differentiation from other conditions associated with avascular peripheral retinal pathologies.

Table 2. Revised familial exudative vitreoretinopathy staging using additional fluorescein angiography by Kashani et al.[14]

Stage	Features
1	Avascular periphery or anomalous intraretinal vascularization 1A. Without exudate or leakage 1B. With exudate or leakage
2	Avascular retinal periphery with extraretinal vascularization 2A. Without exudates or leakage 2B. With exudates or leakage
3	Extramacular retinal detachment 3A. Without exudates or leakage 3B. With exudates or leakage
4	Macula involving subtotal retinal detachment 4A. Without exudates or leakage 4B. With exudates or leakage
5	Total retinal detachment 5A. Open funnel 5B. Closed Funnel

Management: Early stages are managed by laser photocoagulation of the avascular retina, although this can sometimes lead to adverse events like epiretinal membranes, tractional detachments, and retinal tears, or have no effect on the relentless progressive exudation. Advanced cases need additional vitrectomy with or without buckling procedures for treatment and also as prophylaxis against further progression. Early vitrectomy can also be done as prophylaxis in selected cases where laser ablation has the potential to cause problems or is likely to be ineffective. Early-onset severe FEVR with or

without retinal dysplasia is managed by surgery; however, the results suggest that it provides only minimal ambulatory vision in a few cases.[13,15]

To summarize, the often familial, congenital, bilateral peripheral avascular retina in FEVR has unique characteristics of vitreous condensation at the edges, absence of ghost vessels, lifetime of arrested angiogenesis, and varying phenotypes with or without exudation and with variable potential for progression.

Coats' Disease

Coats' disease is a nonhereditary disorder characterized by the formation of abnormal retinal vessels that cause intra- and subretinal exudative changes. It mainly affects boys around the age of 5 years and is unilateral, but rarely affects girls or presents bilaterally.[16,17] The disease may be detected with minor vision loss or visual field abnormalities at school health checkups, while it is often in an advanced stage when the disease is detected early in childhood with white or yellowish pupils and/or strabismus. Coats' disease is progressive, and if not treated appropriately, RD and neovascular glaucoma may develop, ultimately necessitating enucleation of the eye. According to the staging classification proposed by Shields et al.[16] in 2001, the disease is classified into stage 1 with retinal vascular aneurysmal formation without exudative changes, stage 2 with exudative changes, stage 3A with partial RD, stage 3B with total RD, stage 4 with neovascular glaucoma, and stage 5 with phthisis bulbi. Because retinal vascular abnormality mainly occurs in the periphery, widefield color fundus photography and fluorescence angiography are extremely useful. In the following paragraphs, we focus on the differential diagnoses of Coats' disease from retinoblastoma, ROP, FEVR, PFV, and Norrie disease in regards to the peripheral avascular retina.

Coats' disease has been characterized by usually unilateral peripheral retinal telangiectasias and light bulb-shaped microaneurysms surrounded by capillary non-perfusion areas. However, some advocate that Coats' disease may actually be bilateral because of the presence of peripheral vascular changes in the fellow eyes.[18] The most crucial differential of Coats' disease is retinoblastoma, which is life-threatening if misdiagnosed. Advanced Coats' disease with a bullous RD can present with a yellowish pupillary reflex (xanthocoria) rather than white as cholesterol crystals accumulate in the subretinal space. In addition, retinal telangiectasia can be seen on the surface of the detached retina in Coats' disease (Figure 6). On the contrary, in retinoblastoma a whitish-gray pupillary reflex can be seen, and retinal telangiectasia is uncommon.

Unlike ROP, a vascular-avascular junction is rarely seen in Coats' disease. However, aggressive ROP or zone 1 with plus disease with exudative changes can masquerade as Coats' disease (Figure 7). The bulb-shaped peripheral vascular changes in Coats' disease should be pivotal components to differentiate those conditions. RD in Coats' disease is typically exudative, but can sometimes be rhegmatogenous or tractional. Coats' disease with tractional RD may present with fibrovascular membrane, which needs to be differentiated from FEVR or Norrie disease

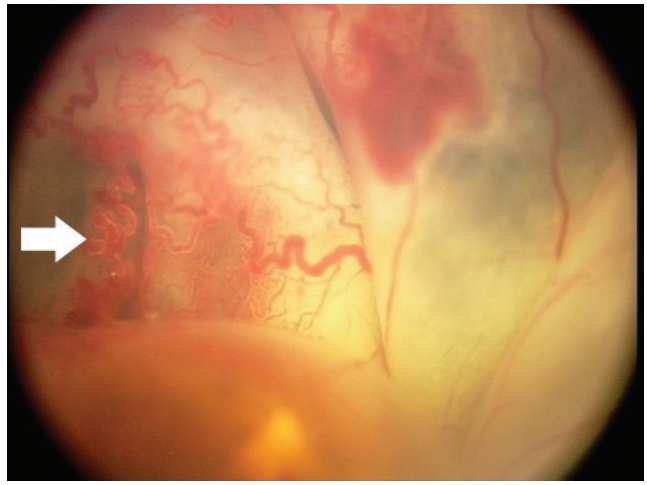

Figure 6. Yellowish pupillary reflex in Coats' disease. A bulbed-shaped retinal telangiectasia (white arrow) overlying the bullous retinal detachment suggests a diagnosis of Coats' disease rather than retinoblastoma (Courtesy of Dr. Shunji Kusaka)

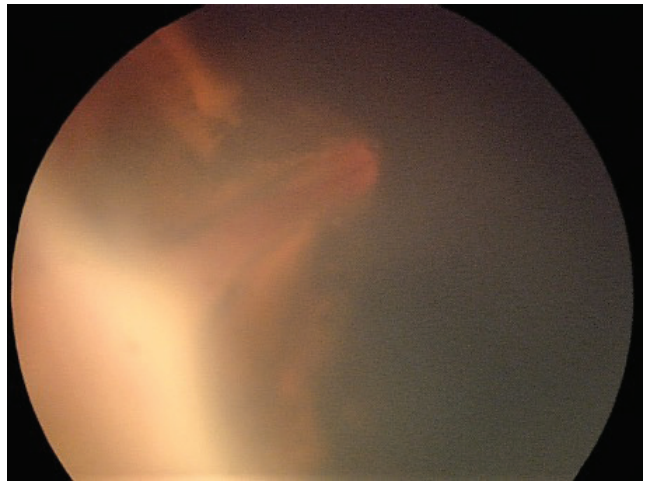

Figure 7. A case of retinopathy of prematurity (ROP) with exudative changes. A falciform retinal detachment with subretinal exudation in a patient with stage 5A ROP mimics Coats' disease (Courtesy of Dr. Shunji Kusaka)

(Figure 8). A dragged disc and macula suggest FEVR, while subretinal exudation and bulb-shaped retinal telangiectasias suggest Coats' disease (Figure 9). Genetic identification of causative FEVR genes (i.e., FZD4, NDP, LRP5, and TSPAN12) and bilateral conditions would support the diagnosis of FEVR. Basically, the fibrovascular membrane is seen posteriorly in Coats' disease if present, but is located temporally in FEVR. PFV also could be a differential diagnosis of Coats' disease. However, the fibrovascular membrane is usually located retrolentally and more to the nasal side in PFV, which does not present with bulb-shaped retinal telangiectasias.

Management: In the early stages, careful observation or photocoagulation of the vascular aneurysms is the mainstay of treatment. In cases with a progressive RD refractory to ablative treatment (stage 3 or higher), surgical treatment is often required. The main surgical procedures include vitrectomy

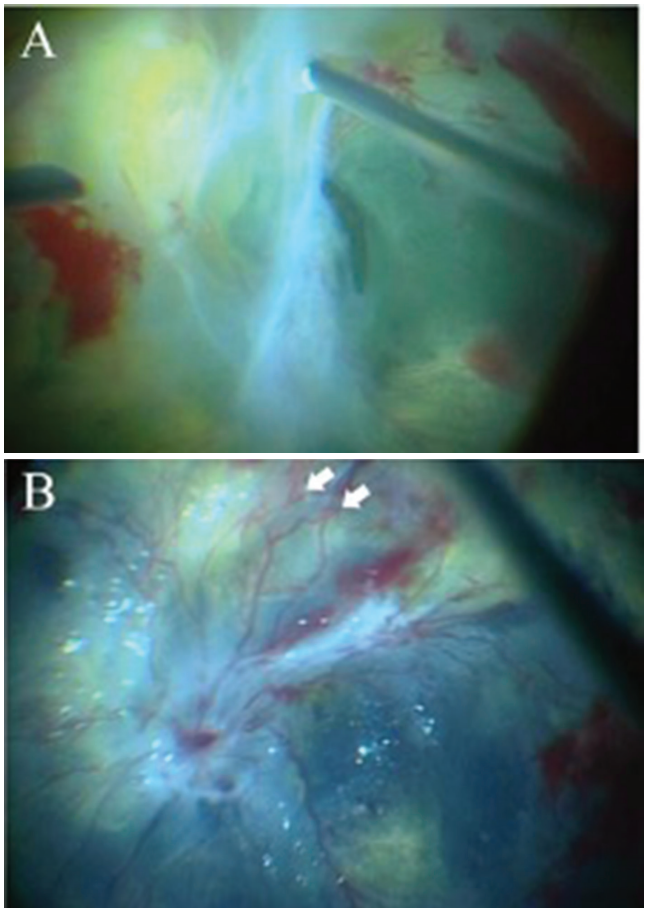

Figure 8. Intra-operative view of Coats' disease with fibrovascular membrane. A fibrovascular membrane was localized posteriorly in a patient with Coats' disease (A). After the removal of fibrovascular membrane, bulb-shaped telangiectasias (white arrows) and subretinal exudates became prominent under perfluorocarbon liquid (B) (Courtesy of Dr. Shunji Kusaka)

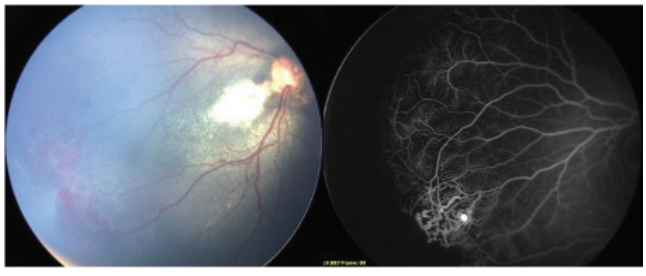

Figure 9. A case of Coats' disease with a peripheral avascular retina, mimicking familial exudative vitreoretinopathy. Color fundus photograph of Coats' disease shows peripheral vascular proliferations and branched vessels, and exudative changes in the posterior pole. Fluorescein angiography of the same case shows peripheral avascular retina with bulb-shaped telangiectasias (white arrow), suggesting the diagnosis of Coats' disease (Courtesy of Dr. Şengül Özdek)

and drainage of subretinal fluid.[19,20] As intraocular VEGF concentrations are known to be extremely high in Coats' disease,[21] a procedure to drain the large amount of VEGF present in the subretinal space from the eye is a logical approach.[22] Other methodological approaches include a non-vitrectomized technique with transscleral drainage and laser photocoagulation[23] or combined scleral buckling surgery.[24] Although the advent of anti-VEGF agents has given us various treatment options for Coats' disease, the visual prognosis is still poor in patients with advanced Coats' disease.[17] It is important to recognize that Coats' disease is progressive, and continuous examinations are needed to determine the appropriate indication for treatments.

Incontinentia Pigmenti

IP, also referred to as Bloch-Sulzberger syndrome, is a rare hereditary condition characterized by generalized abnormality of the ectodermal tissues and varying degrees of abnormality of the retina and central nervous system. IP typically has a bilateral but asymmetric presentation and particularly affects the skin, eyes, brain, and teeth. Its incidence is estimated to be 0.7 cases per 100,000 live births.[25,26,27,28,29,30]

IP is inherited as an X-linked dominant trait caused by a mutation in the NEMO gene (essential modulator gene), located at gene locus Xq28.[25,26,27,28,29,30] The resulting protein regulates the activity of NF-kB, making cells more susceptible to apoptotic signals and leading to increased endothelial cell death. Some infrequent cases also involve a translocation at Xp11. Only women inherit the disease, as it is lethal in males. However, sporadic cases have also been reported in males, most probably a result of de novo mutations. [25,26,27,28,29,30]

Initial symptoms of this disease are skin blisters observed in infants soon after birth. [25,26,27] The stages of IP progression are as follows:

Stage 1 is called vesicular or vesicular-bullous. It is characterized by linear inflammatory bubbles and vesicles which appear during the first two months after birth, with relative sparing of the face. This stage can last from weeks to months.

Stage 2 is called verrucous. During this stage, linear hyperkeratotic papules develop on the distal limbs and scalp and last for varying durations.

Stage 3 is the hyperpigmentation stage. It occurs with the onset of linear hyperpigmented streaks starting in infancy (Figure 10) and gradually disappearing during adulthood.

Stage 4 is the final stage and characterized by hypopigmented macules and hairless patches. Skin biopsies of these patients show dyskeratosis, acanthosis, pigment incontinence and eosinophil infiltration.[25,26,27]

Extracutaneous manifestations are common, observed in up to 80% of IP cases. These can include:[25,26,27,30,31,32]

- **Eye abnormalities** (retinal and corneal abnormalities, microphthalmia, cataract, iris hypoplasia, uveitis, nystagmus, strabismus), which are reported in up to 77% of IP cases.
- **Dental abnormalities** (delayed eruption, malformed teeth, hypodontia, anodontia, delayed dentition), which are present in up to 80% of cases.
- **Nail abnormalities** (mild nail dystrophy, ridging, or disruption).
- **Hair involvement** (alopecia and baldness).
- **Central nervous system involvement** (convulsions, seizures, mental retardation, ischemic strokes, hydrocephalus). Approximately 30% of IP patients have neurologic impairment.

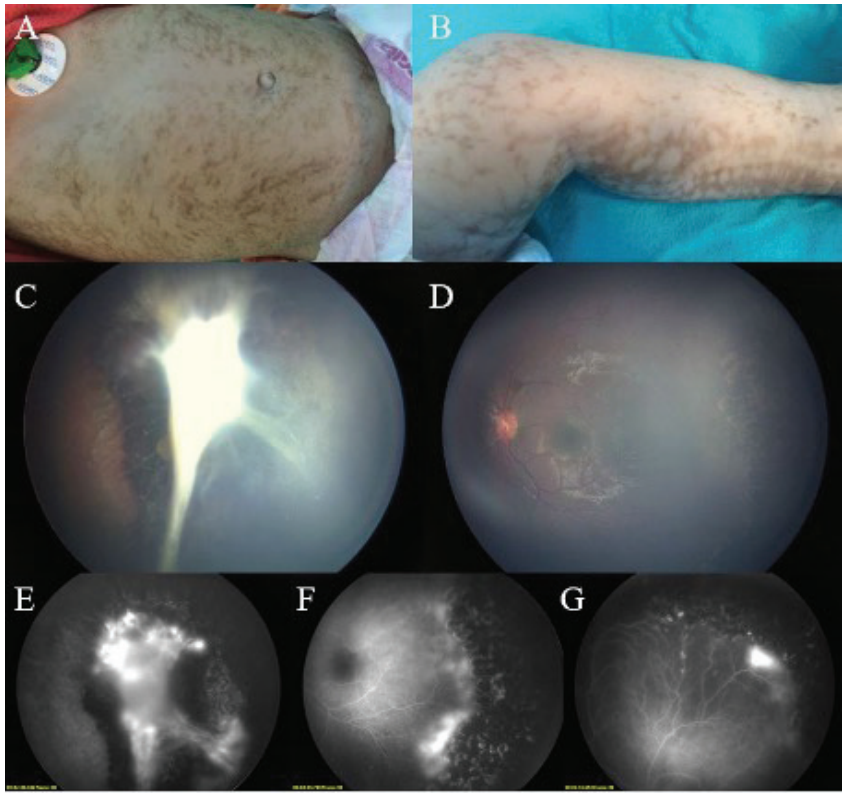

Figure 10. A 2-month-old girl with incontinentia pigmenti and hyperpigmented rash noted on the trunk and lower extremities (A, B). Fundus photograph of the right eye shows total tractional retinal detachment with peripheral avascular retina and fibrovascular membranes causing anteroposterior traction in the center (C). Fundus photograph of the left eye shows near-normal posterior pole and lasered peripheral avascular areas (D). Fluorescein angiography highlights the abnormal vasculature. The right eye shows severe leakage from the fibrovascular membranes and totally avascular periphery (E). The left eye shows leaking pathological vessels at the avascular-vascular junction, posterior to the laser scars (F, G). (Courtesy of Dr. Şengül Özdek)

Affected children can develop hemiplegias, intellectual disability, and cerebellar ataxia. These manifestations pose a significant threat to the normal life expectancy of IP patients.

- **Skeletal abnormalities** (syndactyly, cranial deformities, dwarfism, supernumerary ribs, hemiatrophy, and short limbs).
- **Breast abnormalities** (hypoplasia, unilateral aplasia, supernumerary nipples).
- Immunological changes due to defective neutrophil chemotaxis and lymphocyte function. There is also possibility of malignancies, such as hematological neoplasms, Wilms' tumor, and retinoblastoma.

Retinal Findings: The hallmark of retinal disease in IP is peripheral retinal ischemia leading to neovascularization, vitreous hemorrhage, and tractional RD. Tractional RD may progress to a closed funnel RD with formation of a retrolental mass, eventually leading to phthisis bulbi.[26,27,33] Exudative RD may also occur.

Unlike ROP and FEVR, the ischemia does not follow the developmental vascular pattern with a clear distinction between vascularized retina posteriorly and avascular retina anteriorly. Rather, peripheral ischemia is often accompanied by ischemia of the posterior vascularized retina. Epiretinal neovascularization may develop at this border, which can lead to vitreous hemorrhage, contraction, and traction. In some cases, the foveal avascular zone may enlarge or become irregular because of progressive capillary loss. Approximately one in four children with IP have tractional RDs, with the greatest risk during infancy and childhood.

Another cause of decreased vision in patients with IP is macular pathology, including foveal hypoplasia, RPE mottling, cherry red spots, increased macular pigmentation, subretinal pigmentary changes, epiretinal membrane, macular ischemia, aneurysms, and neovascularization of the optic disc. In addition, changes in the peripheral retina may progress towards the posterior pole. These include peripheral avascular retina, aneurysm-like dilations, arteriovenous anastomosis, vascular loops similar to those seen in aggressive ROP, retinal and extraretinal new vessels, preretinal fibrovascular proliferation, vitreous hemorrhage, RD (tractional or exudative), and exudates.[27,34,35,36]

Less common ocular findings include strabismus, cataracts, conjunctival pigmentation, optic atrophy, retinal pigment abnormalities, foveal hypoplasia, foveal disorganization, and microphthalmia. Reduced vision may also be associated with brain disorders leading to cortical blindness.[26,34]

Disease Staging: The vitreoretinal changes that occur during the course of disease can be classified into five stages:

Stage 1 includes retinal pigment epithelial changes.

Stage 2 includes retinal vascular abnormalities (except neovascularization).

Stage 3 includes retinopathy with neovascularization or other pathologies secondary to retinal vasculopathy like retinal exudation, epiretinal membrane/proliferation and vitreous hemorrhage.

Stage 4 includes RD without end-stage changes. Substages include 4a (partial RD) and 4b (total RD).

Stage 5 is the end stage, with severe ocular complications such as phthisis bulbi and secondary glaucoma.

Investigations: Recent OCT studies using hand-held devices have shown macular abnormalities in IP such as inner and outer retinal thinning, cystoid macular edema, blunted foveal pit, and irregular outer plexiform layer with inner retinal thinning temporal to the fovea.[35,36] Ultra-widefield OCT can simultaneously demonstrate macular and peripheral vitreoretinal changes. OCTA is also an important tool to detect capillary nonperfusion and retinal neovascularization.[35,36]

Management: IP requires a multidisciplinary approach due to the involvement of multiple organ systems. Pediatric dermatology should be consulted for cutaneous lesions, and pediatric neurology for the management of seizures and neurologic imaging. Genetic testing may confirm the diagnosis. Approximately 25-35% of cases are familial, and the remaining are sporadic. Close ophthalmic monitoring is required from birth to prevent blindness, given the high risk of progressive peripheral retinal nonperfusion and neovascularization. These eyes are at risk for life since the onset of retinopathy is variable. As the retinal vascular disease may progress rapidly over the first weeks of life, monthly examinations from birth to 4 months of age and then every 3 months until the age of 1 year is recommended. Examinations can be performed every 6 months after that if the condition is stable. The presence of any ischemia should be carefully monitored since it can be potentially progressive and cause neovascularization and subsequent detachment.[26,27,33] We advise early FA to identify avascular retina in IP patients and early and aggressive laser treatment sparing the macula to prevent terminal complications.[34] RD and vitreous hemorrhage may require pars plana vitrectomy.

Prognosis is variable depending on the degree of skin and organ involvement. Patients without significant ophthalmic or neurological impairment have a good prognosis and normal life expectancy.[37] Patients with seizures and structural CNS abnormalities have the greatest risk of developmental delay and impairment.[37]

Persistent Fetal Vasculature (PFV)

Previously known as persistent hyperplastic primary vitreous, PFV is a congenital eye disorder leading to blindness in up to 5% of children in the United States.[38] This developmental abnormality is caused by failed involution of the embryonic hyaloid vasculature in utero, resulting a various degrees of congenital posterior pole manifestations. First described by Cloquet in 1818, PFV is most often unilateral and sporadic. Bilateral presentation may be noted in up to 10% of cases and this finding should prompt investigation for additional ocular and systemic comorbidities as well as an underlying genetic etiology.

PFV has a spectrum of anatomic presentations and may be classified based on location as anterior, posterior, or combined. Anterior PFV is characterized by persistence of part of the tunica vasculosa lentis, and this may result in some or all of the following findings: retrolental opacity, cataract, elongated ciliary process, shallow anterior chamber, and a membranous transformation of the anterior vitreous face with secondary traction on the peripheral retina in some cases. Posterior PFV results from remnants of the hyaloid artery that form a fibrovascular stalk extending from the optic nerve into the vitreous and up to the retrolental area in some cases (Figure 11). This may lead to retinal folds, retinal or optic nerve dysplasia, traction, and/or focal detachment, as well as retinal or vitreous hemorrhage. Intraocular progression of PFV is related to continued eye growth inducing tractional changes on the retina, lens, and ciliary processes. Additional ocular manifestations of both anterior and posterior PFV may include microphthalmia, leukocoria, strabismus, amblyopia, corneal opacification, angle-closure glaucoma, and phthisis bulbi in advanced cases (Table 3).[39]

Diagnosis of PFV is usually clinical, and peripheral retinal nonperfusion is one of the main retinal findings in posterior PFV. Peripheral capillary nonperfusion was first described on FA

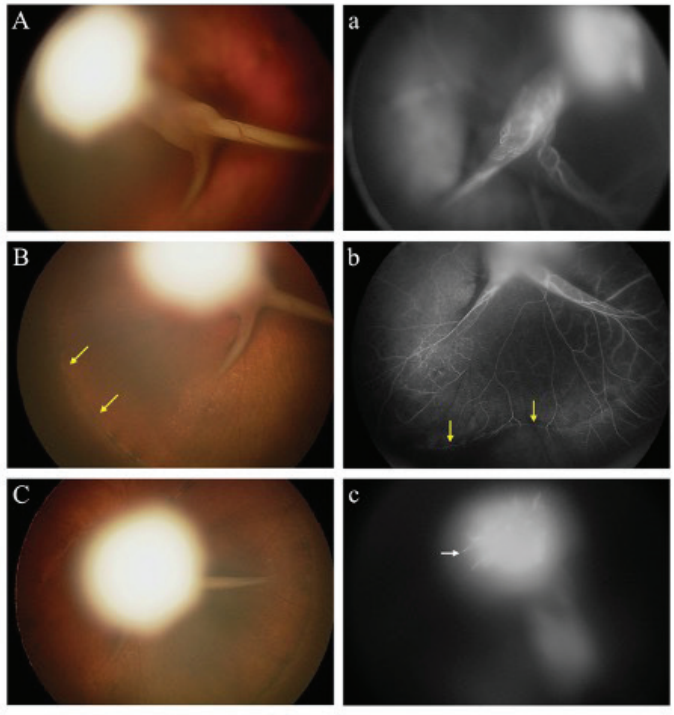

Figure 11. Persistent fetal vasculature in a 6-month-old boy presenting with leukocoria and exotropia of the right eye.40 Color fundus photograph of the right eye revealed a fibrovascular stalk extending from the optic nerve to the posterior lens capsule (A, B, C). Fluorescein angiography of the right eye shows retinal vessels in posterior retinal folds pulled anteriorly into the stalk up to the posterior lens (a, c), as well as peripheral retinal capillary nonperfusion (b). Reprinted from Pictures & Perspectives, 124/4, Jeng-Miller KW, Joseph A, Baumal CR, Fluorescein Angiography in Persistent Fetal Vasculature, Page 455, Copyright (2016), with permission from Elsevier

Table 3. Key features of persistent fetal vasculature	
Common	**Microphthalmia, leukocoria, cataract, strabismus**
Anterior	Persistent pupillary membrane, dilated iris vessels, retrolental fibrovascular membrane, shallow anterior chamber, elongated ciliary process, ectropion uvea, coloboma iridis, peripheral tractional retinal detachment, intralenticular hemorrhages, angle-closure glaucoma, corneal opacification
Posterior	Vitreous membranes and stalk, hypoplastic/dysplastic optic nerve, macular pigmentary disruption or hypoplastic macula, retinal fold/detachment, retinal or vitreous hemorrhage, peripheral avascular retina

in a report of a 6-month-old boy with unilateral PFV (Figure 11).[40] Recent studies have found retinal vascular abnormalities not only in the affected eyes of patients with unilateral PFV but also in their funduscopically normal fellow eyes.[41,42] The fellow eyes had subtle abnormalities that can be revealed through FA.[42,43] Specifically, peripheral avascularity was reported as the most common finding seen in 67% to 90% of the fellow eyes of patients with unilateral PFV.[41,42] However, these angiographic findings are not specific to PFV and can overlap with other pediatric retinal vascular conditions, especially FEVR. A recent case report described a 13-month-old boy with FEVR presenting with a large unilateral fibrovascular stalk mimicking PFV and bilateral peripheral retinal avascularity.[44] Nonetheless, the vascular anomalies are less pronounced in PFV compared to FEVR, thus requiring a higher threshold to treat the avascular retina in PFV. The underlying mechanisms for the peripheral avascular retina and the abnormal vasculature in PFV remain unclear. Of note, the exact regulatory mechanisms responsible for PFV are still poorly understood. Pathogenic variants in the ATOH7, NDP, COX15, ZNF408, and FZD4 genes have been reported in bilateral PFV with different patterns of inheritance. It is possible these pathogenic variants that lead to the cellular defects associated with PFV may also be involved in the development of abnormal retinal vasculogenesis and angiogenesis.[43] Moreover, clinical features that can help differentiate PFV from FEVR and other retinal vascular conditions include microphthalmia, congenital eye abnormalities, absence of family history, laterality, and genetic testing.

Management of PFV includes observation or surgery, depending on visual potential and the location, features, and severity of the disease. Patient age and visual prognosis as dictated by the type of PFV, macular and optic nerve abnormalities, severity of microphthalmia, degree of amblyopia, presence of central lens opacification, and ability to follow up are factors to consider. Observation can be considered in nonprogressive disease without visual axis obscuration, as well as in advanced or chronic disease with poor visual potential characterized by older age at presentation, severe microphthalmia with axial length less than 15 mm, axial length asymmetry greater than 3.5 mm,[45] extensive anterior and posterior pole congenital anatomic involvement, closed funnel RD, retinal dysplasia, and severe optic hypoplasia with a normal contralateral eye. In these cases, surgery may not be beneficial and might increase the risk of postoperative complications such as RD with progressive phthisis or vitreous hemorrhage. Nevertheless, a surgical approach may be an option as without intervention, some eyes with PFV may eventually lose all vision due to RD or glaucoma (reported range from 27% to 70%).[39] Surgery may be indicated in cases of significant media opacities from retrolental membrane or cataract, shallowing of the anterior chamber, uncontrolled glaucoma, ocular hypotony from ciliary process traction, vitreous hemorrhage, and RD secondary to vitreoretinal traction. The goal is to sever the fibrovascular stalk, allow for axial lengthening, alleviate posterior pole and/or ciliary process traction, and prevent progression to tractional RD, glaucoma, phthisis, and vision loss.[46,47] When indicated, early intervention should be performed to maximize visual outcome and avoid glaucomatous complications.[48]

Norrie Disease

Norrie disease is the most severe phenotype in the spectrum of NDP-related retinopathies, which are genetically determined diseases inherited in an X-linked manner and caused by mutations in the Norrin cystine knot growth factor gene, also known as the NDP gene.[49] Warburg[50] extensively studied the characteristics of the disease and referred to it as congenital progressive oculo-acoustico-cerebral degeneration. The ocular presentation is invariably severe, with retinal degeneration occurring before or very shortly after birth and typically being bilateral.[51] Affected patients are male infants owing to its X-linked recessive inheritance. Patients often present with bilateral leukocoria and no light perception at birth or soon after birth.[52] Microphthalmia, shallow anterior chamber and synechiae, iris atrophy, cataract, and elongated ciliary processes are commonly observed. The classic fundus finding is a greyish-yellow, vascularized, immature retinal cell mass consisting of fibrovascular material behind the lens. These dysplastic retinal masses have been referred to as "pseudogliomas" due to their appearance.[52,53,54] The peripheral retina beyond the mass area is often totally avascular and usually shows some pigmentary changes. As the tissue dysplasia and retrolental fibrovascular proliferation progresses, traction on the retina worsens, eventually leading to phthisis bulbi and loss of the eye. Treatment strategies include early laser photocoagulation and vitrectomy to preserve the globe and, if possible, restore some vision, which is usually at the level of light perception.[52,53]

Norrie disease is an important consideration in the differential diagnosis of peripheral avascular retina. The disease phenotype may show considerable overlap with other NDP-related retinopathies, including X-linked FEVR, NDP-related advanced ROP, some cases of Coats' disease, and especially severe PFV types.[47,55,56,57] An important distinction of Norrie disease is its predisposition for bilateral and symmetric manifestations. Also, RD in Norrie disease is often hemorrhagic and vascular lesions are more prominent.[52] Another clue is the associated systemic findings. Cognitive-psychosocial disturbances have been reported at rates of up to 50%.[49,58] Sensorineural hearing loss, which usually begins in adolescence, was originally reported

in more than 30% of patients with Norrie disease.[50] However, more recent studies have suggested that 100% of patients will eventually suffer some degree of hearing loss.[58,59] Nevertheless, the retinal dysplasia that occurs in Norrie disease can be clinically indistinguishable from the presentations of trisomy, 13 Walker-Warburg syndrome, and severe forms of posterior PFV with funnel-shaped RD, and these must be distinguished through genetic testing.

Other Diseases Associated with Avascular Peripheral Retina

Protein C deficiency is a rare autosomal genetic disease caused by a deficiency of the natural anticoagulant protein C.[60] Protein C is dependent on vitamin K to inactivate specific plasma factors, and subsequently the conversion of prothrombin to thrombin.[60] The disease is caused by mutations in the Protein C, Inactivator of Coagulation Factors Va and VIIIa (PROC) gene and predisposes people to fatal thromboembolic attacks and various ophthalmic manifestations.[60] Common ocular findings reported in association with this disorder include anterior and posterior segment dysgenesis, leukocoria, microphthalmia, cataract, anomalous retinal vascular branching, amaurosis fugax, retinal hemorrhages, central retinal vein occlusion and artery occlusion, RD, peripheral retinal avascularity, and retinal neovascularization.[60,61] FA has revealed leakage at the junction of the vascular and avascular retina.[61] In homozygous individuals, ocular findings can present unilaterally or bilaterally at infancy,

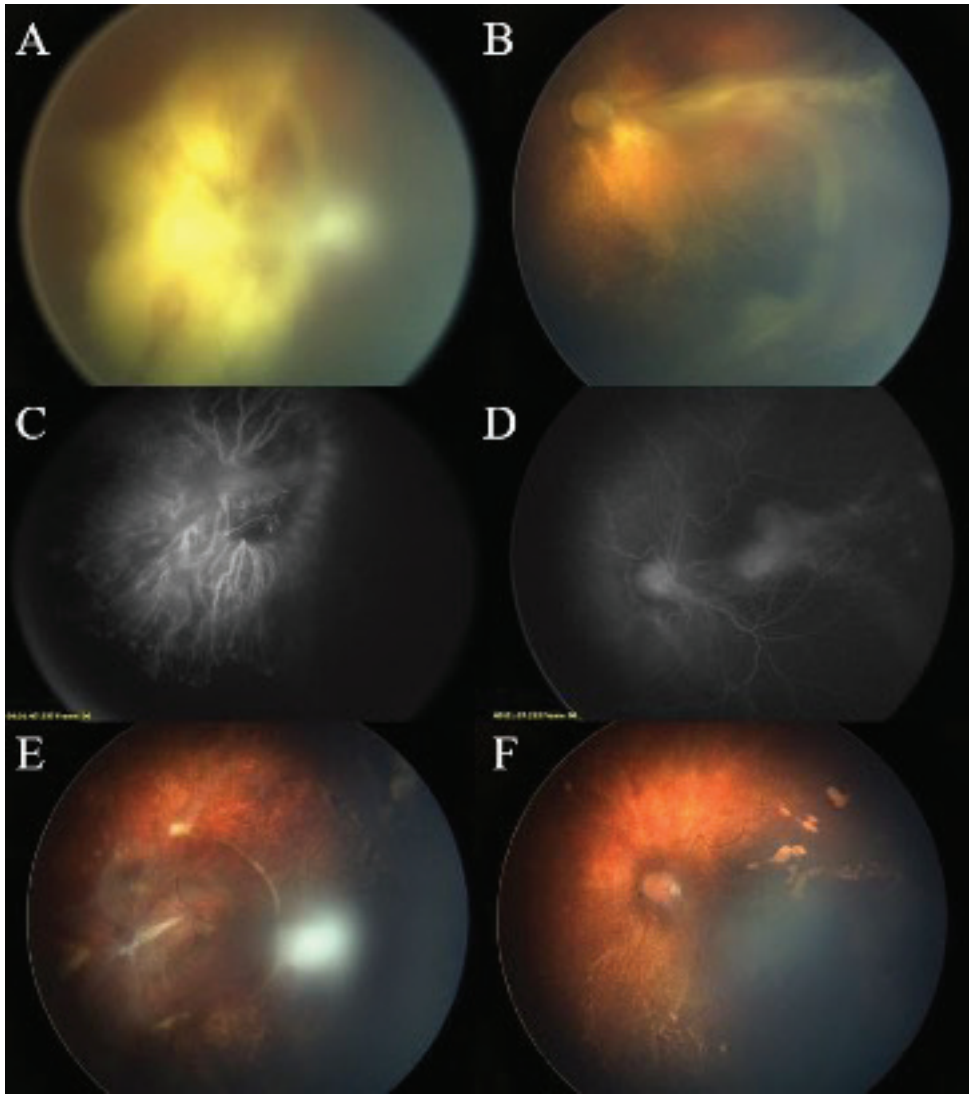

Figure 12. A 40-day-old girl with Adams-Oliver syndrome presenting with tractional retinal detachment in both eyes (A, B). Fundoscopic examination of the right eye revealed extensive fibrosis involving the optic nerve and the posterior pole (A). The left eye showed a radial falciform retinal fold extending from the macula to temporal periphery (B). Fluorescein angiography of the right eye showed dilated leaking vessels at the center and abrupt termination of the vascularization with bulb-shaped ends in the midperiphery (C). The left eye showed tortuous vessels and capillary nonperfusion areas. There was an abrupt termination of vascularization at the temporal macula and straightening of vessels, as well as posterior leakage (D). The patient underwent lens-sparing vitrectomy with membrane peeling and endolaser in both eyes, which resulted in retinal attachment (E, F). Genetic testing revealed homozygous mutation in the DOCK6 gene. (Courtesy of Dr. Şengül Özdek)

and the first ophthalmic manifestations include leukocoria and RDs.[60,61] Severe vital organ complications may be preventable if treated promptly. Therefore, early diagnosis is essential, as it can save the patient's life and vision. Treatment focuses on exogenous protein C administration and symptom management. Ophthalmic treatment includes laser photocoagulation for peripheral avascular retina and intravitreal anti-VEGF for neovascularization.[61,62]

Adams-Oliver syndrome (AOS) is a rare inherited disorder characterized by aplasia cutis and limb defects.[63] Patients may present with neurological, heart, skin, and eye involvement.[63] The disease is caused by mutations in ARHGAP31, DLL4, DOCK6, EOGT, NOTCH1, or RBPJ.[64] The symptoms depend on which gene is involved, and mutations in these genes are only found in approximately 50% of patients.[64] Mutations in the Rho GTPase Activating Protein 31 (ARHGAP31) or Dedicator of cytokinesis 6 (DOCK6) genes involve dysfunctional Cdc42/Rac1 signaling, a pathway that is critical for angiogenesis.[65] The abnormalities are thought to result from genetically decreased stability of the blood vessels, which affects perfusion and results in ischemia.[65] Ocular defects include microphthalmia, microcornea, congenital vasculopathy, ischemic-proliferative retinopathy, rubeosis iridis, peripheral avascular retina with gliosis, and intravitreal neovascularization.[63,66] Patients may present with limbs that are short or completely missing.[63,66] Ophthalmic examination and fundoscopy in children with AOS are warranted. In some patients, the retinal findings have been reported to mimic those of infants with ROP, FEVR, or Norrie disease (Figure 12).[66] Therefore, suspicion of AOS should prompt ophthalmologic evaluation, including FA, to detect and possibly treat the ischemic retinopathy. There is no cure for AOS. Treatment focuses on symptom management and includes skin grafting, surgery to repair skin lesions and skull abnormalities, prostheses for limb malformations, laser photocoagulation to the avascular retina to arrest the potential evolution from ischemia to neovascularization, and intravitreal anti-VEGF for neovascularization.[62,66]

Revesz syndrome, a rare type of dyskeratosis congenita, is an autosomal dominant disease.[67] It is caused by mutations in the TERF1 Interacting Nuclear Factor 2 (TINF2) gene, a component of the telomere-associated shelterin complex that protects against the shortening of telomeres.[68] When telomeres shorten, cellular apoptosis leads to abnormal growth of the skin, bone marrow, and retinal vasculature.[69] The disease is characterized by nail dystrophy, abnormal skin pigmentation, and oral leukoplakia.[67] The retinal findings are similar to those of exudative retinopathy and include peripheral avascularity of the retina, telangiectatic vessels, neovascularization, and tractional RDs.[67,68,69,70] Excess subretinal fluid, intracranial calcifications, and brain abnormalities that lead to postural instability are important features that distinguish Revesz syndrome from other types of dyskeratosis congenita.[67,68,71] The subretinal fluid is often diagnosed in small children because they present with leukocoria.[69] Depending on the degree of retinal disease, severe vision loss and blindness may occur.[70] Due to the extensive nature of Revesz syndrome, its diagnosis and management require a multidisciplinary team consisting primarily of pediatricians, ophthalmologists, hematologists, dermatologists, and neurologists.[67,69,70,71] The management consists of treating specific symptoms. Ocular management includes laser photocoagulation to the avascular retina, intravitreal anti-VEGF for neovascularization, and pars plana vitrectomy for RDs.[62,70] Life-long follow-up is required to monitor for systemic and ocular disease.[69,70]

Conclusions

To summarize, the most common cause of avascular peripheral retina is ROP. Although ophthalmoscopic features may overlap with other retinal vascular diseases, patients who develop ROP almost uniformly have prematurity and low birth weight. Furthermore, active neovascularization in late infancy, significant asymmetry, and family history of disease are not expected. In term babies or those with marked asymmetry, accompanying systemic findings, or a history of similar disease in close relatives, less common causes of similar clinical presentation should be considered in the differential diagnosis. Table 4 summarizes the key differentiating features of these causes.

Table 4. Key differentiating features of diseases presenting with avascular peripheral retina

ROP	• History of prematurity/low birth weight/neonatal oxygen therapy/no family history. • Bilateral, may be slightly asymmetric. • Typical features include avascular peripheral retina, straightening of the vascular arcades with macular and optic disc dragging, vascular proliferation in the form of ridge, tractional RD with concave configuration. • Exudates are not expected in the typical disease stages. • The course is usually progressive and follows distinct stages in a chronological order within the first few months of the life. • Spontaneous regression or cicatrization is common.
FEVR	• Mostly autosomal dominant inheritance. • Family history is positive only in half of the cases. Examination of asymptomatic family members is helpful. • Bilateral and often asymmetric. • Typical features include avascular temporal peripheral retina, straightening of the arcade vessels with macular and optic disc dragging (ROP-like appearance but slower and with unpredictable progression), with or without retinal folds (falciform retinal folds extending mostly to the temporal periphery to the back of the lens). • Straightening of the vessels is typical even in the absence of any visible traction. • Pre-, intra-, or subretinal exudation is common. • Association of posterior hyaloid yellow deposits is very unique for FEVR. • Arrested vascularization does not show any forward movement into the avascular retina at any time point. • RD is typically tractional, but may subsequently develop exudative and/or rhegmatogenous components. • FA is essential for accurate diagnosis and demonstrates peripheral nonperfusion, vessel straightening and anastomoses, telangiectasias, and neovascularization. There is usually irregular vascular sprouting beyond the transition zone, as opposed to the more homogenous and regular vascularization pattern at the ridge of ROP eyes. The foveal avascular zone is typically very small. • Periods of disease inactivity and recurrences are typical throughout life.
Coats disease	• Sporadic, unilateral (90%), male (80%). • Pupillary reflex is more yellow than white (xanthocoria). • Typical features include peripheral retinal telangiectasias, light bulb-shaped microaneurysms, abundant intra- and subretinal lipid exudates, subfoveal nodule, subretinal fibrosis, peripheral capillary non-perfusion areas on FA. • RD is typically exudative, with bullous elevation in advanced cases. • Neovascular glaucoma with rubeosis iridis results in painful red eye in end-stage disease.
IP	• X-linked dominant inheritance, seen mainly in females (lethal in males), mothers may have the same disease. • Multisystemic disease – Neonatal skin lesions are typical (often transient and resolve spontaneously); dental hypoplasia, alopecia, and CNS involvement may be seen. • Bilateral and often markedly asymmetric. • Typical features include avascular peripheral retina leading to neovascularization, retinal hemorrhages, RD, and eventually retrolental fibrovascular mass. • RD can be tractional or exudative. • A blunted foveal pit, absence of normal parafoveal vasculature, and optic atrophy are commonly seen.
PFV	• Mostly sporadic, unilateral (90%). • Microphthalmos, microcornea. • Typical features include prominent iris vessels, elongated ciliary processes, retrolental fibrovascular membrane, hyaloid stalk emanating from the disc (often with retinal folds and RD). • RD is tractional and often tent-shaped, with attachment of the peripheral retina (seldom funnel-shaped RD) fibrotic attachment to the back of the lens is located more on the nasal side. • Retrolental vessels are typically oriented in a radial pattern, and may anastomose with other vasculature in the iris, ciliary body, or circumlental space.
Norrie disease	• Diagnosis at birth or within weeks of birth. • Bilateral, symmetric, X-linked recessive inheritance, male. • Mostly associated with progressive hearing loss and mental retardation. • Microphthalmos, iris atrophy and synechiae, shallow anterior chamber. • Severely dysplastic retina (often with severe subretinal hemorrhage and lipid). • RD is often hemorrhagic and vascular lesions more prominent than PFV. • Confirmation by molecular genetic testing.

ROP: Retinopathy of prematurity, RD: Retinal detachment, TVL: Tunica vasculosa lentis, PFV: Persistent fetal vasculature, FEVR: Familial exudative vitreoretinopathy, AD: Autosomal dominant, FA: Fluorescein angiography, IP: Incontinentia pigmenti, CNS: Central nervous system

Ethics

Peer-review: Externally and internally peer revieved.

Authorship Contributions

Concept: Ş.Ö., Design: Ş.Ö., E.Ö.Z., Data Collection or Processing: Ş.Ö., E.Ö.Z., Analysis or Interpretation: Ş.Ö., E.Ö.Z., Literature Search: Ş.Ö., E.Ö.Z., C.R.B., S.H., N.A.P., A.M.B., A.L-C., H.A., S.K., F.M., S.J., D.L., S.A., Writing: Ş.Ö., E.Ö.Z., C.R.B., S.H., N.A.P., A.M.B., A.L-C., H.A., S.K., F.M., S.J., D.L., S.A.

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