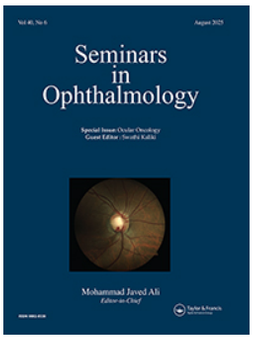

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REVIEW

Coats' Disease: A Comprehensive Review of Its Pathophysiology, Diagnosis, and Advances in Treatment

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ABSTRACT

Background and Purpose: Coats' disease, first described by George Coats in 1908, is a rare ocular disorder primarily affecting young males, often unilaterally. It is characterized by retinal telangiectasia, aneurysms, and exudation, which, in severe cases, can lead to blindness, painful red eye, or ocular atrophy, particularly with early childhood onset. Over the last century, advancements have been made in understanding its natural history, morphology, incidence, and clinical manifestations, showing a male predominance without significant ethnic disparities. This review aims to provide a comprehensive overview of Coats' disease, focusing on its pathogenesis, clinical presentation, diagnostic methods, and management strategies.

Methods: The pathogenesis of Coats' Disease is multifactorial, involving inflammatory, vascular, and potentially genetic components. Early theories suggested inflammation as the primary cause, but modern research highlights the role of vascular endothelial growth factor (VEGF), where ischemic retinal areas elevate VEGF levels, promoting angiogenesis and impairing the blood-retinal barrier. Clinically, the disease is asymptomatic in early stages but progresses to symptoms like reduced visual acuity, strabismus, and leukocoria, typically within the first decade of life. Diagnostic methods include fundus fluorescein angiography, optical coherence tomography (OCT), and OCT angiography (OCTA), with recent studies identifying reduced blood flow density in capillary networks. Management ranges from intravitreal anti-VEGF agents and steroids to surgical options like pars plana vitrectomy and transscleral drainage, with additional techniques such as laser photocoagulation and cryotherapy proving effective in advanced stages.

Conclusion: The prognosis of Coats' Disease heavily depends on the stage of disease at presentation. Early detection and intervention can preserve vision, but advanced stages often result in poor outcomes. Factors such as younger age at presentation, advanced stage, and severe manifestations are associated with more aggressive progression and poorer prognosis. This review highlights the importance of early diagnosis and a multifaceted management approach, emphasizing the need for further research into its pathophysiology and innovative treatment strategies to improve patient outcomes.

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INTRODUCTION

Coats disease is a rare, idiopathic retinal vascular disorder first described by George Coats in 1908.[1] He characterized it as a unilateral retinal vascular abnormality associated with significant exudation, predominantly affecting young males. Over the years, understanding of this condition has evolved, but it remains a diagnostic challenge due to its varied clinical presentation and similarity to other vascular and exudative retinopathies. In 1955, Reese identified similarities between Coats disease and Leber miliary aneurysms, suggesting they form a spectrum of the same pathology characterized by retinal telangiectasia, progressive exudation, and retinal detachment.[2] The primary feature of Coats disease is retinal telangiectasia, defined as irregularly dilated small- to medium-sized blood vessels that leak plasma and lipoproteins into the retinal layers and subretinal space. This leakage leads to exudation, retinal thickening, and, in more advanced cases, exudative retinal detachment.[3] The disease is sporadic, nonhereditary, and typically unilateral, with bilateral cases being exceedingly rare. A recent study in the UK has found the incidence of Coats' disease to be 0.09 cases per 100,000 people.[4] Due to its rarity and potential for severe visual impairment, early diagnosis and appropriate management of Coats disease are critical. Imaging techniques like fluorescein angiography and spectral domain optical coherence tomography (SD-OCT) play a vital role in diagnosing and monitoring disease progression.[5]

A thorough understanding of the clinical features and pathogenesis can help distinguish Coats disease from other retinal conditions, leading to better patient outcomes. Understanding the clinical features, diagnostic criteria, and treatment advancements of Coats disease is essential for ophthalmologists to accurately diagnose and manage this potentially sight-threatening condition.

PATHOGENESIS

The pathogenesis of Coats disease involves a series of complex and interdependent processes driven primarily by abnormalities in retinal vasculature, endothelial dysfunction, inflammatory mediators, and the breakdown of the blood-retinal barrier (BRB). These factors collectively result in the characteristic features of telangiectasia, lipid exudation, and retinal detachment observed in the disease.

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Coats disease begins with congenital or acquired defects in the retinal vasculature, specifically affecting the capillaries, arterioles, and venules. The primary abnormality is the development of retinal telangiectasia, which refers to irregular dilation and tortuosity of small- to medium-sized retinal vessels. These vessels appear bulbous and sausage-like, often referred to as "light-bulb telangiectasia" due to their distinctive shape.[5] The formation of these telangiectatic vessels is attributed to defective or absent pericytes, which are cells responsible for maintaining the structural integrity of the vessel walls. Pericyte dysfunction results in weakened vessel walls, making them more prone to dilation and leakage.[6]

Endothelial dysfunction further exacerbates the issue by disrupting the blood-retinal barrier, a critical structure that normally regulates fluid and solute movement into and out of the retina. When the BRB is compromised, plasma, lipoproteins, and other blood components leak into the intraretinal and subretinal spaces. This leakage results in the accumulation of lipids and proteins, leading to the formation of yellowish intraretinal and subretinal exudates.[7] Over time, these exudates coalesce, causing retinal thickening, cystic changes, and progressive retinal detachment. The exudates tend to settle in the macular region, which is responsible for central vision, and their accumulation significantly impacts visual acuity.

Inflammatory processes play a significant role in the progression of Coats disease. Elevated levels of vascular endothelial growth factor (VEGF) and pro-inflammatory cytokines, such as interleukin-6 and interleukin-8, have been detected in the aqueous humor, vitreous humor, and subretinal fluid of affected eyes.[5] VEGF promotes angiogenesis and increases the permeability of the telangiectatic vessels, leading to further leakage and breakdown of the BRB. The inflammatory cytokines enhance this process by attracting immune cells and perpetuating local inflammation, which contributes to ongoing retinal damage.[6]

Another critical factor in the pathogenesis of Coats disease is retinal ischemia. Areas of non-perfused or poorly perfused retina develop due to the irregular and dysfunctional retinal vasculature. This ischemia creates a hypoxic environment that further stimulates the production of VEGF, perpetuating a vicious cycle of leakage, inflammation, and retinal damage. The ischemic drive, therefore, plays a central role in maintaining the pathological state of the retina and driving disease progression.[5]

As the disease advances, the continued leakage of plasma and lipoproteins results in more severe complications, including retinoschisis and exudative retinal detachment. In advanced cases, the detachment can become bullous or funnel-shaped detachment reaching to the back of the lens with resultant leukocoria and significant visual impairment. The retinal detachment can also cause secondary complications, such as neovascular glaucoma. This occurs when abnormal new blood vessels grow on the iris and in the drainage angle of the eye, leading to increased intraocular pressure, pain, and further loss of vision. Figure 1 depicts the pathogenesis of Coats disease.

Another rare complication of chronic Coats disease is anterior chamber cholesterolosis, where cholesterol crystals migrate from the subretinal space into the anterior chamber. This condition is thought to occur due to the breakdown of the retina and subsequent movement of lipid material through retinal defects into the anterior segment.[5]

In some patients, persistent retinal ischemia and the chronic inflammatory environment can lead to fibrotic changes and the formation of retinal macrocysts or retinoschisis (Figure 2). These cysts typically represent degenerative changes within the retina, often associated with long-standing retinal detachment. However, such bullous retinoschisis in Coats' disease is more often associated with massive subretinal exudation rather than with retinal detachment and typically fall in areas of prominent vascular abnormalities.[8] Probably, profound leakage and hypoxia played a role in cavity development. Additionally, vasoproliferative tumors may develop in response to chronic retinal detachment, representing vascular masses within the retina.[6]

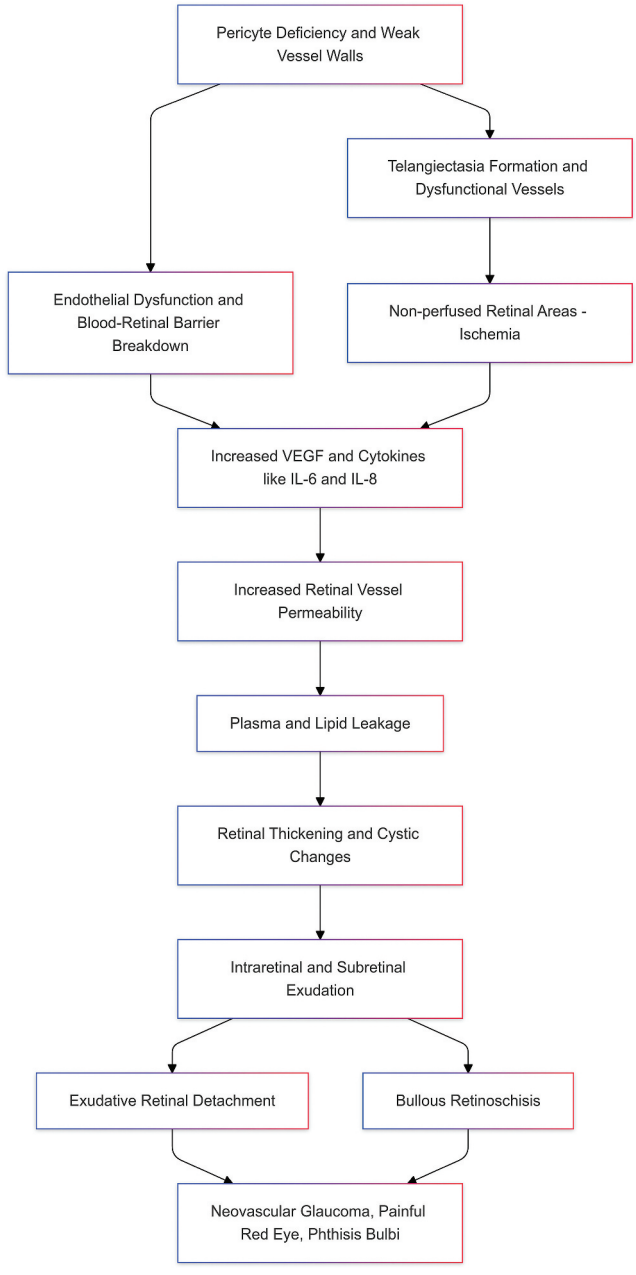

Figure 1. A flow chart depicting the pathogenesis of coats disease.

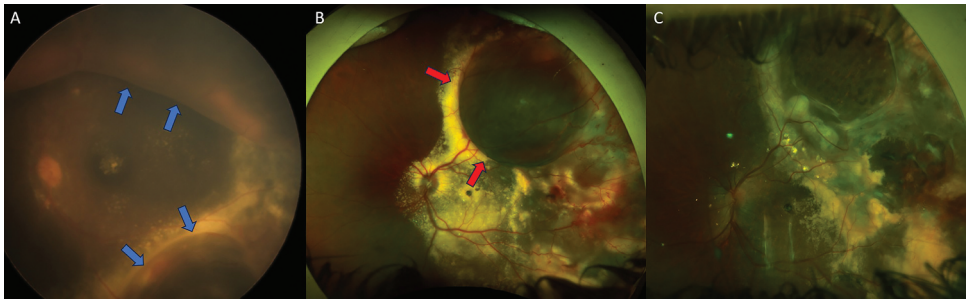

Figure 2. Bullous retinoschisis may be seen secondary to accumulation of the fluid within the sensorial retina during the course of coats' disease, causing a diagnostic challenge. (A) Left eye fundus image of a 9-month-old baby showing hard exudates located in the macula and temporal retina, highlighting the superior larger and inferotemporal smaller bullous retinoschisis areas (blue arrows) associated with coats' disease. (B) Fundus image of a 12-month-old baby with coats' disease showing hard exudates located in the macula, peripapillary area and temporal retina, and telangiectatic vessels temporal to the macula. Note the area of bullous retinoschisis with a convex and smooth surface located in the upper temporal retina (red arrows). (C) Shows the postoperative 2 months appearance of the case after PPV, inner layer retinectomy and laser treatment to telangiectasias. Note the decrease in exudations short time following surgery.

CLINICAL FEATURES AND STAGING

It's important to differentiate Coats' Disease from other similar conditions in children. The disease is mostly unilateral, with rare cases of bilateral occurrence. In an extensive analysis of 351 consecutive Coats' Disease cases, the vast majority were young males.[9] Coats' Disease often begins without noticeable symptoms in children. However, as the disease progresses, signs such as reduced visual acuity, strabismus, leukocoria, glaucoma, and ocular discomfort emerge, typically within the first 10 years of life. Adults can also develop the disease, typically with milder symptoms than those seen in children.[6,10]

During slit lamp examination in the early stages, the anterior segment of the eye usually appears normal. In the advanced disease, noticeable changes including conjunctival redness, a cloudy cornea, and a shimmer in the anterior chamber due to cholesterol deposits and new blood vessel formation in the iris may become apparent in the anterior segment.[11] Additionally, different types of cataracts, such as complete white cataracts and posterior subcapsular cataracts, may develop.[12,13]

Fundus examination typically reveals abnormal leaking telangiectasias primarily in the temporal part of the retina.[14] Changes resembling bulb-like aneurysms and dilated areas near the macula are frequent. Exudates are commonly found beneath and within the retina in the macular area, leading to serous retinal detachment.[12] A common finding is a dense exudate in the macula, forming a nodule known as a "subfoveal nodule," which can lead to scarring and fibrosis in the macula over time.[15] Initially, the vitreous remains clear, but it can become disorganized as the disease progresses with vitreous hemorrhage and may lead to vitreous membranes causing retinal traction.[9,12]

A prior study utilizing ultra-wide field fundus fluorescein angiography (FFA) revealed that 77.8% of the asymptomatic, opposite eyes in patients with Coats' disease exhibited areas of non-perfusion in the peripheral retina and retinal telangiectasia.[16] This finding has been corroborated by more recent researches and shown to be non-progressive, thereby requiring no treatment.[17,18]

The system for classifying Coats' disease, first introduced by Shields and colleagues, relies on observations made during an eye examination.[19] This system categorizes the disease into five stages: Stage 1 is identified by the presence of abnormal blood vessels in the retina; Stage 2 is marked by these abnormal vessels and fluid leakage, with 2A involving areas outside the central retina and 2B affecting the central retina; Stage 3 involves the retina detaching due to fluid accumulation, with 3A being a partial detachment and 3B a total retinal detachment (TRD); In stage 4, the patient experiences TRD along with a secondary condition called neovascular glaucoma; Finally, stage 5 represents the terminal phase of the disease (Figure 3). This classification is crucial for deciding on treatment methods and forecasting the patient's visual outcomes. Notably, Daruich et al.[15] proposed a refinement to this classification, adding subcategories to stage 2B based on the presence of subfoveal nodules (Table 1).

Yuksel et al. revealed significant findings in their study on the development of subfoveal nodule in patients with Coats' disease. Their retrospective analysis included 44 eyes from 43 patients, primarily children with an average age of approximately 7 years, observed over an average period of 33 months. They found that subfoveal nodule prevalence increased from 48% initially to 91% at the final follow-up. Interestingly, the study showed no significant variation in baseline demographic and clinical characteristics across different stages of subfoveal nodule development. However, younger patients (under 7 years) and those receiving fewer intravitreal anti-VEGF or steroid injections annually were more likely to develop subfoveal nodule earlier. Moreover, a higher frequency of these injections correlated with better final visual outcomes, indicating a potential therapeutic benefit in delaying subfoveal nodule progression and preserving vision.[20]

DIFFERENTIAL DIAGNOSIS AND INVESTIGATIONS

Retinoblastoma (RB) is the most challenging differential diagnosis in some of the advanced Coats' disease. A striking fact about Coats' disease is that approximately half of the cases are initially misidentified as other conditions, predominantly RB. In an analysis of 604 patients referred for suspected retinoblastoma, 22% were found to have pseudoretinoblastoma, with 40% of these cases being Coats' disease.[21] This misdiagnosis has grave implications, as RB is the most common intraocular malignancy in children and can be fatal if not treated.[22] The

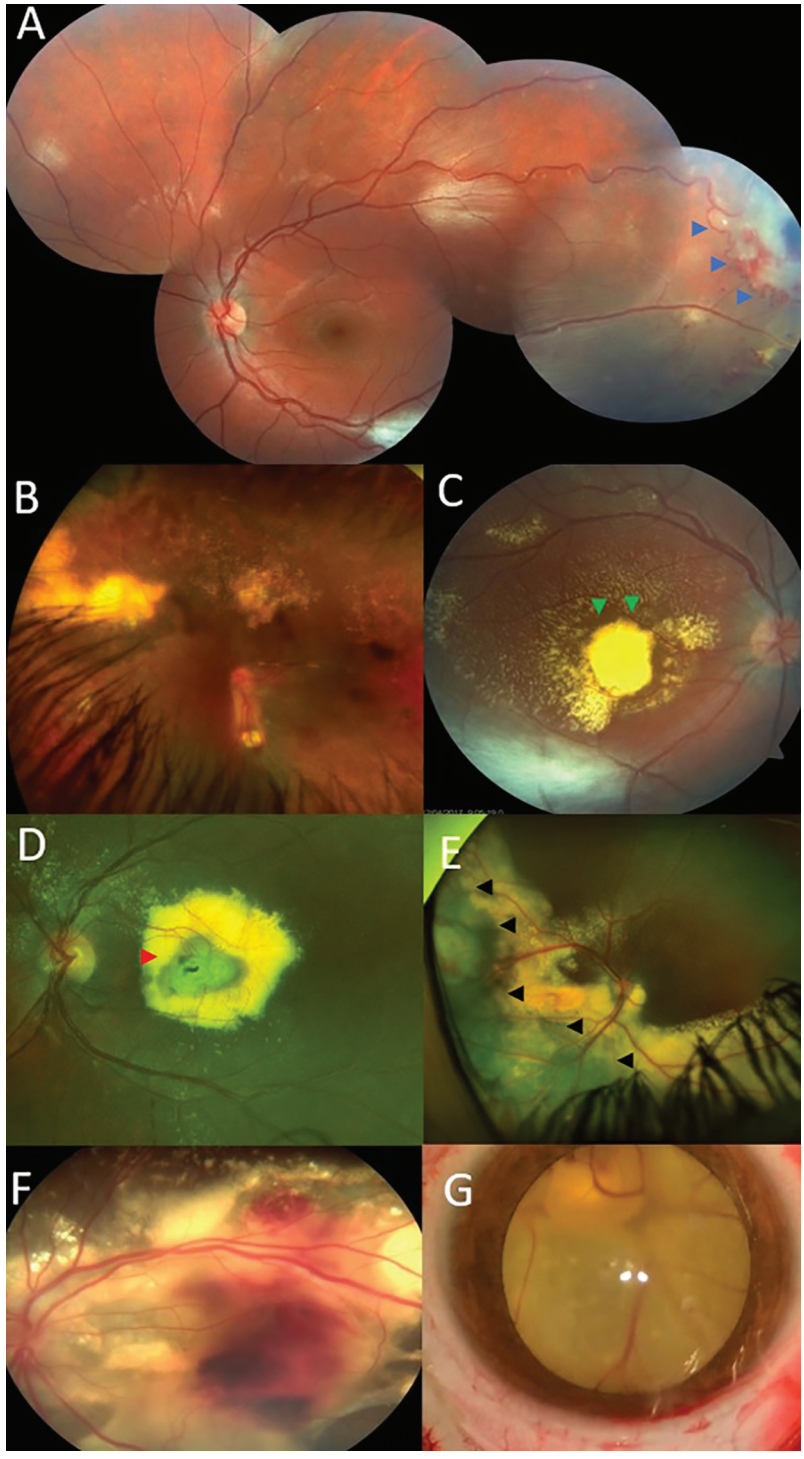

Figure 3. The stages of coats' disease. (A) Stage 1, note the abnormal telangiectatic vessels (blue arrowheads) associated with mild exudation in the temporal periphery; (B) Stage 2A, note the subretinal exudation not extending the fovea; (C) Stage 2B1, note the subfoveal exudation without subfoveal nodule (green arrowheads); (D) Stage 2B2, note the subfoveal exudation with subfoveal nodule (red arrowhead); (E) Stage 3A1, note the partial serous RD inferotemporal to the macula (black arrowheads); (F) Stage 3A2, note the serous RD extending into the entire macula; (G) Stage 3B, note the total exudative RD causing xanthocoria.

main differential diagnostic tips are given in the Table 2, however, younger age, positive family history, bilaterality, whitish appearance of the tumor instead of yellowish, calcifications in the B scan and CT, vitreous seeds, diving tumor vessels are all for the RB diagnosis in summary. However, there are still cases where the differential could not be clearly made which need to be enucleated (Figure 4).

Coats' Disease can also be confused with other paediatric retinal diseases characterized by peripheral avascular retina (PAR) and exudative retinal detachment (ERD) such as FEVR (Familial Exudative Vitreoretinopathy) and ROP (Retinopathy of Prematurity) if it occurs in premature babies.[23] When it is misdiagnosed as FEVR or ROP and laser photocoagulation is applied only to the avascular retina,

Table 1. Updated classification system for coats' disease.

Stage	Definition	Suggested treatment
1	Retinal telangiectasia only	Laser photocoagulation or observation
2A	Telangiectasia and extrafoveal exudation	Laser photocoagulation ± Intravitreal anti-VEGF/steroid injection
2B	Telangiectasia and foveal exudation 2B1 without subfoveal nodule, 2B2 with subfoveal nodule	Laser photocoagulation ± Intravitreal anti-VEGF/steroid injection
3A	Subtotal exudative retinal detachment (3A1 with extrafoveal involvement, 3A2 with foveal involvement)	External drainage of subretinal fluid, Laser photocoagulation/cryotherapy, ± Intravitreal anti-VEGF/steroid injection
3B	Total exudative retinal detachment	External drainage of subretinal fluid ± Vitrectomy, Laser photocoagulation/cryotherapy, ± Intravitreal anti-VEGF/steroid injection
4	Total exudative retinal detachment and glaucoma	External drainage of subretinal fluid, Vitrectomy, Laser photocoagulation/cryotherapy, ± Intravitreal anti-VEGF/steroid injection Occasionally observation
5	End-stage disease	Observation if asymptomatic Topical steroids Enucleation if painful

From Daruich AL, Moulin AP, Tran HV, Matet A, Munier FL. Subfoveal nodule in Coats disease: Toward an updated classification predicting visual prognosis. Retina (Philadelphia, Pa.) 2017;37:1591.

without photocoagulation of the telangiectasias, continuous leakage from the telangiectasias may lead to development of bullous ERD during follow up (Figure 5). Bullous retinoschisis may also develop during the course of the Coats' disease rarely which should be distinguished from congenital X-linked retinoschisis where exudation is much less if there is any (Figure 2). Similarly, retinal hemangioblastoma and retinal vasoproliferative tumors may also be confused with Coats' disease because of the severe exudation and exudative RD. However, feeder vessels and pinkish hemangioblastoma lesions help to differentiate it from Coats' disease. Vasoproliferative tumors are usually associated with some other underlying retinal pathologies (uveitis, retinal dystrophies, chronic retinal detachments etc) and they are solid fibrovascular mass lesions in the periphery of the retina producing hard exudates and serous RD. Leber's Miliary Aneurysm has usually more benign and slowly progressive course and, unlike Coats' Disease, may follow an asymptomatic course which may be incidentally detected.

Furthermore, retinal dragging is generally absent except in rare cases which may occur following ablative treatments.[12] These features help to differentiate Coats' disease from retinal vascular diseases like ROP, FEVR, and Norrie disease.[24] Table 2 summarizes the differential diagnosis of Coats' disease.

Clinically, severe Coats' disease is characterized by leukocoria due to ERD, often reaching the posterior capsule of the lens and exhibiting a distinctive yellow or yellow-orange hue (xanthocoria). This contrasts with the grey-white appearance of leukocoria in retinoblastoma. Ultrasonography in advanced cases of Coats' disease may reveal a linear echo indicative of TRD, with the subretinal fluid being acoustically clear. It is critical to differentiate these findings from the dense echoes of calcification seen in retinoblastoma.[5] However, calcification may be seen in long standing cases of Coats disease too.

FFA is pivotal in Coats' disease diagnosis, showing hyperfluorescence of retinal telangiectasia in the venous phase, capillary dropouts, and late leakage from abnormal vessels.[3,19,25] The recent advent of ultra-wide field FFA has enhanced the ability to diagnose Coats' disease earlier and document changes in the asymptomatic fellow eye.[16,26–28] Moreover, ultra-wide field imaging is also useful to see the whole picture to evaluate the effectiveness of laser therapy by comparing it with the pretreatment pictures (Figure 6).

SD-OCT is a useful tool in documenting cystoid macular oedema, macular exudation and subfoveal nodule formation (Figure 7).[23] Yuksel et al[20] analyzed and staged the subfoveal nodule formation in Coats' disease from stage 0 indicating no subfoveal exudation, to stage 4 for fully developed fibrovascular nodule with associated sensorineural atrophy and very thick ERM connected to the nodule. Hautz et al.[29] conducted a study into the efficacy of SD-OCT and OCTA (Optical Coherence Tomography Angiography) in evaluating Coats' disease in a pediatric cohort consisting of nine patients. The study revealed that employing OCTA in conjunction with FFA and SD-OCT can be beneficial for the diagnosis and ongoing assessment of Coats' disease. Moreover, recent research has indicated that in Coats' disease, there is a decrease in blood flow density within the superficial, deep, and choriocapillaris capillary networks, and this reduction is observed regardless of the disease's stage.[30,31] While OCTA correlated well with the findings of FFA, it was determined that OCTA alone does not suffice as a standalone diagnostic tool and cannot replace conventional angiography, which remains the definitive standard. The integration of these imaging modalities, along with color fundus photography, provides a thorough and detailed overview of the pathologies associated with Coats' disease. This multimodal imaging strategy enables enhanced visualization of both the superficial and deep vascular plexuses, an aspect where FFA alone falls short, as it is unable to effectively visualize the deep vascular plexus.[32,33]

While computed tomography (CT) scans can be confounding in retinoblastoma cases without calcification, they are beneficial in ruling out retinoblastoma in Coats' disease.[22] However, in advanced Coats' disease, bone formation and calcified nodules can mimic calcification on CT scans. Magnetic Resonance Imaging, with its distinct contrast between Coats' disease and retinoblastoma on T1 and T2 weighted images, offers more utility in advanced cases.[34]

MANAGEMENT

The various treatment modalities for Coats' disease can be categorized into conservative and surgical approaches. Conservative treatments include ablative treatments such as laser photocoagulation and cryotherapy to the telangiectatic vessels and capillary drop out areas and intravitreal

Table 2. Characteristics of diseases in the differential diagnosis of coats' disease.

Disease	Birth history/ Gender	Age at Presentation	Presenting Complaints	Family History	Bilaterality	Ophthalmological Findings	Systemic abnormalities	Imaging	Diagnosis
Coats' Disease	Term/ male	Average 3–4 years	Poor vision, strabismus, Leukocoria	none	Mostly unilateral	Temporal telangiectatic vessels, subretinal exudates, serous retinal detachment, leukocoria	No systemic associations	FFA shows leaking telangiectasias and light bulb aneurysms. USG shows acoustically clear subretinal fluid and diffuse medium reflective echoes of subretinal exudates. MRI shows subretinal exudate that appears as hyperintense on both T1 and T2	Diagnosis is usually based on clinical examination and imaging
FEVR	Term/f=m	Average 6 years (but can occur at any age)	Poor vision, strabismus, Leukocoria	Positive family history (18–48%) Family screening is strongly advised	Bilateral (often asymmetric)	PAR, neovascularization in the transition zone, straightened retinal vessels, macular/retinal dragging mostly towards temporal periphery sometimes reaching the back of the lens, hard exudates, Vitreous haemorrhage, ERD, TRD, RRD	Common systemic associations include hearing loss, cognitive deficits, impaired osteogenesis, muscle hypotony, microcephaly	FFA shows PAR and NV at the transition zone, late leakage from the vessels (LAPPEL sign) Tractional RD in US	Diagnosis is generally based on family history no history of premature birth or low birth weight, clinical features, and wide-field FFA findings.
Retinoblastoma	Term/f=m	Postnatal months/ 1–2 years	Leukocoria, strabismus	Positive family history (10%)	Unilateral (67%) or Bilateral (hereditary form)	Whitish colored mass with diving vessels, endophytic or exophytic tumor, vitreous seeds, exudative retinal detachment	Pineal tumour, retinoblastoma can also metastasize to central nervous system, lymph nodes, skeleton, or lung	Hyperechogenic mass with microcalcification, and RD on B scan US. Tumor with calcifications on CT. Iso/hyperintense mass relative to vitreous on T1, hypointense on T2 on MRI.	Diagnosis is usually based on clinical examination, imaging and the family history of Rb.
Vasoproliferative Tumour	Term/f=m	All ages, but rarely seen in pediatric ages	diminution of vision	none	Mostly Unilateral (over 90%)	May be primary or secondary to other inflammatory or vascular retinal diseases, Red to orange colored solitary mass, subretinal hard exudates ERD, vitreous hemorrhage, CME, ERM	No systemic associations	US shows solid tumor with medium internal reflectivity; Ultrawide-field FFA shows far peripheral hyperfluorescence and late leakage	Typical tumor with mix of vascular and glial proliferation, reactive nature is important; history of LPC, cryotherapy and retinal surgery should be considered in diagnosis. Underlying diseases like uveitis, RD, retinitis pigmentosa may be found.
Retinal Haemangioblastoma	Term/f=m	All ages, but rare under 4 years old.	Diminution of vision, strabismus, leukocoria	Associated with VHL disease, an AD-inherited condition.	40% bilateral involvement (VHL disease)	Multiple nodular tumours arising near optic disc or within retina; dilated and tortuous feeder blood vessels, subretinal hard exudates, ERM, associated ERD and Tractional RD	VHL disease: Hemangioblastomas found in the brain and spinal cord, pheochromocytomas, renal cell carcinoma, pancreatic cyst	USG shows solid tumor with high internal reflectivity; Ultrawide-field FFA spots both peripapillary- or peripherally-located highly hyperfluorescent tumors.	History of VHL and typical clinical features and imaging help to make diagnosis
ROP	Preterm/ f=m	Postnatal weeks	Routine screening Strabismus, leukocoria (advanced stages)	none	Bilateral (may be asymmetric)	AROP: Dilated vessel due to plus disease, PAR, ridge Tractional RD, Exudative RD can also sometimes occur after extensive laser photocoagulation	No systemic associations except from prematurity related problems	FFA shows abnormal vessels on the ridge and peripheral avascular retina	Prematurity, oxygen therapy history, and examination findings.
CXLR	Term/ male	often school age, but as young as 3 months.	Poor vision, strabismus, nystagmus	X-linked recessive inheritance	Mostly bilateral	Inner retina behind the lens, bullous schisis overriding the fovea, vitreous hemorrhage, intraschitic hemorrhages, rare hard exudates, vitreous veils Foveoschisis, NV, Peripheral dendritic figures	No systemic associations	OCT shows splitting of fovea; FFA shows abnormal peripheral vessels and capillary drop out areas; electronegative ERG	Genetic testing for RS1 mutations, detected in 90–95% of patients with clinical diagnosis.

(*Continued*)

Table 2. (Continued).

Disease	Birth history/ Gender	Age at Presentation	Presenting Complaints	Family History	Bilaterality	Ophthalmological Findings	Systemic abnormalities	Imaging	Diagnosis
Incontinentia pigmenti	Term/ female	Postnatal days	nystagmus, strabismus	X-linked dominant inheritance	Bilateral/ asymmetric	PAR leading to neovascularization and membrane formation subretinal pigmentary changes, vitreous hemorrhage, TRD, cataract, strabismus, uveitis	skin blisters, linear hyperkeratotic papules, malformed teeth, hypodontia, alopecia, Neurologic disorders (30%) including seizures, motor and mental retardation	FFA shows peripheral avascular retina along with ischemic areas in the posterior pole	Genetic testing (NEMO gene mutation) confirms the diagnosis
Persistent fetal vasculature	Term/f=m	Postnatal weeks	Leukocoria, strabismus	Mostly none (bilateral cases rarely have family history)	90% unilateral	Microphthalmos, cataract, prominent iris vessels, elongated ciliary process, retrolental mass, hyaloidal artery remnant	Bilateral cases may be associated with Trisomy 13, Walker-Warburg syndrome, anencephaly, oculo-dento osseous disease, and oculopalatal cerebral dwarfism	USG shows short axial length, hyaloidal stalk, TRD	Presence of fetal vascular remnants confirms the diagnosis
Norrie Disease	Term/ male	Postnatal weeks	Leukocoria	X-linked recessive inheritance	Bilateral (often symmetric)	Cataract, retrolental fibrovascular proliferation, retinal dysplasia, PAR, total RD, pumpkin-shaped RD, closed funnel RD	cognitive-psychosocial disturbances, sensorineural hearing loss	US shows retrolental mass, closed funnel RD FFA shows extensive PAR and NV	Affects only male infants, bilateral symmetric involvement, associated systemic symptoms are diagnostic aids. Definitive diagnosis with genetic testing for NDP gene.
Leber's Miliary Aneurysms	Term/ male	Typically seen in young males	Diminution of vision (often asymptomatic)	none	Mostly unilateral	Localized, slightly elevated white intraretinal exudates over saccular and fusiform dilatations in the blood vessels, often in the peripheral retina.	No systemic associations	FFA shows characteristics miliary aneurysms	Considered a variant of Coats' disease, usually non-progressive or slowly progressive clinical course easily controlled with LPC.

AD, autosomal dominant; CT, computed tomography; CME, cystoid macular oedema; ERM, epiretinal membrane; ERG, electroretinography; ERD, exudative retinal detachment; FEVR; familial exudative retinal detachment; FFA, fundus fluorescein angiography; OCT, optical coherence tomography; MRI, magnetic resonance imaging; PAR, peripheral avascular retina; Rb, retinoblastoma; RD, retinal detachment; RRD, rhegmatogenous retinal detachment; ROP, retinopathy of prematurity; TRD, tractional retinal detachment; VHL, Von Hippel Lindau; CXLR, Congenital X-linked retinoschisis.

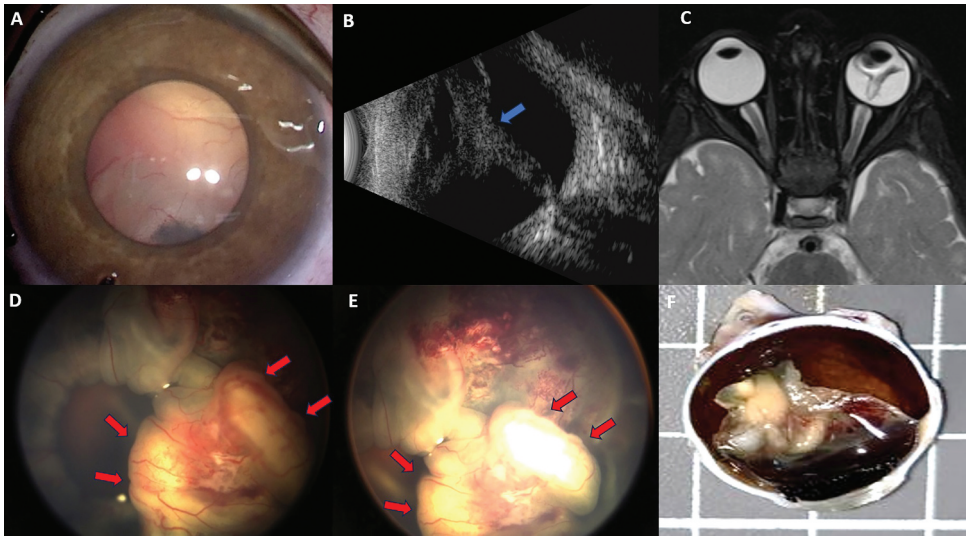

Figure 4. An 18-month-old boy with leukocoria. Total retinal detachment can be seen behind the lens (A). B mode ultrasonography demonstrates the closed funnel retinal detachment (B, blue arrow). T2-MRI shows no mass lesion (C). After the confirmation of diagnosis, the patient underwent combined pars plana vitrectomy and external drainage surgery. Intraoperatively, inferotemporal white mass-like lesion seemed very suspicious of retinoblastoma (D and E, red arrows). Accordingly, the patient underwent enucleation; histopathological examination revealed that it was coats' disease (F).

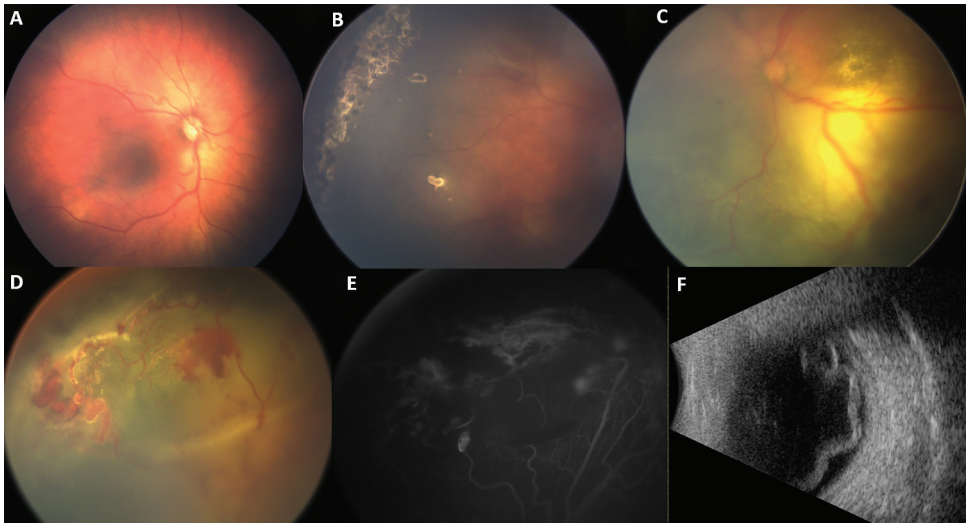

Figure 5. An infant born at 29 weeks of gestation initially diagnosed as aggressive ROP because of the dilated vessels which were misdiagnosed as plus disease, and subsequently treated with bilateral laser photocoagulation multiple times in elsewhere and was referred to us since it was still progressing. Fundus examination of the right eye revealed no vascular pathology (A) but only some peripheral laser scars (B). On the other hand, fundus examination of the left eye revealed shallow total retinal detachment with widespread hard exudates more concentrated in the inferotemporal arcuate (C) and telangiectatic and dilated twisted vessels in the highly elevated superonasal retina (D). Fundus fluorescein angiography highlights telangiectatic vessels and avascular retinal areas (E). Ultrasonography reveals total serous retinal detachment (F). Unilateral disease with extensive exudation and telangiectatic vessels were suggestive of coats' disease in a premature baby. Laser photocoagulation of the peripheral avascular retina without ablating the telangiectatic vessels has most probably led to the development of exudative RD from continuous leakage from the telangiectasis.

pharmacotherapy like anti-VEGF agents and steroids. These methods primarily focus on controlling the disease's progression by targeting abnormal blood vessel growth and reducing retinal exudation. Surgical options are typically reserved for advanced cases where conservative treatments are insufficient, like transscleral drainage of subretinal fluid together with ablative treatment and/or pars plana vitrectomy (PPV). These surgical interventions aim to address severe complications such as significant vitreous haemorrhage, advanced RD, epiretinal and vitreous membranes causing tractional RD, bullous retinoschisis and glaucoma offering a more direct approach to preserving eyeball.

Ablative Treatments: These are the mainstay of the treatment of Coats' disease either alone (in early-stage disease) or in conjunction with intravitreal pharmacotherapy or surgery (in advanced disease).

Laser Photocoagulation

Laser photocoagulation (LPC), first introduced as a treatment for Coats' disease by Pesch and Meyer-Schwickerath in the 1960s,[35] aims to stop leakage from abnormal and aneurysmal vessels via direct photocoagulation. This is achieved by laser ablation of these vessels, typically using a green or yellow laser

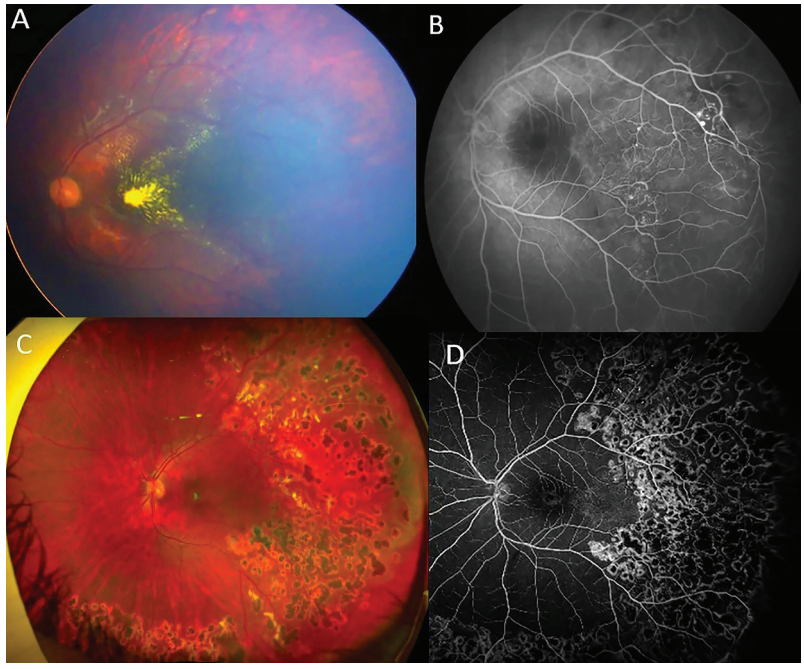

Figure 6. (A) 6-year-old patient with stage 2B coats' disease had a vision of 20/400. (A) Fundus picture shows subfoveal exudates. (B) Late phase image of the fundus fluorescein angiography of the same patient. Note the leaky abnormal vessels at temporal retina, indicating the need for ablative treatment. (C) Ultra-wide field fundus picture after 8 years of follow up shows that most of the exudates has disappeared leaving a small subfoveal nodule and laser photocoagulation scar in the peripheral retina. (D) Fundus fluorescein angiography shows that there are no active leaking vessels at temporal fundus. The final vision remained unchanged.

with a duration of 0.2–0.5 seconds for effective vessel closure.[36–38] The technique also involves treating nonperfused and leaky areas adjacent to the abnormal vessels, which are prone to VEGF production (Figure 6). It is usually necessary to apply multiple sessions to dry the leakage totally and since it is a life-long disease, there is always risk of formation of new telangiectatic vessels which needs additional ablative treatments. While LPC is effective for cases with simple exudation, its success is less pronounced in cases where the abnormal vessels are on a detached retina, necessitating additional treatments like cryotherapy and surgery.[39]

Selective LPC, a method pioneered by Nucci et al.,[40] involves the targeted application of a 577 nm yellow-dye laser to coagulate telangiectasis with superior precision. This laser's wavelength is particularly effective because it is more efficiently absorbed by haemoglobin compared to other dye lasers, allowing for focused treatment. This technique has demonstrated promising outcomes, notably in younger patients diagnosed with Coats' disease, by selectively treating affected areas without damaging surrounding tissues. Moreover, Shapiro et al.[41] have reported improved outcomes using green diode laser ablation therapy in 14 eyes with advanced Coats' disease, with 93% showing no active exudation after approximately 39.5 months. In a study by Levinson et al.,[42] 17 eyes with Coats' disease treated with a 577-nm yellow laser required an average of 2.9 treatment sessions over 21 months, with 94% achieving complete resolution of telangiectasias and subretinal fluid.

A recent study has demonstrated the effectiveness of a minimally invasive two-port nonvitrectomy pars plana endolaser photocoagulation technique in treating 25 patients with stage 3 Coats' disease.[43] This method resulted in successful reattachment of the retina in 96% of cases, with approximately 29% of patients experiencing an improvement in vision. The authors of this study endorse this technique, highlighting its ability to precisely target enlarged capillaries while minimizing thermal damage to the retinal pigment epithelium. This approach is noted for its safety and effectiveness in managing advanced cases of Coats' disease, particularly those with exudative RD. Compared to the traditional three-port vitrectomy, this technique is less invasive and provides a more accurate and efficacious treatment option. In Figure 8, you can see our technique of direct lasering of the telangiectatic vessels with only one port non-vitrectomy pars plana endophotocoagulation technique with a lighted probe.

Cryotherapy

Cryotherapy is predominantly employed for patients displaying peripheral telangiectasia, significant exudation, and RD. Its use is more common in severe cases of Coats' disease, as it has shown greater efficacy in closing vessels even in areas of detached retina. The procedure can often involve two or three applications of the freeze-thaw technique within a single session, guided by indirect ophthalmoscopy. However, it's important to note that cryotherapy can temporarily exacerbate retinal fluid accumulation shortly after surgery, due to significant disruption of the blood-retinal barrier. There is also evidence suggesting that cryotherapy may heighten the risk of developing a cyclitic membrane and vitreoretinal traction. Despite these concerns, cryotherapy continues to be valuable and effective method for reducing subretinal exudation and addressing microvascular dilation in Coats' disease.[14]

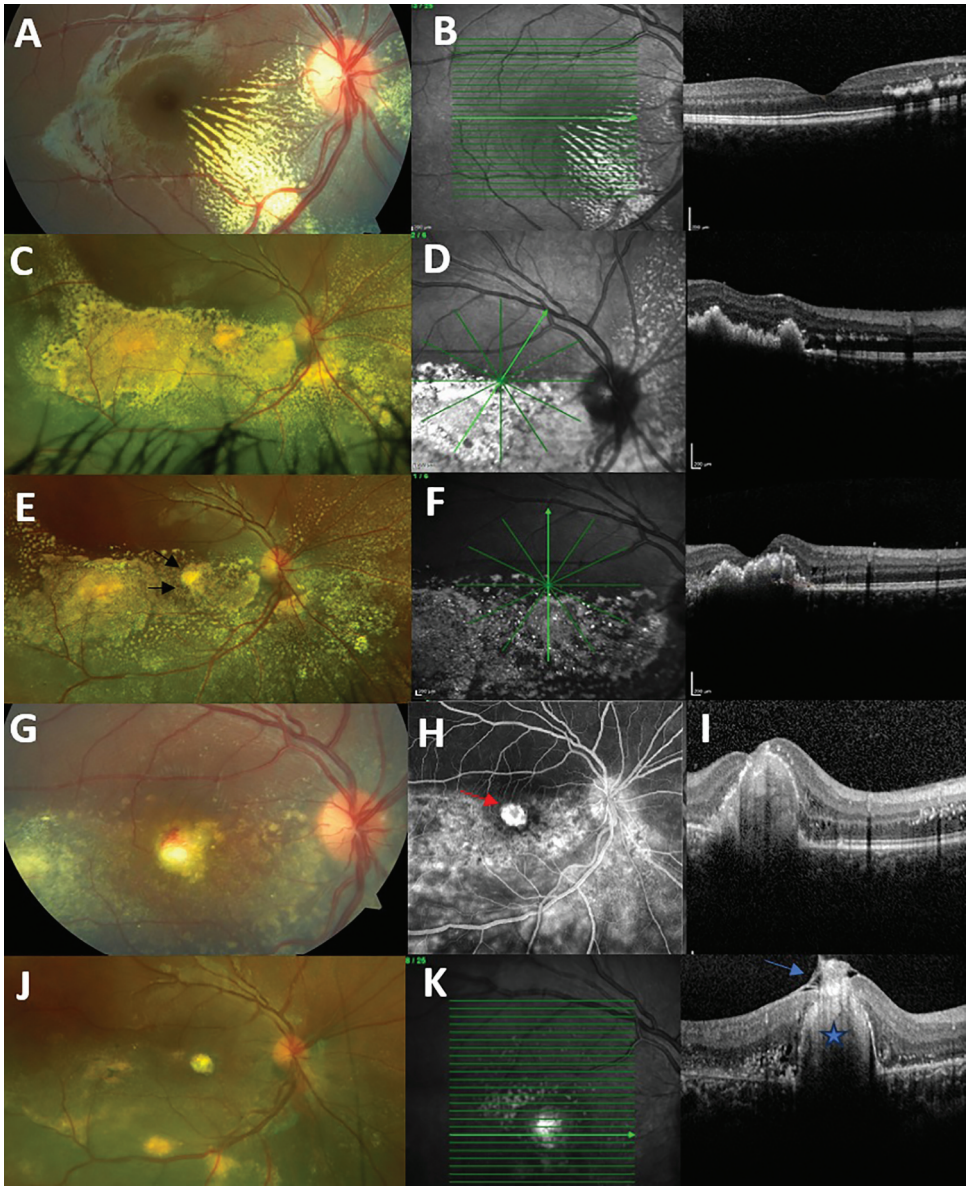

Figure 7. Developmental stages of subfoveal nodules.[20] stage 0-macular exudation without subfoveal hard exudate (A and B). stage 1- subfoveal exudation along with dense and scattered subretinal exudates (C and D). stage 2-consolidation of exudates in the subfoveal area (black arrows) with a well-circumscribed hyperreflective line (E and F). stage 3- subfoveal nodule becoming evident (G, I) and vascularization of subfoveal nodule on FFA (H, red arrow). stage 4-subfoveal fibrotic scar with hyperpigmentation (J) and severe sensorineural retinal atrophy and thick ERM on OCT (K).

Intravitreal Anti-VEGF Agents

Anti-VEGF agents have become notable additions to the treatment options for Coats' disease. Their use, though mainly documented in limited case studies and smaller series, acts as a complement to traditional therapies.[44–48] These agents are effective in reducing abnormal blood vessel growth, decreasing macular edema and fluid leakage, thereby aiding in stabilizing or enhancing vision. However, this treatment does not address the disease's root cause.

Studies have found increased levels of VEGF in eyes with Coats' Disease.[49–51] Notably, research by He et al.[49] showed a significant reduction in VEGF levels following treatment with bevacizumab. Bevacizumab has been particularly used in treating more advanced stages of Coats' Disease, such as stage 2B and beyond. Zhao et al.[46] further suggested a direct relationship between Coats' Disease severity and VEGF levels in the eye.

Clinical evidence supports the use of intravitreal anti-VEGF injections, like bevacizumab, ranibizumab, aflibercept, conbercept, and brolucizumab in significantly reducing macular oedema and fluid buildup.[52–58] Two previous studies found that combining ranibizumab with laser therapy reduced vessel permeability, enhancing treatment efficacy.[57,59] Used alongside other treatments, anti-VEGF drugs can greatly improve visual outcomes and prevent serious complications. On the other hand, this therapy requires general anaesthesia for most children, and the difficulty in administering monthly injections may hinder effective treatment.

However, use of these drugs is not without potential risks, including the development of vitreoretinal fibrosis and tractional RD. Some studies, such as those by Kam et al.[60] and Ramasubramanian et al.,[61] have noted these adverse effects, suggesting the need for caution. Conversely, studies by Villegas

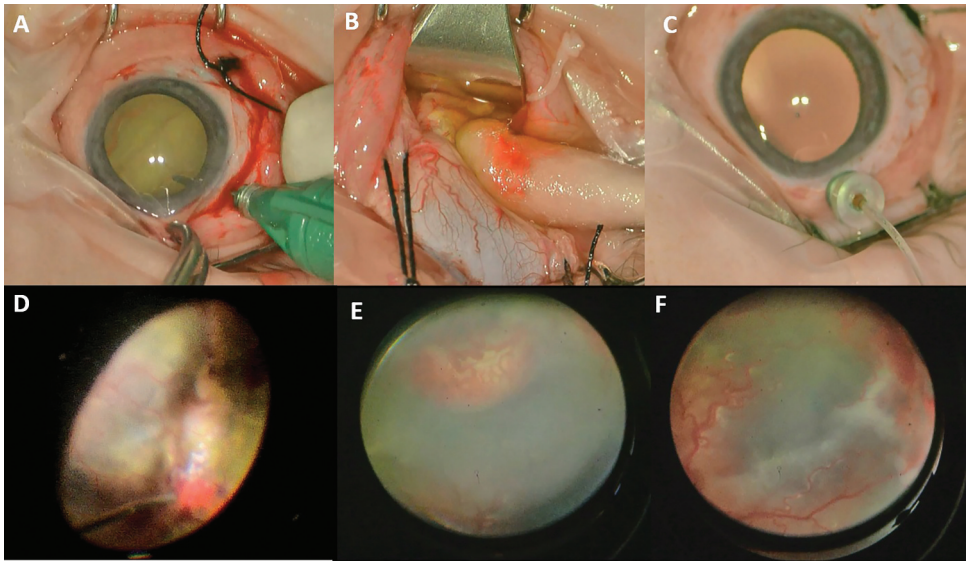

Figure 8. Surgical steps of external drainage followed by direct lasering of the telangiectatic vessels with lighted laser probe without vitrectomy. (A) The placement of one trocar cannula superiorly which will be used for multiple purposes; repressurizing the eye with BSS following external drainage of subretinal fluid, for chandelier placement to view the fundus and for the lighted laser probe entry. (B) Transscleral drainage with the help of cotton bud. (C) Red fundus reflex obtained after the drainage. Fundus can be viewed with chandelier light fixed to the same one trocar. (D) Direct laser photocoagulation with illuminated laser probe. (E) Cryo-application by indenting sclera under chandelier light. (F) Attached retina at the end of the procedure.

Table 3. Summary of surgical outcomes in coats' disease.

Author	Year	Number of eyes	Mean or median age (range)	Stage	Main treatment	Final outcome	Follow-up
Adam et al.[14]	2007	10	Mean 4.6 y (1.8–7)	2b: 2, 3a:2, 3b:6	ED + Ablative treatment: 8 PPV + Ablative treatment:2	5 (50%) retinal attachment	2.3 (1–4.5) years
Mrejen et al.[80]	2008	15	Median 1 y (3 mo-15 y)	3a:4, 3b:11	Ablative treatment alone: 7 ED +Ablative treatment: 2 PPV + Ablative treatment: 6	12 (80%) anatomical improvement	28 (6–78) months
Muftuoglu et al.[71]	2011	5	Median 18 y (6–25)	3a or 3b:5	PPV+ ID + Ablative treatment: 5	5 (100%) retinal attachment	18.8 (6–36) months
Suesskind et al.[81]	2014	13	Median 5y (1–17)	2b:2, 3a:8, 3b:3	PPV + Ablative treatment: 13	10 (77%) retinal attachment	37 (18–66) months
Cai et al.[43]	2015	25	Median 5y (1–17)	3a:20, 3b:5	2-port NV + Ablative treatment: 20 Combined 2-port NV + ED + Ablative treatment :5	24 (96%) retinal attachment	10.1 (1–20) months
Mino et al.[82]	2015	1	26 y	2a	PPV + Ablative treatment:1	1 (100%) retinal attachment	13 months
Stanga et al.[75]	2016	8	Mean 9.5y (4–13)	3a:5, 3b:3	ED + Ablative treatment: 8	8 (100%) retinal attachment	33 (9–60) months
Bhat et al.[72]	2016	7	Mean 34 mo (10–84)	3b: 7	ED+ Ablative treatment: 7	6 (85.7%) retinal attachment	19 (8–43) months
Imaizumi et al.[73]	2016	1	16 mo	3b:1	Combined ED + PPV + Ablative treatment:2 (2 surgeries 1 month apart)	1 (100%) retinal attachment	11 months
Karaçorlu et al.[70]	2017	23	Mean 8.7y (2–18)	2b:4, 3a:14, 3b:5	PPV +Ablative treatment: 13 Combined PPV+ID+ Ablative treatment: 10	20 (87%) retinal attachment	55.2 (12–120) months
Li et al.[74]	2018	16	Mean 3.4y (0.8–15)	3b:16	ED:6, PPV:12, SBP:8	12 (75%) anatomical improvement	114.6 (59–153) months
Mastropasqua et al.[77]	2020	2	Mean 16.5 y (16–17)	3a: 1, 3b:1	Ablative treatment alone: 1 ED + Ablative treatment: 1	2 (100%) retinal attachment	28.5 (22–57) months
Rishi et al.[78]	2020	32	Mean 3.8 y (1–12)	≥3b:32	ED + Ablative treatment: 32	17(53%) anatomical improvement 6(19%) retinal attachment	7 (0.5–15.7) years
Ucgul et al.[83]	2021	31	Mean 47.8 mo (2–156)	3a:11, 3b:17, 4:3	ED+ Ablative treatment: 15 Combined ED+PPV+ Ablative Treatment: 16	12 (75%) retinal attachment in ED alone group, 14 (93.3%) retinal attachment in the combination group	34.8 (6–128) months
Mano et al.[76]	2021	26	Mean 9.1 y (0.6–19)	3a:5, 3b:18, 4:3	PPV +Ablative treatment: 12 Combined ED+PPV+ Ablative Treatment: 14	12 (75%) retinal attachment in PPV alone group, 14 (100%) retinal attachment in the combination group	41.4 (8–126) months

ID, internal subretinal fluid drainage; ED, external subretinal fluid drainage; NV, non-vitrectomy technique; PPV, pars plana vitrectomy; SBP, scleral buckling procedure.

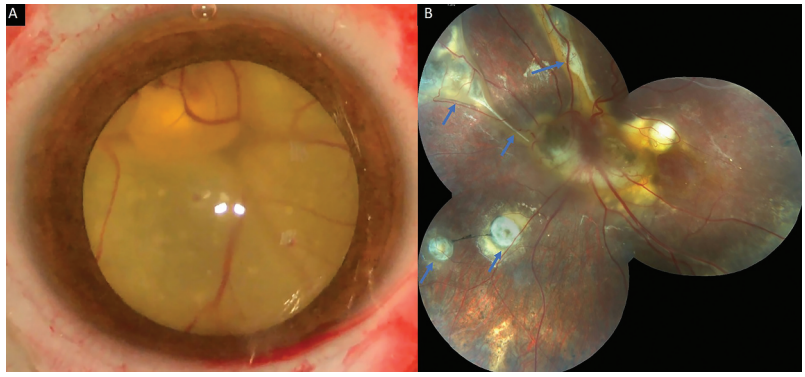

Figure 9. (A) A preoperative image of 2-year-old girl with stage 3B coats' disease, shows total exudative retinal detachment and widespread abnormal telangiectatic vessels. This patient underwent combined external drainage and vitrectomy surgery. (B) Retina was reattached completely in one month (blue arrows indicate some of the subretinal fibrosis).

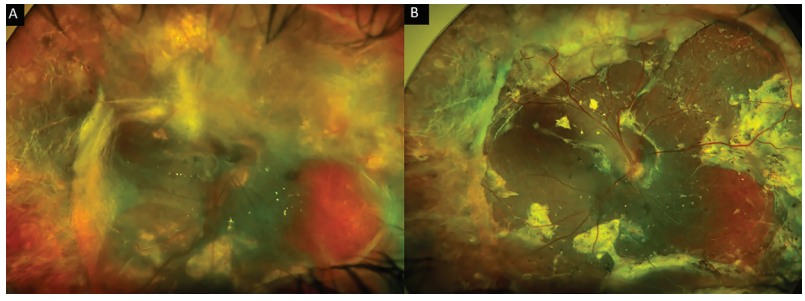

Figure 10. This patient has a history of drainage of subretinal fluid and cryotherapy when he was 2 years old in elsewhere. He had multiple laser photocoagulation and cryotherapy sessions during the following four years of the follow-up. (A) Shows dense epiretinal and vitreous membranes causing tractional retinal detachment four years after initial surgery. The vision was questionable light perception. He underwent lens sparing vitrectomy with air tamponade as a second vitreoretinal surgery at 6 years old. (B) Shows completely attached posterior retina together with widespread peripheral subretinal fibrosis one year after the surgery. The final visual acuity improved to hand motions level.

et al.,[62] Li et al.,[63] and Lin et al.[45] reported positive outcomes with no significant complications, underscoring the importance of careful application and monitoring.

Intravitreal Steroids

Intravitreal corticosteroids, known for reducing vascular leakage and inflammation, have been used in Coats' Disease management.[64] Othman et al.[65] observed improved visual acuity when triamcinolone acetonide was combined with laser or cryotherapy. However, this treatment was often complicated by cataract formation, with a development rate of 40%, and increased intraocular pressure leading to a glaucoma development rate of 6.7%, limiting its broader use.[65]

Dexamethasone implants present as a safer alternative with fewer side effects.[64] Saatci et al.[66] reported favorable results with intravitreal dexamethasone combined with laser photocoagulation in a case report. Kumar et al.[67] successfully used dexamethasone implant as a primary treatment in a patient with significant exudation, followed by laser photocoagulation to treat abnormal blood vessels. This dual approach, using intravitreal steroids with laser or cryotherapy, offers a promising route for long-term disease management.

Surgical Procedures

In cases of Coats' disease with extensive exudative RD, conventional ablative therapies and intravitreal anti-VEGF/steroid treatments may not be sufficiently effective in stabilizing the condition.[68,69] Additionally, LPC often struggles to create effective burns on a detached retina. While direct LPC of abnormal vessels through non-vitrectomizing entry to the eye or cryotherapy is possible, it may only have a limited impact, especially in eyes with TRD where peripheral vessels are often not visible. Although anti-VEGF therapy has shown effectiveness in such cases,[46] it is usually inadequate on its own for extensive RDs. Some surgeons opt for internal drainage,[70,71] but this approach is more invasive and is linked to complications like proliferative vitreoretinopathy and rhegmatogenous RD. The most prevalent surgical intervention in these situations involves external drainage of subretinal fluid, a method practiced for several years. External drainage appears safer and preserves retinal integrity better. This technique involves creating a drainage sclerotomy at the site of the most significant subretinal fluid accumulation. Maintaining ocular tonus through a limbal incision or infusion cannula during this process helps in more effective drainage and reduces the hypotonia related problems including the expulsive choroidal haemorrhage (Figure 8). Studies[72–80] have demonstrated the effectiveness of combining various treatments, such as PPV, external drainage ablative treatments and intravitreal bevacizumab injections, in managing advanced Coats' disease (Table 3).

In a previous study of our group on advanced Coats' disease, a comparison between the external drainage of subretinal fluid alone vs in combination with PPV as an adjunct to ablative therapies was reported. The findings underscore the importance of external drainage in managing the disease, with

a notable anatomical success rate of 75% for external drainage alone. However, when PPV is added to external drainage, the success rate increased to 93.3%, highlighting the added value of this combined approach. The combined surgery not only yielded a higher success rate but also reduced the need for further treatments. Specifically, the study observed a lower incidence of epiretinal membrane formation, fewer laser photocoagulation procedures, and less need for anti-VEGF treatments in the long term for patients undergoing combined procedure compared to external drainage alone. Despite these advancements, the overall visual improvement remained modest, with only a small percentage of patients showing significant vision enhancement. This study underscored the complexity of managing advanced Coats disease and the potential benefits of combining external drainage with PPV to improve outcomes and reduce the necessity for additional interventions[83] (Figure 9).

In cases with macrocysts, ablative treatments in association with anti-VEGF/steroid injections may help to control the disease. However, in eyes with bullous retinoschisis, PPV with inner layer retinectomy and direct laser to the telangiectatic vessels may be needed to control the disease.[8]

The removal of the epiretinal membrane during surgical procedures has been shown to enhance visual function, as ongoing traction can worsen retinal exudation (Figure 10). Karacorlu et al.[70] have demonstrated that combining 23-gauge PPV with cryotherapy, laser photocoagulation, and intraocular tamponade is an effective strategy for treating advanced Coats' disease. This approach not only achieves significant anatomical success but also stabilizes or improves visual acuity, reducing the need for further treatments. Similarly, Mino et al.[82] effectively managed a case of adult-onset Coats' disease, characterized by a proliferative epiretinal membrane, using 25-gauge PPV along with membrane peeling, LPC and cryotherapy. This technique addresses both the immediate symptoms and also significantly reduces cytokines in the vitreous, which plays a crucial role in halting disease progression.

Enucleation, the surgical removal of the eye, is generally considered when retinoblastoma cannot be definitively ruled out through clinical evaluation and diagnostic testing.[7] This procedure is also indicated in cases of painful end-stage Coats' disease or in stage 4 disease that does not respond to anti-glaucoma treatments.[84]

PROGNOSIS

The prognosis of Coats' disease is primarily determined by the stage at which it is diagnosed.[85] Early detection, particularly before the fovea is affected, often allows for the preservation of normal vision, underscoring the screening of children and significance of advances in diagnostic methods. However, in more advanced stages, such as stage 2B where the fovea is involved, the efficacy of ablative treatments is limited, with only a minority of patients achieving a visual acuity of 20/200 or better.[9]

Another significant predictor of a poor prognosis in Coats' disease is the presence of a subfoveal nodule.[15] Patients with a subfoveal nodule accompanied by fibrosis typically experience very low visual acuity, ranging from mere light perception to the ability to count fingers, even after receiving effective treatments.[20,86]

Furthermore, Coats' disease diagnosed in children under three years of age is often more severe, leading to worse visual outcomes and an increased likelihood of needing enucleation.[83,87] Recent research has identified some other factors that contribute to a poorer prognosis, especially in advanced stages of the disease. These factors include diagnosis at a later stage, more severe disease presentation, development of cataracts, vitreoretinal fibrosis, vitreous haemorrhage, tractional or combined retinal detachment, proliferation of the anterior hyaloid and lack of opportunities for visual rehabilitation.[88]

METHOD OF LITERATURE SEARCH

A comprehensive search was conducted on Medline, spanning publications from 1908 to July 2024. The focus was on manuscripts closely related to the topic, particularly those published in English-language, peer-reviewed journals. The selection criteria for clinical studies emphasized randomized controlled trials. Additionally, particularly relevant case series and single case reports were also included. A total of 480 abstracts were initially reviewed, from which articles pertinent to the authors' discussion were carefully chosen for further analysis. The search words were "Coats disease" and "pars plana vitrectomy" or "surgical management"or "external drainage or "prognostic factors" or "laser photocoagulation" or "cryotherapy" or "anti-VEGFs".

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