Review Article

Rare pediatric retinal diseases: A review

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Rare pediatric retinal disorders present significant challenges in diagnosis and management due to their limited prevalence and diverse clinical manifestations. This paper provides a comprehensive review of select rare retinal disorders affecting the pediatric population, focussing a brief on their epidemiology, clinical characteristics, diagnostic modalities, and therapeutic interventions. Through a systematic examination of current literature and clinical case studies, this review aims to elucidate the distinct features and challenges associated with each disorder. Despite the rarity of these conditions, their impact on visual function and quality of life necessitates heightened awareness among clinicians and researchers to facilitate timely diagnosis, appropriate management, and improved outcomes for affected children as their visual systems are still developing. Furthermore, advancements in diagnostic modalities such as fundus fluorescein angiography, optical coherence tomography, electroretinography, and genetic testing are examined for their role in enhancing our understanding of rare pediatric retinal disorders and facilitating early intervention strategies. The literature selection for this article was conducted through PubMed, Google Scholar, and the Cochrane Library databases. A thorough systematic search was carried out for the concerned diseases. Relevant review articles, original research studies, case series, and reports were examined. Additionally, references from these sources were reviewed and included if they provided pertinent information on the topic. The search was not restricted by publication date.

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Pediatric retina is a unique subspeciality within the field of retina. Although still in infancy, it is gaining in importance because the retina and part of the central nervous system continue to develop during the early years of life and retinal diseases unique to children often need unique skill sets to diagnose and treat. Beyond medical or surgical care, managing these conditions demands a holistic approach. "Retinal plasticity" allows improved visual development if diseases are detected and treated early, influencing milestones and enhancing long-term outcomes, positively impacting the rest of the child's life.

Common pediatric retinal conditions, such as retinopathy of prematurity (ROP), are now better understood, with revised national and international management guidelines.[1] However, rarer conditions pose challenges due to potential misdiagnosis, inadequate evaluation, and improper or delayed treatment.

This article focuses on these less common pediatric retinal diseases, including vascular, congenital, inherited, inflammatory, and traumatic diseases and tumors. It simplifies existing literature to serve as a clinical guide for specialists. Literature was selected through systematic searches of PubMed and Google Scholar. Relevant studies, including reviews, research, case series, and reports, along with their references, were analyzed without date restrictions.

Coats Disease

First described by George Coats in 1908, it is a rare, idiopathic pediatric retinal vascular disorder predominantly affecting males in the first decade. It is unilateral in over 95% of cases and defined by retinal telangiectasias in small to medium vessels, leading to extensive exudation without underlying vitreoretinal traction [Fig. 1a]. Subtle changes in contralateral eye have also been reported.[2,3]

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The pathophysiology involves blood-retinal barrier dysfunction, causing plasma protein leakage, vessel wall thickening, and abnormal pericyte activity, ultimately leading to aneurysm formation and exudation.[4] Somatic, postzygotic NDP mutations in retinal tissue are implicated, with overlaps with conditions like Norrie disease and familial exudative vitreoretinopathy.[5] A case report noted NDP-related Coats disease in a woman whose son had the Norrie disease ocular phenotype.[6]

Shields introduced a classification system for Coats' disease in 2001, updated by Daruich *et al*.[7] in 2017:

- Stage 1: Retinal telangiectasias.
- Stage 2: Telangiectasias with extrafoveal (2A) or subfoveal (2B) exudation (2B1: without subfoveal nodule; 2B2: with subfoveal nodule).
- Stage 3: Subtotal (3A) or total (3B) exudative retinal detachment (RD).
- Stage 4: Total detachment with glaucoma.
- Stage 5: Advanced end-stage disease.[7]

Multimodal imaging including OCT angiography (OCTa) aids in diagnosis and management.[5,8] Fluorescein angiography (FFA) reveals peripheral nonperfusion, vascular leakage, and aneurysms [Fig. 1b]. Subtle angiographic abnormalities have been reported in fellow eyes [Fig. 1c]. OCT shows intraretinal or subretinal fluid, exudates in the outer plexiform layer, fibrotic nodules, and macular scar. OCTa demonstrates anomalous retinal anastomoses and foveal vascular loops, with subtle abnormalities in fellow eyes.[9]

Coats Plus syndrome (Labrune syndrome) is rare life-threatening disorder linked to CTC1 mutations, characterized by bilateral Coats disease, along with systemic features like cerebroretinal microangiopathy with calcifications and cysts, leukodystrophy, growth retardation, and gastrointestinal bleeding.[10]

Retinoblastoma is a common mimicker and must be excluded, particularly in advanced cases with xanthocoria or strabismus. In retinoblastoma, presentation typically includes white leukocoria, along wjth positive family history, while yellowish mass hue and presence of dilated telangiectatic vessels characterize Coats' disease. Ultrasonography and computed tomography can be useful in detection of calcification in retinoblastoma which is randomly distributed within the mass, while Coats generally follows a curvilinear pattern. MRI shows characteristic T1 hyperintensity and T2 hypointensity in retinoblastoma, while Coats' disease lacks a mass and shows hyperintense exudates on T1 and T2.[11]

Management includes laser photocoagulation, cryotherapy, anti-VEGF injections, intravitreal steroids, and surgical intervention depending on the stage:

- Stages 1, 2: Laser or cryotherapy.
- Stage 3: Laser or cryotherapy; external drainage for RD.
- Stage 4: External drainage or vitreoretinal surgery.
- Stage 5: Observation if asymptomatic; enucleation for painful eyes along with adjuvant intravitreal steroid or anti-VEGF injections.[12]

FA-guided laser ensures optimal outcomes. Visual prognosis depends on the presenting disease stage and subfoveal scarring.[4,7]

Familial Exudative Vitreoretinopathy (FEVR)

FEVR is a retinal vascular developmental disorder, mostly inherited autosomal dominantly; however, autosomal recessive or X-linked recessive patterns exist. Family history is positive in less than 50% cases. Expressivity may be asymmetric and highly variable. Mutations in genes such as LRP5, FZD4, TSPAN12, NDP, ZNF408, and KIF11 disrupt the Wnt/Norrin signaling pathway, which is crucial for normal retinal vascularization, contributing to the disease's pathogenesis.[13,14] The age at diagnosis is usually 6–7 years. The peripheral retinal avascular zone, arteriovenous or venous-venous shunt formation, loops, vitreous adherence, retinal folds, temporal ectopia of the macula, retinal breaks, rhegmatogenous, and exudative RD are the most common clinical features. In 1998, Pendergast and Trese described a 5-stage FEVR classification scheme, which has been guiding treatment and follow-up since then [Fig. 2].[15] FA is the key to diagnosis [Fig. 3] with milder forms in asymptomatic patients detected only with FA.[16] Asymptomatic patients are typically identified during routine adolescent exams for myopia or family screenings or when examining the fellow eye of a patient with RD or unexplained neovascular glaucoma.

In 2014, Kashani *et al*.[17] proposed a revised clinical staging system using wide-field angiography, categorizing the condition into distinct stages based on specific clinical features.

- Stage 1 – avascular periphery or anomalous intraretinal vascularization,
  Stage 1A without exudate or leakage, and Stage 1B with exudate or leakage.
- Stage 2 – avascular retina with extraretinal neovascularization,
  Stage 2A, without exudate or leakage, and Stage 2B, with exudate or leakage.
- Stage 3 – extramacular tractional RD
  Stage 3A without exudate or leakage, and Stage 3B with exudate or leakage.
- Stage 4 – subtotal tractional RD involving macula,
  Stage 4A without exudate or leakage, and Stage 4B with exudate or leakage.
- Stage 5 – total RD,
  Stage 5A with an open funnel and Stage 5B with a closed funnel.

Differential diagnosis includes diseases with peripheral avascular retina like ROP, Norrie disease, incontinentia pigmenti (IP), diseases with exudation like Coats' disease, diseases causing TRD like PFV, and diseases causing leukocoria like retinoblastoma.[18]

Recently, the term ROPER was considered where FEVR-like features were noted in the presence of prematurity and especially critical in cases with findings unusual for ROP. These patients may manifest a more unpredictable and long-term course than those with ROP. Genetic testing is key to confirm diagnosis.[19,20]

Treatment is usually conservative with laser photocoagulation (LPC) in early phases and vitreoretinal surgery in late phases with ERM and TRD [Fig. 2]. Rhegmatogenous RD is common in these eyes where combined scleral buckling and vitrectomy are needed. Anti-VEGF injections may help decrease the exudation when it persists despite other treatments.

Incontinentia Pigmenti (IP)

IP, commonly called Bloch-Sulzberger syndrome, was first introduced by Garrod in 1906. It is rare X-linked dominantly inherited syndrome predominantly affecting

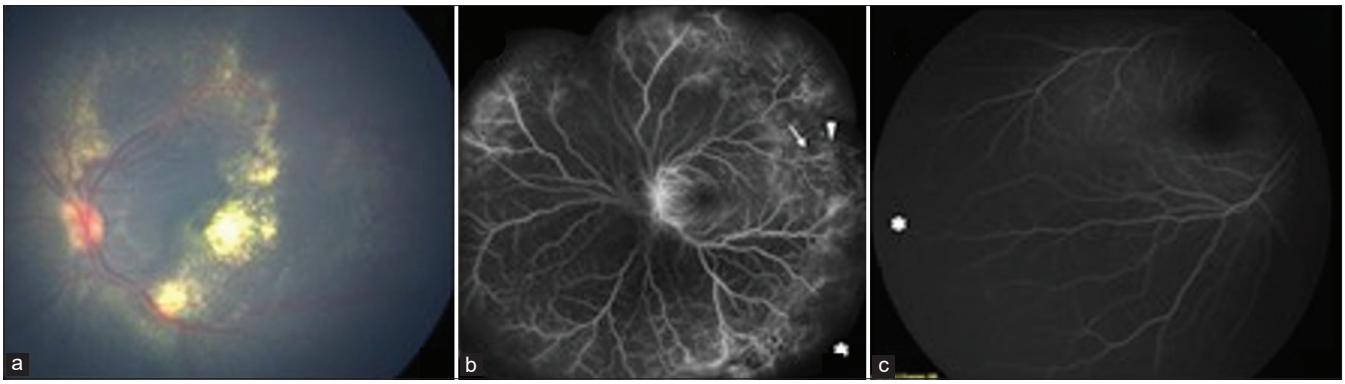

Figure 1: (a) Fundus photography (Optos®, UK) shows subretinal exudates involving macula, suggestive of Stage 2B Coats' disease. (b) Fluorescein angiography shows peripheral nonperfusion (asterisk), retinal vascular leakage, and vascular telangiectasias (white arrowhead) with focal aneurysms (white arrow) in the periphery. (c) The contralateral eye shows peripheral nonperfusion areas (asterisk)

females and is potentially lethal to male fetuses. It is primarily a dermatological condition in which 36.5% have been reported with ocular pathology and 60% to 90% of those have retinal issues. Pathologic changes in the central nervous system, teeth, and hair are also common. It presents more commonly as a sporadic disease, and less than 25% are said to be familial. Males who are living with IP are believed to have Klinefelter syndrome with an extra X chromosome.[21]

The mutation in IKBKG gene, which encodes the NEMO protein involved in inflammation regulation, is responsible.[22] Inflammation is believed to be a common pathway, contributing to vaso-occlusion and ischemia, which in turn leads to the manifestation of multiple signs, especially in the skin, eyes, and nervous system.

IP is characterized by a variety of dermatological, ophthalmological, neurological, and other systemic abnormalities.

a. Dermatological – observed in nearly all cases, which appear at birth or in the first few months of life and progress through four stages, often continuing into adulthood:
   - Stage 1: Vesicular stage – fluid-filled blisters seen around birth in approximately 90% patients.
   - Stage 2: Verrucous stage – wart-like verrucous papules and keratotic patches in the first few weeks of life in 70% cases.
   - Stage 3: Hyperpigmented stage – swirling or whirling macular patches of hyperpigmentation; usually fades by early adulthood in 98% cases, [Fig. 4a] and
   - Stage 4: Hypopigmented stage – whorl-like or streak-like patchy areas of hypopigmentation, present by early adulthood; occurs in 28% patients.[23]
b. Ophthalmic – About 36.5%–77% of IP patients experience ocular involvement, with a significant portion of these (56%–90%) facing vision-threatening complications.[24] Retinal abnormalities typically manifest within the first year of life and include various peripheral and macular changes. A hallmark feature is an avascular peripheral retina resembling ROP, where neovascularization at the vascular–avascular junction can lead to hemorrhages and RD [Fig. 4b]. Arborized and anastomotic vessels are often observed at the equator, along with fibroglial tissue indicative of tractional forces or regressed neovascularization. Peripheral retinal pigmentary mottling, caused by ischemic damage to the retinal pigment epithelium, is also common. Less frequent macular changes may involve a blunted foveal pit, absent parafoveal vascular pattern, foveal hypoplasia-like appearance, intraretinal microvascular anomalies, and central retinal artery occlusion with associated sequelae.[25] Nonretinal ocular findings include strabismus and nystagmus (17% to 18%), optic atrophy (5% to 17%), cataracts, uveitis, conjunctival pigmentation, corneal epithelial and stromal keratitis, iris hypoplasia, and cortical vision impairment.[21]
c. Neurological – occur in approximately 30% of cases and include convulsive disorders, spastic paralysis, motor delays, cortical vision impairment, and intellectual disability.
d. Others – Other signs include dental abnormalities, alopecia, nail abnormalities, and breast abnormalities.

Diagnosis is primarily based on clinical presentation [Table 1], with characteristic dermatological stages. Genetic testing to detect mutation, along with eosinophilia and skin biopsies, can support diagnosis.[26] FA is a key diagnostic tool for identifying retinal abnormalities such as macular ischemia, capillary nonperfusion, leakage, and neovascularization, which may not be immediately visible on routine examination [Fig. 4d]. The differential diagnosis includes ROP, FEVR, Eales retinopathy, sickle cell retinopathy, Norries disease, and shaken baby syndrome.

IP currently has no cure, with treatment focused on symptomatic management and supportive dermatological care, as the disease stages often resolve naturally by adulthood. Ocular management often involves treatments similar to ROP, such as laser therapy [Fig. 4c] or cryotherapy, with occasional use of anti-VEGF therapy, though outcomes vary; despite these measures, up to 10% of patients may still develop complications like vitreous hemorrhage, RD, or fibrosis.[27] Neurological symptoms require symptomatic management, including interventions for developmental delays, seizures, or other neurological complications.

A dilated retinal examination is recommended at birth, monthly for the first 4 months, every 3 months for a year, and twice yearly until age 3. However, if no retinal signs are present by 1 year, they are unlikely to develop later, though rare cases of RD have been reported even after age 40.[21]

Persistent Fetal Vasculature

Persistent fetal vasculature (PFV) is a congenital developmental anomaly that arises from the failure of regression of primary vitreous and hyaloid vasculature during fetal development.[28] PFV exhibits a spectrum of clinical manifestations determined by the extent of involution of hyaloid and tunica vasculosa lentis (TVL). It typically presents as a unilateral condition in full-term infants without systemic associations.

PFV is classified into anterior and posterior subtypes based on the predominant structures involved. Anterior PFV commonly presents with leukocoria in early infancy due to a retrolental fibrovascular membrane, with or without cataract. The retrolental membrane, arising from persistent posterior TVL, varies in size and configuration. Characteristic features may include elongated and centrally dragged ciliary processes along with peripheral retina and microphthalmia though subtle in some cases. Other abnormalities such as persistent pupillary membranes and radial iris vessels with hairpin loops may also be seen. These may cause pupil deformation, including corectopia, small sphincter notches, or congenital ectropion uveae. Hyphema may occur in association with fine vessels of the persistent anterior TVL. In rare cases, severe zonular maldevelopment due to persistent iridohyaloid vessels can result in congenital lens subluxation.

A shallow anterior chamber may result from anteriorly displaced or swollen lenses, extensive posterior synechiae, and peripheral anterior synechiae, potentially progressing to secondary angle-closure glaucoma. Although microphthalmia is a common feature, eyes with glaucoma may appear normal in size or buphthalmic. In purely anterior cases, the posterior pole, optic nerve, and macula may be unaffected, though a thin hyaloid stalk typically extends from the optic nerve head to vitreous without any evidence of retinal fold.[29]

Posterior PFV is characterized by an epiretinal or vitreous membrane and a stalk originating from the optic nerve, retinal fold, or both. The stalk may present as a columnar structure extending between the lens and optic nerve or posterior retina or as an inverted Y-shape with additional attachments to the disc and retinal surface. Retinal traction caused by the stalk leads to tractional RD, commonly in a tent-like configuration and less frequently as a closed-funnel detachment. The patient can present with vitreous hemorrhage. The optic nerve and macula can be hypoplastic or dysplastic because of the tractional component. The lens is often clear in isolated posterior PFV.

Combined or Mixed PFV: Most cases exhibit features of both anterior and posterior subtypes. [Fig. 5]. PFV can also co-occur with other ocular abnormalities, such as Peter's anomaly, microcornea, uveal coloboma, and morning glory disc anomaly. Diagnosis is generally by B-scan ultrasonography in cases with limited or absent fundus views. It helps to visualize the vitreous stalk extending from the posterior pole to the lens and provides additional information about axial length, lens status, and RD.

Differential diagnoses include other conditions associated with leukocoria; mainly, retinoblastoma should be excluded. It is characterised by normal-sized globe and solid lesion with calcifications visible on B-scan and computed tomography (CT). Other causes of leukocoria like congenital cataracts, FEVR, Coats' disease, ROP, ocular toxocariasis, and, more rarely, uveitis and IP should also be considered [Table 2]. Severe posterior PFV with bilateral closed-funnel RD should be differentiated from Norries disease, an incurable condition in male infants characterized by hemorrhagic and pronounced vascular lesions.

Congenital X-linked Retinoschisis (CXRS)

It is an inherited retinal degenerative disease affecting 1 in 5000–25,000 live births globally. First described by Haas in 1898, it is bilateral, although sometimes asymmetric, and is the leading cause of juvenile macular degeneration in males due to its X-linked inheritance. Females are typically asymptomatic carriers with normal retinal findings, though rare heterozygotes may show clinical signs.[30] CXRS results from mutations in the retinoschisin1 (RS1) gene on chromosome Xp22.1, disrupting the retinoschisin protein critical for photoreceptor and bipolar cell structural and functional integrity.

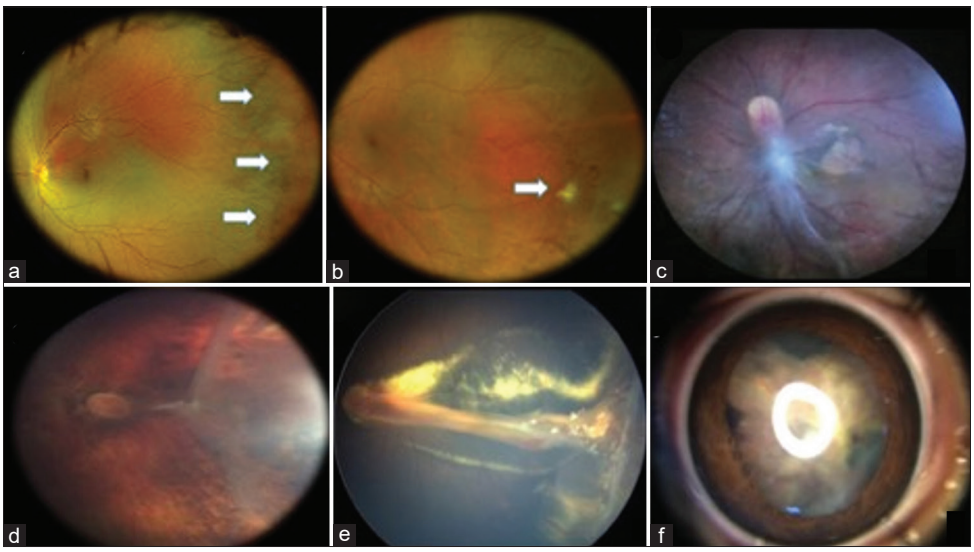

Figure 2: Fundus in FEVR (a) Stage 1 with temporal peripheral avascular retina (PAR) (arrows), (b) Stage 2B: Extraretinal neovascularization (NV) with exudation (arrow), (c) Stage 3A: Subtotal tractional retinal detachment (TRD) sparing macula with macular atrophy, (d) Stage 4A: Subtotal TRD involving macula (e) Stage 4B: Subtotal TRD causing macular fold with exudation, (f) Stage 5: Total TRD

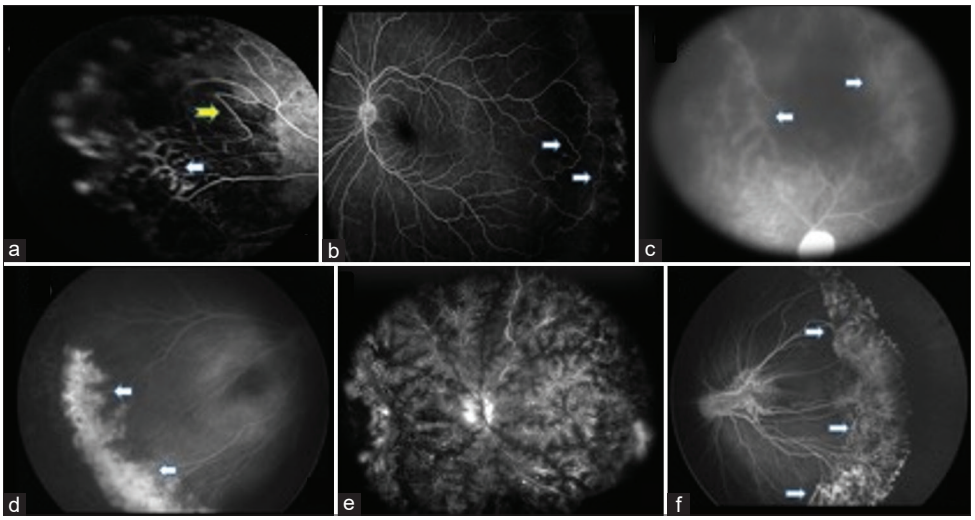

Figure 3: FA in FEVR (a) Abnormal vascular anastomosis and telangiectatic vessels (arrows), (b) Venous shunt vessels, (c) LAPPEL (late phase angiographic posterior and peripheral vascular leakage), (d) NVs at vascular-avascular junction causing leakage, (e) Diffuse leakage. (f) Macular distortion, narrowing of arcades secondary to ERM, PAR, and NVs causing leakage

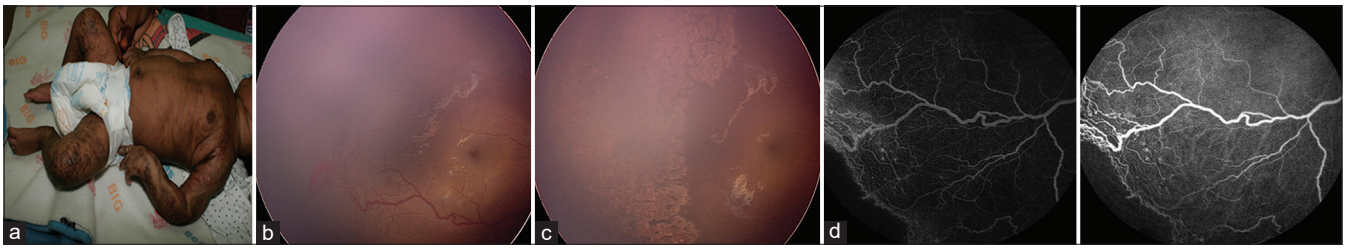

Figure 4: (a) Verrucous stage of IP. (b) Fundus of IP infant showing PAR with NV and abnormal telangiectatic vessels (c) Fundus post laser treatment showing healed laser scars with NV regression in the same patient. (d) FA and ICGA images showing PAR and abnormal anastomotic vessels

Table 1: Modified Diagnostic Criteria for IP by Minić[23]

Family history	Parameters	Criteria
If affected relative exists	(1) History or evidence of typical skin lesions; (2) pale, hairless, atrophic linear skin streaks; (3) dental anomalies; (4) alopecia, wiry coarse hair; (5) retinal disease; or (6) multiple miscarriages of male fetuses	Any one of the parameters
No affected relative/no genetic data available	Major criteria: Skin lesions, occurring in stages from infancy to adulthood: • Erythematous lesions followed by vesicles anywhere on the body, sparing the face, usually in a linear distribution • Hyperpigmented streaks and whorls respecting lines of Blaschko, occurring mainly on the trunk and sparing the face, fading in adolescence • Pale, hairless, atrophic linear streaks or patches Minor criteria: • Hypodontia or anodontia, microdontia, abnormally • shaped teeth • Alopecia, wiry coarse hair • Mild nail ridging or pitting, hypertrophied, curved nails Minic's expansion: • Retinal abnormalities central nervous system abnormalities, extra-retinal ocular anomalies, multiple miscarriages of male fetuses, typical skin histologic findings, dental abnormalities, hair and nail abnormalities, nipple and breast abnormalities, palate anomalies, and IP pathohistological findings.	One major criteria and two or more minor criteria are needed for diagnosis (*Minor criteria were expanded by Minic*)

Diagnosis typically occurs in boys aged 5–10 years following eye exam failure or academic difficulties, though severe cases may present in infancy with nystagmus or strabismus. Severity varies, with visual acuity ranging from mild (20/60–20/120) to profound blindness.[31] The hallmark feature is bilateral macular layers splitting (schisis) in the outer plexiform layer

showing a spoke-wheel pattern, visible on OCT [Fig. 6]. Over time, these microcysts flatten. Peripheral schisis, predominantly in the inferotemporal retina, occurs in about 50% of cases and may progress toward central retina or flatten leaving retinal pigment epithelium abnormalities or scars. Additional findings include optic nerve pallor, dragged disc, optic nerve head neovascularization, macular hole and dragging, diffuse white retinal pigments resembling fundus albipunctatus, perivascular sheathing, and dendriform vessels in the peripheral retina.[31] CXRS patients may present an unusually whitish fundus appearance when the dark-adapted retina is exposed to light, known as Mizuo phenomenon due to abnormal potassium processing in the retina. This phenomenon disappears after vitrectomy after removing the vitreoretinal interface.[32] Vitreous veils and inner retinal vessels in vitreous may be observed as a result of the separation of the inner wall of a peripheral schitic cavities and enlargement of inner wall holes.[30,31] Vessels bridging these schitic cavities are highly susceptible to hemorrhage, with vitreous hemorrhage serving as a presenting feature. The most common vision threatening complications include vitreous hemorrhage (4–40%) and RD (5–22%).[31]

OCT has improved diagnosis, revealing subtle findings and assessing disease extent. Prior to OCT, the term "lamellar schisis" described schisis present in clinically normal appearing retina.[33]

Prenner's classification system uses clinical and OCT findings:

- Type 1: Foveal schisis only.
- Type 2: Foveal schisis with lamellar macular schisis.
- Type 3: Foveal schisis plus peripheral schisis.
- Type 4: Combined foveal and peripheral schisis.[34]

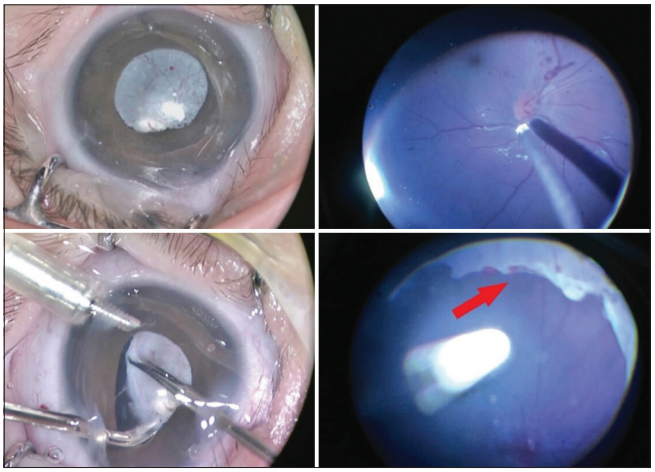

Figure 5: Anterior PFV case in which the peripheral retina was continuous with the anterior fibrovascular tissue. Cutting the fibrovascular tissue resulted in an iatrogenic retinotomy (arrow). In this case, posterior hyaloid was separated, 360-degree laser photocoagulation and silicone tamponade were applied

Table 2: Key differentiating features of persistent fetal vasculature from other simulating disorders

From ÖzdemirZeydanlıE, Özdek Ş. Persistent Fetal Vasculature Syndrome. In: Özdek Ş, Berrocal A, Spandau U, editors. Pediatric Vitreoretinal Surgery. Cham: Springer; 2023.

Retinoblastoma	• Diagnosis typically occurs within months to years of birth (average: 1.5 years). • Unilateral or bilateral • Exudative retinal detachment with subretinal fluid and seeds. • Calcifications seen on ultrasonography and CT. • FFA reveals dilated, tortuous vessels feeding the hyperfluorescent tumor.
Norrie disease	• Dx within weeks of birth • Bilateral and symmetric • Microphthalmos with severely dysplastic retina associated with severe subretinal hemorrhage and lipids • Mostly associated with progressive hearing loss and mental retardation
ROP (Stage 4 or 5)	• Dx at birth or within weeks of birth • History of prematurity/low birth weight/oxygen therapy • Bilateral, asymmetric • Tunica vasculosa lentis may be seen; • Straightening of the vascular arcades with macular and optic disc dragging is typical • Tractional and exudative RD noted
FEVR	• Dx within years of birth (average: 6 years) • Bilateral and often asymmetric • Peripheral avascular retina, straightening of the vascular arcades with macular and optic disc dragging with exudation • RD is tractional or exudative • FA confirms the diagnosis.
Coats' disease	• Dx at 5–10 y of age • Unilateral (90%), male (80%), • Subretinal lipid exudates with telangiectatic retinal blood vessels • RD is typically exudative
Toxocariasis	• Dx at childhood (usually >3 years) • History of exposure to puppies, eating dirt • Unilateral • Peripheral or posterior retinal granuloma with endophthalmitis

Ling *et al*.,[33] using handheld OCT to image infants as young as 7 months, demonstrated the ability to assess and monitor the spectrum of retinal layer involvement and response to medical and surgical interventions. Electroretinogram (ERG) typically shows a reduced b-wave amplitude with a normal a-wave, reflecting delayed signal conduction through schitic cavities.[35]

FFA is not diagnostic but can differentiate schisis cavities from cystoid macular edema. Peripheral nonperfusion and leakage from abnormal capillaries may be noted. Molecular diagnosis of CXRS may be established by DNA sequencing of the XLRS1 gene.

Oral and topical carbonic anhydrase inhibitors (CAIs), such as dorzolamide, have shown efficacy in reducing macular cystic cavities and improving vision in children and adults.[36] The mechanism involves enhanced fluid transport by retinal pigment epithelium toward choroid. However, the long-term safety of systemic CAIs in children is uncertain.

Rhegmatogenous or tractional RD can occur in CXRS, often involving both inner and outer retinal breaks. Detachment around an inner break may remain stable and can be observed before intervention. Scleral buckling is preferred for accessible outer breaks due to its less invasive nature, especially in infants where hyaloid peeling is challenging. Vitrectomy is reserved for persistent vitreous hemorrhage or failed buckling. Enzymatic degradation of the vitreoretinal junction may aid in relieving traction.[31]

Inherited Retinal Degenerations/Diseases (IRDs)

IRDs are traditionally described by the cells they primarily affect – rods/cones. IRDs are genetically and phenotypically highly heterogeneous. The important overlap of clinical features with known genes has been documentated.[37] The data are constantly updated in the referenced electronic databases [Table 3]. Especially in infants and young children, the disease may be progressive and keep evolving [Fig. 7]. Furthermore, diagnosis is difficult due to nystagmus, usually noticed around the age of 6 to 10 weeks.[38] Retinal imaging, phenotypic variations, genetic and allelic heterogeneity, intrafamilial variability, and disease progression from childhood into young adulthood have been recently published.[37] Multimodal investigations like electrophysiology, OCT, and FAF can identify specific phenotypes, though nystagmus might hinder image quality.

Managing a child with IRD involves ocular and genetic investigations [Table 4].[39] Age-appropriate methods are crucial for reliable results. Challenges include subtle fundoscopic signs, limited compliance in children, examiner expertise, and difficulty with functional tests. Handheld and portable imaging devices can be invaluable in these cases. Additionally, suspected IRD cases require a comprehensive neuropediatric evaluation.

Genetic testing is essential for accurate diagnosis and genotype–phenotype correlations. It helps in patient counseling

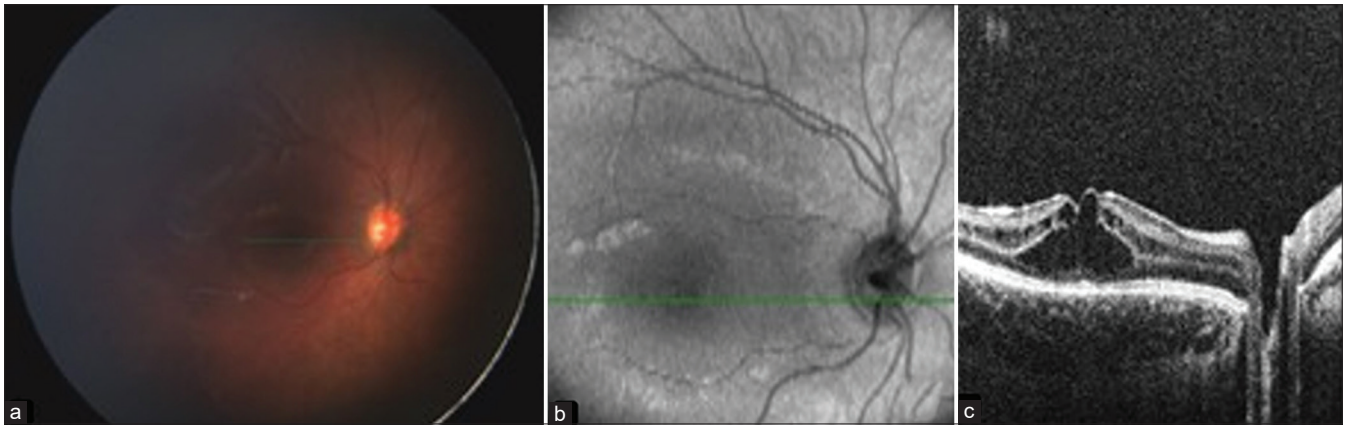

Figure 6: RetCam fundus photo and handheld spectral domain OCT images of a 5-year-old male with congenital x-linked retinoschisis showing (a) Blunted foveal reflex (b, c) Central macular schisis involving the inner nuclear and outer plexiform layers and disruption of the ellipsoid zone at the fovea

Table 3: The spectrum of inherited retinal degenerations (IRD) associated with mutations in genes of the visual cascade and the retinol cycle (according to OMIM (http://omim.org/), RetNet (https://sph.uth.edu/retnet/ and GeneBank (https://www.ncbi.nlm.nih.gov/gene/), updated 02/2020 modified after: Inherited retinal degenerations in the pediatric population. B. Lorenz and MN Preising, in A quick guide to Pediatric Retina. Ed Wei-Chi Wu, Wai-Ching Lam. Springer 2021

Function	Disease entities	Genes
Visual cascade	ACHM	*CNGA3*, ***CNGB3***, *GNAT2*, *PDE6C*, *PDE6H*
	Blue Cone Monochromacy (BCM)	*OPN1LW*, *OPN1MW*
	CRD	*GUCA1A*, ***GUCY2D***[&], *PDE6A*, *RD3*[&], *OPN1SW*
	RP/RCD	*CNGA1*, *CNGB1*, *GRK1*, *GUCA1B*, *PDE6B*[$], *PDE6G*, *PRKCG*, *R9AP*, *RGS9AP*, *RGS9*, *RGS9BP*, ***RHO***[$], *SAG*
	CSNB	*GNAT1*, *GNB3*
Retinol cycle	RP/RCD	*RDH11*, *RGR*, *RBP3*, *LRAT*, ***RPE65***[&], *RLBP1*[$]
	CRD	*RBP4*, ***ABCA4***[$], *RDH12*[&], *RDH5*[$]

Bold: frequent: sequence variations underlying overlapping phenotypes from allelic heterogeneity. [$]with Retinitis pigmentosa (RP/RCD), [$]with congenital stationary night blindness (CSNB), [&]predominant early-onset phenotypes

about prognosis, recurrence, and clinical trial recruitment. To accelerate diagnosis and research, several global consortia have been established with an Asian Eye Genetics Consortium founded in 2016. Recently, the Israel Inherited Retinal Disease Consortium (IIRDC) reported a nationwide prevalence of IRD genotypes as 1:1043 in 9396 patients.[40] An overview on major gene therapy trials in ophthalmology using AAV vectors is given in Table 5. The permanently updated list of clinical trials is best searched in the electronic database https://clinicaltrials.gov/.

Genetic ophthalmology and pediatric ophthalmogenetics are rapidly evolving fields. An overview by Drack *et al*.[41] highlights current diagnostic tests, the roles of pediatric ophthalmologists and retinal specialists in identifying suitable patients, and the benefits and limitations of genetic testing. Thus, genetic testing improves diagnostic accuracy, while phenotypic correlations aid in patient counseling, prognosis, and guiding emerging gene-based therapies.

Focus on RPE65-mutation associated IRD

Biallelic RPE65-mutation-associated IRD remains the only inherited retinal degeneration with approved gene therapy, though updates in other conditions are ongoing.[38,42] Biallelic RPE65 mutations give rise to a spectrum ranging from LCA to EOSRD (early onset severe retinal dystrophy) to juvenile RP.[43] RPE65 codes for RPE isomerase essential for retinol recycling, with some mutations retaining residual activity,

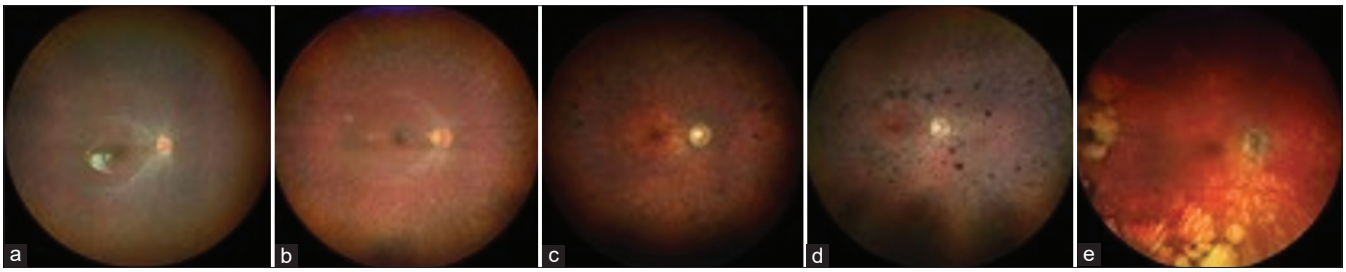

Figure 7: Cross-sectional imaging in patients with confirmed disease causing biallelic mutations in RPE65. (a) 9 y old patient, (b) 19 y old patient, (c) 28 y old patient, (d) 32 y old patient, (e) 29 y old patient. Demonstrated is progression with age (a-d) and some phenotypic variability (d, e)

Table 4: Summary of useful ophthalmic and genetic evaluations in suspected/known IRDs. From Tavares J, Lorenz B, van den Born I, Marques JP, Lacey S, Scholl H, EVICR.net. Current management of Inherited Retinal Degenerations (IRD) subjects in Europe. Results of an international survey by the EVICR.net. IOVS Abstracts. 2020

Imaging	Electrophysiology	Psychophysics	Genetics
Wide-field Fundus photography contact/non contact	Full-field ERG	Visual Acuity Visual Field Testing	Pedigree Charting
Fundus Autofluorescence Handheld/table mounted optical coherence tomography	mfERG	Color vision Dark adaptation Dark adapted VF testing Full-field stimulus threshold testing	Chromosomal analysis Molecular genetic testing, counseling

Table 5: Overview of actual AAV- vector trials in ophthalmology
From: Xue K, MacLaren RE. Correcting visual loss by genetics and prosthetics. *Curr Opin Physiol*. 2020;16:1-7

Disease	Disease gene	Target	Animal model	AAV vector	Clinical trial stage
Leber congenital amaurosis 2	RPE65	RPE	RPE65 mutant (Briard) dog	AAV2-RPE65	FDA approved, AAV5 and 4 vectors under investigation
Autosomal recessive retinitis pigmentosa	MERTK	RPE	Mertk -/- mouse	AAV2-MERTK	Phase I
Choroideremia	REP1	RPE	Rep1 -/- mouse (no disease), Rep1 -/- zebrafish	AAV2-REP1	Phase I-III
Achromatopsia	CNGA3	PR	Cnga3 -/- mouse	AAV8-CNGA3	Phase I/II
Achromatopsia	CNGB3	PR	Cngb3 -/- mouse	AAV8-CNGB3	Phase I/II
Autosomal recessive retinitis pigmentosa	PDE6B	PR	Pde6b mutant (rd1) mouse, PDE6B mutant dog	AAV5-PDE6B	Phase I/II
X-linked retinitis pigmentosa	RPGR	PR	Rpgr -/- mouse, XLPRA1 and XLPRA2 dogs	AAV8-coRPGR	Phase I/II
X-linked retinoschisis	RS1	BC	Rs1 -/- mouse	AAV8-RS	Phase I/II
Leber hereditary optic neuropathy	ND4	RGC	Mutant Nd4 mouse	AAV2-ND4	Phase II-III
Neovascular AMD		RPE	Laser-induced CNV mouse	AAV2-sFLT1	Phase I
Atrophic AMD		RPE	A range of mouse models	AAV2-CFI	Phase I/II

presenting as juvenile-onset rod-cone dystrophy (RCD).[44] Hallmarks include severe night blindness and lack of fundus autofluorescence to blue light in early years when retinal appearance is subtle.[45] Phase 1–3 trials of subretinal gene augmentation therapy led to the approval of Voretigene Neparvovec (Luxturna™) by the FDA (2017), EMA (2018), and others. Results show significant improvement in low-light vision, with younger patients showing variable response.[46,47] Most patients report significant improvement in their daily activities reflecting the enhancement of rod vision. Recently, the 3 years experience collected within the postmarketing registry PERCEIVE required by EMA and funded by Novartis EUPAS31153, http://www.encepp.eu/encepp/viewResource.htm?id¼37005) has been reported.[48] Our monocentric study on 30 eyes and others confirm better outcomes in less advanced disease, particularly in younger patients. Though side effects rarely impact visual acuity, exceptions exist, emphasizing the need for detailed patient counseling on risks and benefits.[49] Potential side effects like chorioretinal atrophy and accelerated degeneration, possibly linked to inflammation or immune responses, have been reported, requiring further research. Though side effects rarely impact visual acuity, exceptions exist, emphasizing the need for detailed patient counseling on risks and benefits.

The number of patients eligible for RPE65 gene therapy likely exceeds current estimates.[39] Challenges include limited access to genetic testing and underdiagnosis of biallelic mutations.[39,43] Areas with high consanguinity may see higher prevalence, with increasing reports from Taiwan, China, India, and beyond highlighting global distribution.[46,50]

Stickler syndrome

It is a hereditary disease of the vitreous collagen matrix described by Stickler in 1965. It is characterised by ocular, skeletal, auditory, and orofacial abnormalities. The Online Mendelian Inheritance in Man (OMIM) identifies six types of Stickler syndrome.[51] Stickler syndrome type I (STL 1) is the most common type accounting for approximately 80–90% cases and is caused by the heterozygous mutation in COL2A1. STL1 patients with pathogenic variants in exon 2 exhibit an ocular-only phenotype due to alternative splicing of the gene. Stickler type II (STL2) is caused by heterozygous mutation in COL11A1 gene; type IV (STL4) is caused by a homozygous mutation in COL9A1; type V (STL5) is caused by a homozygous mutation in COL9A2 gene, and type VI (STL6), caused by mutation in the COL9A3 gene. Formerly known as Stickler syndrome type III (STL3), the "non-ocular stickler disease" is caused by a heterozygous mutation on COL11A2.

The nonocular manifestations include craniofacial anomalies such as midfacial hypoplasia, broad flat nasal bridge, mandibular hypoplasia associated with Pierre Robin sequence, and cleft palate to bifid uvula. Skeletal defects are

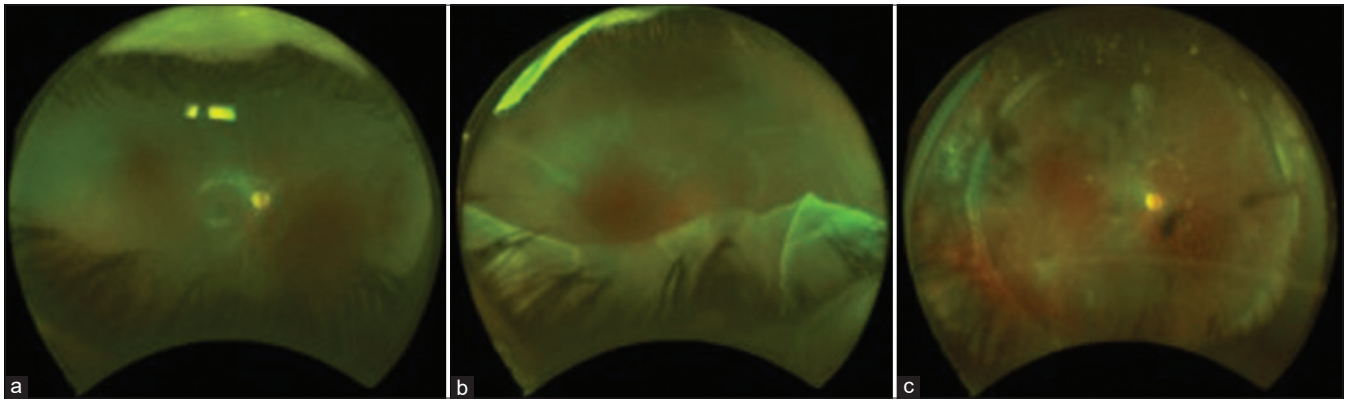

Figure 8: Fundus photos of the right eye (a, b, c) of a 9-year-old, with Stickler syndrome with a confirmed COL2A1 mutation, a) Normal at presentation, b) a giant retinal tear superiorly, a year later, c) attached retina with peripheral laser scars on the scleral buckle

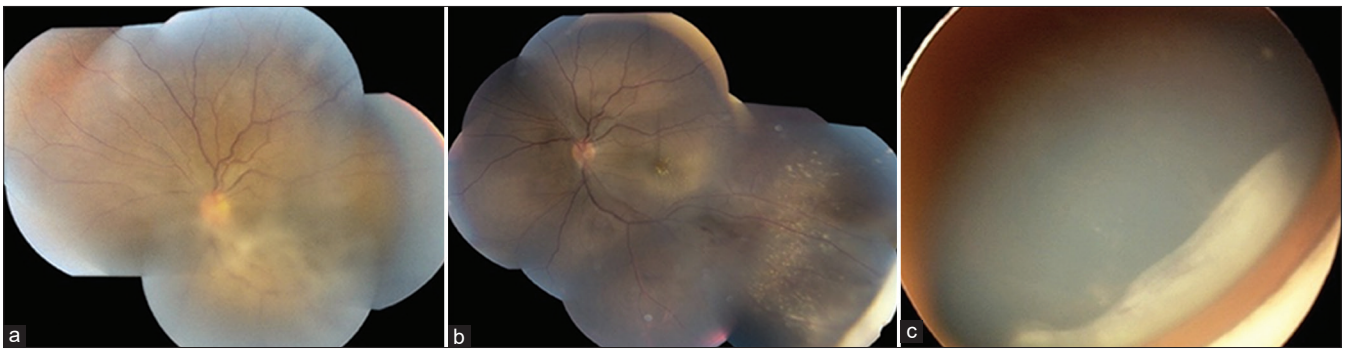

Figure 9: (a) Fundus montage image of 14 y/o girl with ocular toxocariasis (positive serologies) with severe vitritis and engorged vessels. (b) Same patient with peripheral granuloma seen in the very far inferotemporal periphery. (c) Retcam image of the same patient with peripheral granuloma secondary to Toxocara *(Image credit: Thomas Albini, MD-permission obtained)*

confirmed by radiological evidence such as flat epiphyses, spondyloepiphyseal dysplasia, kyphotic deformities, premature arthritis, and joint hypermobility. It is also associated with predominantly high-frequency sensorineural hearing loss, noted more in type II patients than type I.[52,53]

Ocular abnormalities reported are high myopia and vitreoretinal abnormalities characterized by vitreous liquefaction, fibrillary collagen condensation, cortical lens opacities, and both radial perivascular and circumferential lattice degeneration.[54] Membranous vitreous is characteristically seen in STL1, whereas individuals with STL2 exhibit a beaded appearance. It is the leading cause of RD in children, with around 50% of patients experiencing due to giant retinal tears.[Fig. 8] About 60–70% of STL1 patients may experience RD, with roughly half of these cases being bilateral.[55] Most patients, apart from those with high myopia, have no vision loss until RD occurs.

Clinical diagnostic criteria for STL1 are based on the scoring system which includes clinical features, family history, and molecular data; however, this scoring has not been validated.[55] OCT, B-scan, and wide-field fundus photography may be useful addendums to clinical evaluation in Stickler syndrome and to document retinal abnormalities. In a recent OCT study, patients with Stickler syndrome were found to have mild foveal hypoplasia with persistence of inner retinal layers.[56] Genetic testing is pursued in any individual for whom Stickler syndrome is suspected. Additionally, a molecular genetic diagnosis of the individual can assist in the testing of at-risk family members and in guiding medical management and screening.

Although the risk of rhegmatogenous RD is lifelong, they typically occur between 10 and 30 years of age. Prophylactic cryotherapy or laser retinopexy is recommended to patients with Stickler syndrome. The Cambridge prophylactic cryotherapy protocol was developed with the rationale of preventing RD due to giant retinal tears in patients with type I Stickler syndrome which reduced the risk of RD. The Manchester protocol involves applying 3–4 rows of 360-degree laser photocoagulation posterior to the ora serrata, including circumferential lattice degeneration. Linton *et al*.[57] found this prophylactic approach effective, with only 9% of treated eyes experiencing RD compared to 23% of untreated eyes over 6 year follow-up. However, despite successful prophylaxis, RD may occur from breaks in the posterior retina.[58] RD can be managed by combined scleral buckle vitrectomy with gas or silicone oil tamponade.[59] Early genetic testing and prophylactic measures are thus essential in preventing severe complications.

Pediatric uveitis

It accounts for only 5–10% of all uveitis but presents unique diagnostic and therapeutic challenges. Children may remain asymptomatic despite severe inflammation, and delays in diagnosis and treatment can lead to permanent vision loss, including the risk of amblyopia. Anterior uveitis is the most common form of uveitis in children worldwide, with juvenile idiopathic arthritis (JIA) being the most common associated condition. Recent studies in the United States report a lower prevalence of posterior uveitis (3.2%) than previously reported (6.31–24.9%), likely due to a lower prevalence of toxocariasis and toxoplasmosis in Western countries.[60]

Uveitis may be idiopathic or secondary to an underlying systemic autoimmune disease or infection. Masquerade syndromes can mimic noninfectious uveitis, so it is crucial to rule out conditions like retinoblastoma, the most common childhood intraocular malignancy, and leukemia.

TORCH infections

Toxoplasmosis, Other (syphilis, varicella-zoster, etc.), Rubella, Cytomegalovirus (CMV), and Herpes simplex virus (HSV) are significant causes of congenital uveitis, with unique retinal findings in neonates. These infections, acquired in utero, can lead to severe ocular and systemic consequences.

Toxoplasmosis is the most common cause of posterior uveitis worldwide in immunocompetent subjects. Most often the infection is congenital but can be acquired later in life. Symptoms vary depending on age with very young children presenting with strabismus and possibly leukocoria; older children might complain about blurry vision, floaters, pain, and redness, while others are asymptomatic. Chorioretinitis can be seen in the posterior pole (>50% of cases) or periphery and can be solitary or multifocal. Typically, there is a chorioretinal scar with reactivation at the lesion's edge seen as an area of retinal necrosis with adjacent vasculitis and vitritis.[61] Patients can have anterior uveitis with granulomatous or nongranulomatous keratic precipitates and iris nodules. The majority of immunocompetent hosts present with unilateral involvement (>70%).[62] There could also be atypical presentations including neuroretinitis, papillitis, and intraocular inflammation without chorioretinitis. Diagnosis is clinical, and laboratory confirmation is based on detection of antibodies and T.gondii DNA using polymerase chain reaction (PCR). Classic treatment consists of oral pyrimethamine and sulfadiazine plus systemic corticosteroids, but considerable toxicity of these drugs and cost are limiting factors which have resulted in several different treatment approaches (i.e., trimethoprim and sulfamethoxazole with prednisone), of which none are curative. Reported complications of ocular toxoplasmosis include retinal tears, RD, retinal vascular occlusions, macular edema, preretinal membranes, vitreous hemorrhage, and rarely choroidal neovascularization.[63]

Congenital CMV infection frequently results in severe retinitis, which, if not identified and treated promptly, can cause extensive retinal damage, including RD. While less common in immunocompetent newborns, presentation can still be aggressive, leading to visual impairment due to macular involvement or optic atrophy.[61]

Rubella, though less common due to vaccination, can cause retinopathy, cataracts, and pigmentary changes, leading to lifelong visual deficits. HSV and Varicella-zoster virus (VZV) can cause acute retinal necrosis (ARN) in newborns, far more aggressive, leading to extensive scarring and RD and phthisis if untreated. Early detection through neonatal screenings is crucial, with immediate referral recommended for suspected cases.

Ocular toxocariasis

It is a rare infection caused by Toxocara canis or Toxocara cati, primarily affecting children who ingest eggs from contaminated soil. Symptoms are similar to toxoplasmosis and include decreased vision, strabismus, and leukocoria.[64] It typically presents with a unilateral (>90%) peripheral or posterior retinal granuloma with endophthalmitis [Fig. 9].[65]

The gold standard for diagnosis is detecting anti-toxocara antibodies by ELISA, but these antibodies are often undetectable,

and a negative result does not rule it out.[64] Corticosteroids are the main treatment to control inflammation and prevent tractional membranes. The role of antiparasitic therapy is unclear. Other complications, such as macular edema, vitritis, epiretinal membrane, CNV, and RD may require intervention. Advances in vitreoretinal surgery have improved outcomes and are considered safe and may be used earlier to prevent severe complications.[64]

Viral Uveitis – Acute Retinal Necrosis (ARN)

ARN is a necrotizing retinopathy characterized by discrete, rapidly progressive areas of circumferential retinal necrosis, uveitis, and vasculitis. Varicella zoster virus (VZV) is implicated in 80% cases with the other commonly associated viruses being herpes simplex virus type 1 (HSV-1), herpes simples virus type 2 (HSV-2), cytomegalovirus (CMV), and Epstein–Barr virus (EBV). VZV typically affects older adults (mean age 52.4), HSV-1, the middle-aged adults (mean age 44.3), and HSV-2, the younger individuals (mean age 24.3). Some reports suggest this pattern of HSV-2-related ARN reflects reactivation of viral infection contracted at birth.[66] The most common symptoms were decreased vision, redness, periorbital pain, and photophobia. The anterior segment can present with episcleritis, scleritis, or granulomatous uveitis associated with raised intraocular pressures. Classically, the posterior segment presents with confluent areas of retinal whitening which vary from small thumbprints to broad zones along with vascular sheathing.[67] The other less common features include optic nerve edema and vascular occlusions. In chronic stage, complications like optic nerve pallor, chorioretinal scarring, retinal tears, and traction leading to rhegmatogenous RD and proliferative vitreoretinopathy are noted.

PCR assays of aqueous or vitreous samples confirm viral etiology. The gold standard treatment in adults is IV acyclovir (15mg/kg/day divided in three doses for 7–10 days), followed by oral antivirals (valacyclovir or famciclovir) with possible adjuvant use of oral corticosteroids.

Pars planitis

It is a chronic intermediate uveitis predominantly affecting children and adolescents with idiopathic etiology.[68] It accounts for 5%–26.7% cases with the highest prevalence in 6–10 years of age. Usually, there is bilateral involvement, although it can be asymmetrical. Association with certain haplotypes (HLA-DR2, -DR 15, -B51, and DRB1 * 0802) has been described. The most common symptoms are blurred vision and floaters with secondary strabismus and leukocoria. Anterior segment findings can include inflammation, band-shaped keratopathy, peripheral corneal endotheliopathy, and posterior synechiae. Common posterior findings include diffuse vitreous cells, vitreous haze, snowballs, snowbanks, and retinal vascular sheathing. Diagnosis is based on clinical findings after ruling out infectious causes and systemic associations, particularly sarcoidosis and multiple sclerosis, which are strongly linked. Diagnosis is often delayed in the pediatric population due to its chronic asymptomatic nature. Complications include cataracts, macular edema, vitreous opacities, epiretinal membranes, vitreous hemorrhage (VH), neovascularization, RD, and cyclitic membranes. The modified Kaplan approach is most commonly used and consists of periocular corticosteroids, oral nonsteroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids, systemic immunosuppressants, cryotherapy, and vitrectomy. PPV is an important part of the treatment in patients

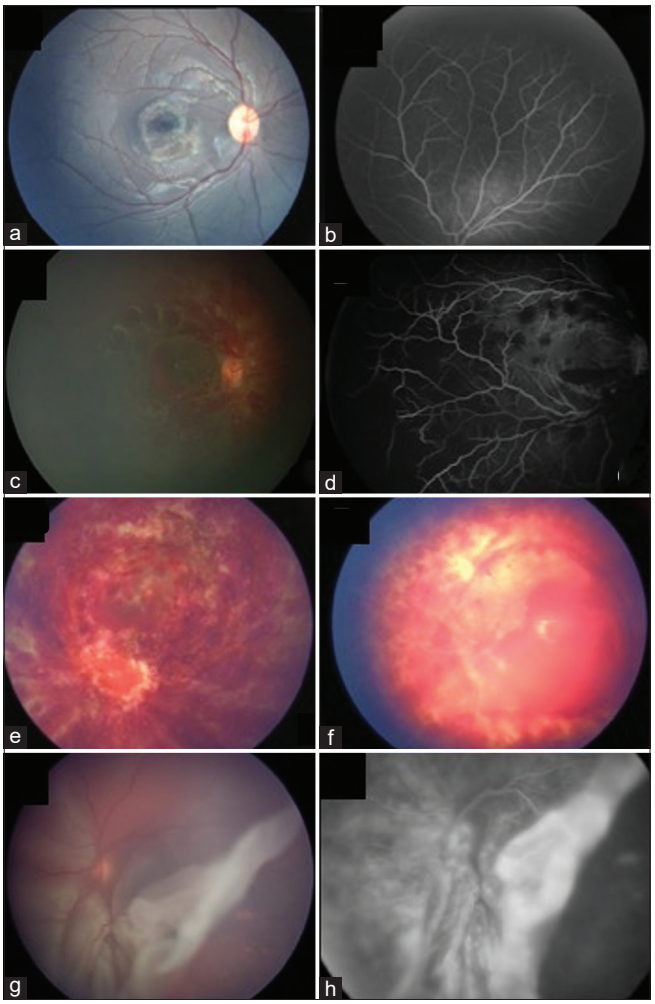

Figure 10: Nonaccidental trauma (NAT)/shaken baby syndrome. (a, b) Normal fundus photograph of 5 months post NAT showing persistent peripheral non-perfusion on FFA, (c, d) Fundus photograph post NAT at presentation showing mild multilayer retinal hemorrhages with marked peripheral nonperfusion on FFA (e, f) Fundus photograph post NAT showing severe multi-layer retinal hemorrhages, (g, h) Fundus photograph 7months post NAT showing a total RD and giant retinal tear

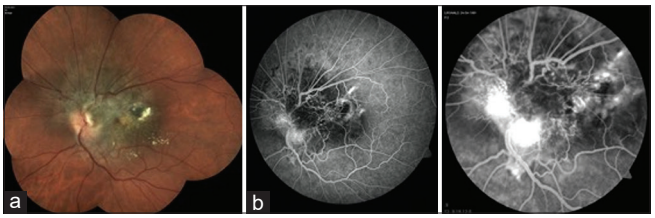

Figure 11: (a) Fundus photo of combined retinal and retinal pigment epithelium hamartoma (CHRRPE) -Ill-defined, greyish retinal lesion on the optic nerve, extending to the peripapillary retina, with a hyperpigmented margin, exudation, vessel tortuosity. (b) Fundus fluorescein angiogram - Early phase showed hypofluoresent peripapillary lesion with early punctate hyperfluorescence, and telangiectatic retinal vessels. Late phase showed increasing juxtapapillary leakage and juxtafoveal pigmented CNVM temporally

developing some of the aforementioned complications or in patients not responding well to medical therapy.[68]

Other important entities that are rare in the pediatric population but have significant posterior involvement are Vogt-Koyanagi Harada (VKH) and Behcet's disease.

Shaken Baby Syndrome – Nonaccidental Trauma (NAT)

NAT is the leading cause of traumatic death in children with an incidence of 14–40 cases per 100,000 infants.[69] Diagnosis requires a thorough examination, including physical, ocular, and radiologic assessments. Clinical signs include nonspecific neurologic findings, such as seizures, loss of consciousness, skull fractures, rib fractures, and subdural hemorrhages. Ocular findings like multilayer retinal hemorrhages are pathognomic, with other features such as perimacular folds, retinoschisis, VH, papilledema, and optic nerve atrophy. Retinal hemorrhages tend to appear within the first 2 days of injury and resolve in 1–2 weeks. Preretinal hemorrhages resolve in weeks to months, and VH takes longer.[70] Examination should occur within 24–48 hours after admission for accurate assessment [Fig. 10].

The diagnosis is based on synthesizing clinical and radiologic findings. Imaging, like CT, may not detect NAT early, so retinal examination is critical. A history of skull/rib fractures and inconsistent reports heightens suspicion.[71] FFA can detect nonperfusion areas in resolved cases [Fig. 10 c and d].[72] It is crucial to rule out other causes of retinal vasculopathy and hemorrhages, including birth trauma, genetic conditions (e.g. FEVR, Coats), and bleeding diatheses.

NAT injuries are caused by high-velocity acceleration–deceleration forces, resulting in vitreous and preretinal hemorrhages, retinal tears, holes, and detachments due to shearing of vitreoretinal adhesions.[73,74] Intracranial bleeding may lead to Terson syndrome, contributing to multilayered retinal hemorrhages and retinoschisis.[75] Increased pressure on the lamina cribrosa secondary to intracranial blood may also resemble a central retinal vein occlusion-like picture.[71]

Almost one-quarter of NAT cases result in fatality,[75] and survivors present with life-lasting sequelae of neurologic, behavioral, and cognitive impairments.[76] Prophylactic laser treatment is suggested for retinal ischemia, though adverse effects warrant careful selection. In cases of dense VH, typical ultrasound features showing tornado-like configuration hyperreflective echoes with the apex at the ONH and the base anteriorly toward the lens (also known as Cloquet canal hemorrhage) can also aid in diagnosis.[77] Vitrectomy may be used for dense VH, while intravitreal t-PA and SF6 are proposed for subhyaloid hemorrhages.[78-80] Regular follow-up with angiography is crucial to monitor for neovascularization, and laser photocoagulation is recommended if needed.

Tumors (Nonretinoblastoma)

The most common entity of tumors other than retinoblastoma that occur in the pediatric population is phacomatosis. First described by Dutch ophthalmologist Jan van der Hoeve, it is a group of congenital disorders with more than 30 entities, characterized by hamartomatous skin and nervous system lesions.

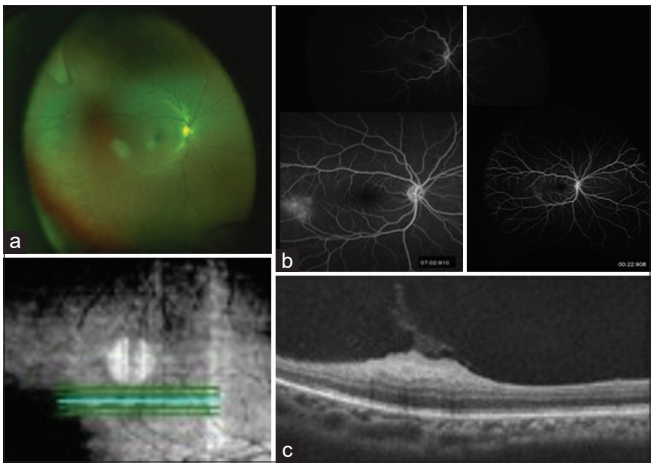

Figure 12: (a) Optos ® widefield fundus photo showing a small semilucent grayish white lesion located temporal to the macula. (b) Fundus fluorescein angiography showed a hyperfluorescent lesion with late leakage. (c) OCT showing hyperreflective lesion involving the inner retina layers

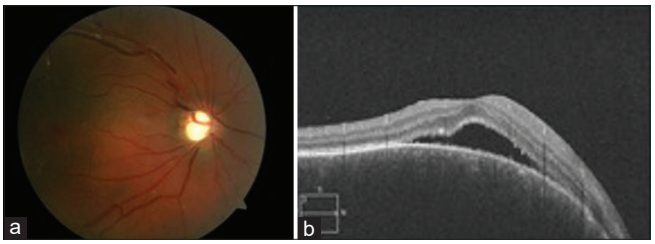

Figure 13: (a) Fundus photo showing reddish orange color lesion temporal to the disc. (b) OCT through the lesion showing the smooth choroidal elevation with complete replacement of the choroidal vasculature and exudative foveal detachment

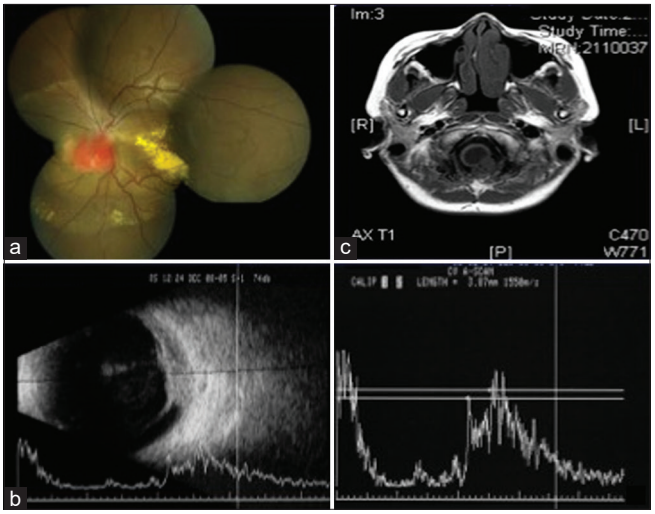

Figure 14: (a) Fundus photo of large hemangioblastoma of the left optic nerve with submacular exudates and subretinal fluid. (b) Ocular ultrasound A and B scan showed medium to high intensity elevated mass. (c) Axial T1-weighted MRI image showed low density cystic lesion with a posterior peripheral soft tissue density that enhances homogeneously with IV contrast, likely a hemangioblastoma of the brain stem

A. Neurofibromatosis

There are two types of neurofibromatosis, including types NF1 and NF2. They are genetically different and have different clinical presentations.

NF1, or von Recklinghausen disease, is the most common type with an incidence of 1 in 3500, while NF2 occurs in 1 in 50,000. Both are autosomal dominant disorders, with de novo mutations in about 50% of cases. NF is a disorder of the neuroectodermal cell line mainly involving the RAS pathways with NF1 gene mutation on chromosome 17q11 and NF2 on chromosome 22.[81]

Key clinical features of NF1 include Lisch nodules (pigmented iris hamartomas), retinal astrocytic hamartomas, and optic pathway gliomas. Lisch nodules are more common in adults, seen in all individuals over 21 years old but only in 5% of children under 3 years.[82] Retinal astrocytic hamartomas are benign and typically near the optic disc.[83] Optic pathway gliomas, seen in 15%, often present in young children with visual loss or proptosis.[84] Patients are at increased risk of glaucoma, particularly when associated with plexiform neurofibromas. Other features include café-au-lait spots and cutaneous/visceral neurofibromas.

NF2 is multiple neoplasia syndrome characterized by bilateral vestibular schwannomas, meningiomas of the brain, and schwannomas of spinal cord dorsal roots. Retinal hamartomas and Lisch nodules are seen, though less frequently than in NF1. Cataracts and secondary exposure keratopathy are common due to facial palsy.

Children with NF1 should have annual ophthalmic checkups to monitor optic pathway tumors. CT/MRI is used for symptomatic cases like optic nerve glioma. FFA and OCT help assess lesion progression. Treatment for retinal astrocytomas, optic nerve gliomas, glaucoma, and other manifestations varies based on severity.

B. Combined hamartoma of retina and retinal pigment epithelium

CHRRPE is a rare congenital benign condition, but complications like secondary choroidal neovascularization (CNV) occur in 6% of cases[85] [Fig. 11]. CNV membranes are typically located beneath or around CHRRPE, though remote associations have been reported.[86,87] A new classification system considers tumor location, retinal status, and OCT anatomy to predict visual outcomes and guide follow-up.[88] A study by Chawla *et al*.[89] found that CHRRPE primarily affects inner retinal layers, sparing the retinal pigment epithelium in most cases. Vitreo-retinal surgery with membrane peeling may offer modest vision improvement.[90]

C. Tuberous Sclerosis Complex (TSC) and retinal astrocytic hamartoma

TSC is an autosomal dominant genetic disorder marked by systemic hamartomas. The most common ocular finding is retinal astrocytic hamartoma (RAH), present in about 50% of TSC patients[91] [Fig. 12]. While RAH is typically benign and slow-growing, it can enlarge, leading to RD and neovascular glaucoma.[92] Treatment is usually needed for complications like choroidal neovascularization, exudative RD, and vitreous hemorrhage, with options including AntiVEGF injections, laser therapy, and vitrectomy.[93,94]

D. Sturge-Weber syndrome and diffuse choroidal hemangioma

It is the third most common neurocutaneous disorder[95] characterized by facial port-wine birthmark, malformed leptomeningeal blood vessel, and glaucoma. It occurs exclusively sporadically caused by GNAQ mutation.[96] A recent case identified the GNAQ mutation in the choroidal vessels of a patient with choroidal hemangioma and Sturge-Weber syndrome, suggesting the term choroidal capillary malformation.[97] Most patients with diffuse choroidal hemangioma are asymptomatic [Fig. 13].

E. Von Hippel-Lindau syndrome (VHL) and retinal capillary hemangioma

VHL syndrome is a dominantly inherited genetic disorder caused by defect in the VHL suppressor gene. The most common ocular feature is retinal capillary hemangioma (RCH) [Fig. 14]. RCH can be solitary or bilateral and multiple. About 50% of patients with solitary RCH and all with multiple RCH have systemic associations with VHL. More recently, Venkatesh *et al*.[98] have proposed a zonal classification dividing lesions into preclinical and clinical stages: intraretinal, extraretinal, RD, and advanced disease (neovascular glaucoma, vitreous hemorrhage, or blind eye).[99]

High-risk children should be screened from age 5, including dilated fundus exams, physical exams, blood pressure checks, renal ultrasound, and 24-hour urine tests for vanillyl mandelic acid and catecholamines annually. MRI of the brain and abdomen is advised every 3 years until 40 and then every 5 years. Treatment depends on tumor size and location and includes laser therapy, cryotherapy, transpupillary thermotherapy, plaque radiotherapy, photodynamic therapy, and intravitreal anti-VEGF or triamcinolone injections. Vitrectomy is reserved for complications like vitreous hemorrhage or epiretinal membranes.

Conclusion

The field of pediatric retina represents a critical and constantly evolving subspecialty. Managing unique retinal conditions in pediatric patients requires specialized expertise, timely intervention, and a comprehensive understanding of disease pathophysiology to achieve optimal outcomes. Successful treatment often combines medical and surgical approaches tailored to each condition. Continued research will be crucial in furthering our knowledge in this vital field. We hope this article provides readers with valuable insights and aids in effectively handling these cases as discussed by expert ophthalmologists in the field.

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