

Coats' Disease in Children: A Review of Clinical Manifestation, Diagnosis and Management

Lia Meuthia Zaini¹, Siti Hajar^{1,2}, Annisa Meivira Budiman³

¹Department of Ophthalmology, Faculty of Medicine, Universitas Syiah Kuala/ Zainoel Abidin General Hospital, Banda Aceh, Indonesia

²Department of Biochemistry, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia

³Department of Ophthalmology, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

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Abstract

Retinal disease affects children and adolescents worldwide. There are several types of retinal diseases that children and adolescents may suffer from. One of them is Coats' disease. Coats disease is characterized by telangiectasia and exudate, which often affects boys' unilateral eye. The severity, treatment, and prognosis of this disease varies widely, depending on each stage of the disease. Regular checkups are important, because early diagnosis and early treatment may delay the progression of retinal diseases. Although this disease is not uncommon, there are still many people who are not familiar with Coats' disease. This paper aims to describe the updated management of Coats' disease, which is becoming more common today.

Corresponding Author: lia_mzaini@unsyiah.ac.id (Lia Meuthia Zaini)

INTRODUCTION

Coats' disease is idiopathic childhood eye disease characterized by retinal telangiectasia and aneurysmal changes in the retinal vessels. Retinal telangiectasia is a small and medium blood vessel with dilated, irregular caliber. The telangiectatic vessels may lead to intraretinal and subretinal exudation. It is resulted from defect

during development of retinal vascularization.¹⁻⁵ The incidence of Coats' disease is reported as minimum as 0.09% per 100,000. The course of the disease depends primarily on age at onset. It usually begins at age 3-4 months and progress rapidly. About 60-70% cases of Coats' disease present in the first or second decades of life, with average age of diagnosis is between 8 to 16 years.⁵⁻⁷ There are no

ethnic predominance, however, it generally affects males more frequently with male:female ratio of 3:1 or more.^{8,9} Previous studies reported up to 95% of cases of Coats disease occurs unilaterally. Conversely, recent research demonstrated bilateral involvement of the disease using optical coherence tomography angiography (OCTA) and ultra-widefield imaging.⁹

ETIOLOGY

Coats’ disease is caused by mutation of Norrie disease protein (NDP) gene, CRB1, and PANK2. NDP gene mutation results in deficiency of norrin, an essential protein for normal vasculogenesis in retina. CRB1 is a transmembrane protein presents in brain and retina. As CRB1 gene mutation is also involved in other exudative retinopathies, Coats’ disease has been associated with several conditions including Senior-Loken syndrome, Turner syndrome, and Hallermann-Streiff syndrome.^{5,9}

Two pathological mechanisms are involved in Coats’ disease. First, blood-retinal barrier damage at endothelial level causes plasma leakage to blood vessel wall and results in thickened, sausage-like shape of the vessel. Second, degeneration of abnormal pericyte and endothelial cell in retinal vessel leads to aneurysm and abnormal retinal vasculature. This ischemic process is also involved in diabetic retinopathy. Damage of pericyte and endothelial cells accompanied by dilated telangiectasic arterioles will induce leakage of hematological components such as lipids, lipid-laden macrophages, and cholesterol crystals into retina and sub-retinal spaces. This leakage of yellowish subretinal exudate may result in cyst formation, thickening of retina, or retinal detachment.^{3,5,6,9}

Histopathology characteristic of Coats’ disease shows subretinal exudate, mononuclear celular infiltrate, and cholesterol crystals. Inner retinal layer frequently exhibits foam or “ghost cells” (histiocytes) and glial proliferation, whereas retinal pigment epithelial layer demonstrates fibroid metaplasia usually after photocoagulation. Electron microscopy examination displays thickening of retinal capillary adventitia and loss of pericytes and vascular endothelium. Previous

studies suggest the role of cellular immunity in the pathogenesis of Coats’ disease. Profiling of aqueous humor reveals potential biomarkers for Coats’ disease, such as crystalline-related proteins CRYBB1, CRYBB2, CRYGS, CRYGD, vitamin A-related proteins, tropomyosin skeleton proteins, apolipoprotein C-1 (APOC1), and fibrinopeptide B (FGB).^{8,9}

CLASIFICATION AND CLINICAL MANIFESTATIONS

Coats’ disease is classified according to Shield’s criteria. Stage 1 demonstrates only telangiectasia. Stage 2 is characterized by telangiectasia and exudation and is further subcategorized based on foveal involvement. Stage 3 represents subtotal retinal detachment and is subcategorized depending on foveal involvement. Stage 4 involves total retinal detachment and glaucoma. Stage 5 exhibits severe end-stage disease with painless pre-phthisis disease. Classification of Coats’ disease is shown in Table 1.^{1,3,6,10}

Table 1. Classification of Coats’ disease.⁸

Stage 1	Retinal telangiectasia only
Stage 2	Telangiectasia and exudation A. extrafoveal exudation B. foveal exudation 1. without subfoveal nodule 2. with subfoveal nodule
Stage 3	Exudative retinal detachment A. subtotal detachment 1. extrafoveal 2. foveal B. total retinal detachment
Stage 4	Total retina detachment and glaucoma
Stage 5	Advanced end-stage disease

Coats’ disease is asymptomatic in early stages and commonly found during routine examination.^{5,8}

Younger children are often present with strabismus or leukocoria, whereas older children are most likely to present with unilateral decreased vision.² Most patients with Coats' disease have significant poor vision (logMAR vision ≤ 1.0), varying from 20/20 to no perception of light.^{2,7} The presence of subfoveal exudates, subfoveal fibrosis, or hemorrhage, macular edema, epiretinal membrane, and optic atrophy contribute to poor vision in Coats' disease. Other symptoms that can be present includes eye pain, heterochromia of the iris, squinting, xanthocoria, and glaucoma.^{5,7,10} The severity of the disease are related to age of presentation. Previous studies show that younger patients had worse presenting visual acuity and more advanced stage of Coats' disease.^{4,7} Conversely, adult-presenting Coats' disease is usually less severe.²

DIAGNOSIS

The gold standard for clinical diagnosis of Coats' disease, as well as staging of the disease, is examination of fundus by indirect ophthalmoscopy.^{3,6,7} Figure 1 shows fundus appearance in Coats' disease. Ophthalmoscopy may reveal variety of findings based on the stage of the disease. Retinal telangiectasia and aneurysm of retinal vasculature are found in almost all cases. Bulbous terminal configuration of these fusiform-

shaped telangiectatic vessels with extensive yellow exudates are described as "light bulb telangiectasia". They are often found in peripheral zones between the equator to ora serrata and commonly involved inferior and temporal quadrants. Intraretinal and subretinal exudation tends to gravitate toward the macular region. They may be accompanied by macular edema, exudative macular detachment, and epiretinal membrane. Advanced macular disease is frequently involved nodular fibrotic lesion called "subfoveal nodule" which may progress to macular scarring, macular fibrosis, and macular holes.^{5,7,8}

Anterior segment is typically clear in patients with early Coats' disease. The cornea, iris, and lens are unaffected. With the development of the disease, the conjunctiva may be congested, and the anterior chamber has a glint caused by cholesterolosis and rubeosis iridis. Advanced stages may also demonstrate ischemic and inflammatory anterior segment sequelae, including cataract, hyphema, aqueous cellular reaction and flare, and neovascularization of the iris and/or angle. Abnormality of anterior segment indicates more severe disease, poor prognosis, and worse visual outcome. The vitreous generally remains clear unless hemorrhage, neovascularization, or retinal leakage are present. Vitreoretinal traction, fibrosis, or proliferative vitreoretinopathy are rare.^{6,7,8,9}

Ultrasonography is used to evaluate posterior

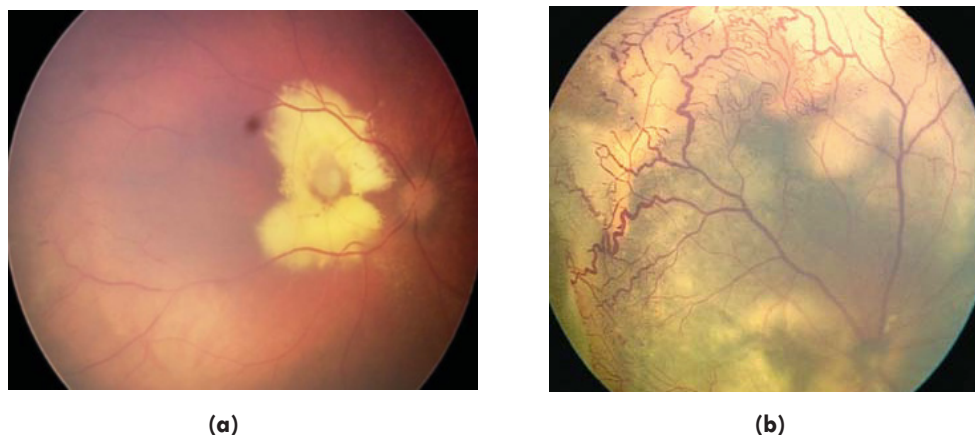


Figure 1. (a). Light-bulb appearance in Coats' disease. (b) Advance stage of Coats disease. Diffuse retinal vessel anomalies, massive subretinal lipid exudates and exudative retinal detachment.^{5,11}

segment that can be limited due to media opacity or poor patient cooperation. Ultrasonography can also be used to confirm the degree of the disease. Ultrasonography demonstrates the presence and extent of retinal detachment and retinal elevation, as well as subretinal opacities as a result of cholesterosis from the exudates. The presence of calcification, which indicates a potential malignancy, can be assessed through ultrasonography examination. Therefore, it is helpful in differentiating Coats' disease with retinoblastoma, as it allows visualization of intra-ocular space. Fluorescein angiography is a useful tool in diagnosis and assessment of disease progression. It allows visualization of slight vascular changes on retinal periphery and posterior pole. Consequently, it is helpful for early detection of vascular abnormalities in stage 1 of Coats' disease.^{5,6,7,9} Fluorescein angiography reveals hyperfluorescence of early retinal telangiectasia and hypofluorescence in the areas of late retinal exudation. Aneurysms are visible particularly in larger blood vessels, described characteristically as "light bulb dilations". Additional angiographic findings includes vascular leakage, tortuosity, and blockage from overlying exudates. Ultra-widefield angiography is able to visualize far peripheral retinal pathology because it captures 30° to 200° of fundus in one image. Therefore, wide-angle fluorescein imaging and wide-angle digital retinal imaging system may improve detection of lesions associated with Coats' disease or help with early detection of disease progression.^{8,9}

Spectral-domain optical coherence tomography (SD-OCT) and optical coherence tomography angiography (OCTA) provide cross-sectional images to evaluate the extent of macular involvement. They are useful in identifying cystoid macular edema, epiretinal membrane, vitreomacular traction, subretinal/intraretinal fluid, central macular thickness, subfoveal choroidal thickness, and assessing the integrity of specific retinal layers. OCTA examination allow detailed assessment of the deep and superficial retinal plexus which are involved in Coats' disease. OCTA combined with fluorescein angiography and OCT help in diagnosing and monitoring Coats'

disease.^{7,8,9}

Diverse manifestations of Coats' disease may overlap with other eye disorders. Some of differential diagnoses for Coats' disease are retinoblastoma, retinopathy of prematurity, hemangioma, and Norrie disease. Coats' disease is the most common reason for which eyes are enucleated with the misdiagnosis of retinoblastoma. Both of this disease can present of a retinal detachment, subretinal mass, and dilated retinal vessels.¹² Therefore, it is very difficult to make a diagnosis using only funduscopy.

Computed tomography (CT) examination in Coats' disease exhibits thickening in the ipsilateral eye wall with crescent-shaped and "V"-shaped high-density areas behind the vitreous. In advanced Coats' disease, CT reveals hyperdense area of lipif exudates within the orbit and retinal detachment. CT is particularly useful in ruling out retinoblastoma which has similar clinical picture with cases of advanced Coats' disease. Patients with retinoblastoma may present with solid tumor and calcifications as seen on CT, whereas these solid lesions are commonly absent in patients with Coats' disease.^{5,7,8,9} However, in rare cases, Coats disease can be seen with calcification. At our hospital, we have found advance stage Coats disease in a 9 years old boy with small calcsification on CT (fig 3). Saatci, et al¹³ have reported finding calcification in cases of moderate Coats disease. So, it is highly recommended to do imaging test to rule out the possibility of retinoblastoma.

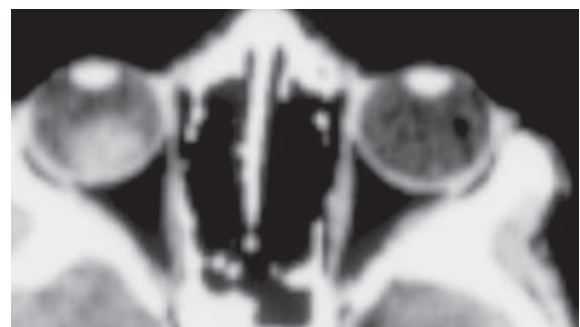


Figure 2. CT Scan of orbit of a girl with Coats disease shows unenhanced mass along right retina, normal sized globe, and no calcifications.¹⁴

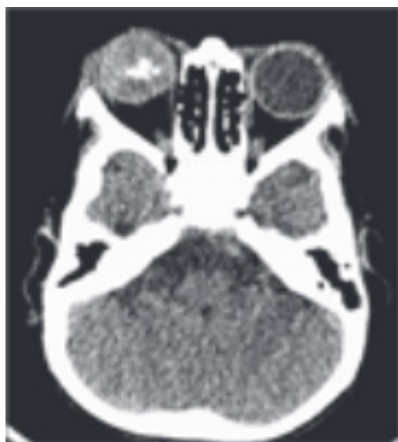


Figure 3. Retinoblastoma. CT image reveals a hyperdense calcified mass in right globe.¹⁵



Figure 4. Late stage Coats disease with calcsification on CT

CT should not be use in differentiating cases of retinoblastoma without calcification. Magnetic

resonance imaging (MRI) is even more helpful in ruling out retinoblastoma because the difference between mass and subretinal exudation is clearer. In Coats' disease, MRIs exhibit hyperintense T1- and T2-weighted signal converging on the optic nerve head corresponding to exudative retinal detachment. Conversely, the tumor in retinoblastoma is hyperintense on T1-weighted images and hypointense on T2-weighted images. The use of gadolinium contrast, which enhances solid tumors in retinoblastoma, can also aid in the differential diagnosis of retinoblastoma.^{5,7,8,9}

TREATMENT

The aim of treatment in Coats' disease is to eliminate the telangiectatic vessels in order to achieve resolution of intra- and subretinal exudates. This, in turn, will accomplish preservation of comfort and vision of the patients and prevent disease progression.^{1,5,7,11} The choice of treatment for patients with Coats' disease varies depending on the stage of the disease. If the condition is mild and not vision-threatening, as seen on stage 1 to stage 2 of Coats' disease, patients should be observed periodically. Patients with stage 2 to stage 3A of Coats' disease, cryotherapy or laser photocoagulation is generally performed. Surgery is recommended for patients with retinal detachment (stage 3A or higher), whereas enucleation is preferred in patients with stage 4 and severe eye pain. Patients with stage 5 of Coats' disease are observed, as they typically had very poor visual acuity with no hope for return of vision. Table 2 shows treatment

Table 2. Treatment of Coats' disease based on disease stage.⁵

Mild Coats' disease stage 1, 2	Laser photocoagulation/cryotherapy
Mild Coats' disease stage 1, 2 without progression	Observation
Advanced Coats' disease stage 3, 4	Vitreoretinal surgery
Advanced end-stage Coats' disease stage 5 with painful eye	Enucleation
Advanced end-stage Coats' disease stage 5 with comfortable eye	Observation
Adjuvant therapy	Intravitreal triamcinolone
Adjuvant therapy	Anti-VEGF agents

recommendations for patients with Coats' disease.^{1,3,5,6}

In early Coats' disease stage 1 to stage 3A, treatment is aimed at delaying the proliferation of abnormal retinal vasculature by cryotherapy or laser photocoagulation.^{6,7} Cryotherapy is primarily used in patients with far peripheral telangiectatic vessels accompanied by total exudative retinal detachment. Cryotherapy may be performed under indirect ophthalmoscopy two or three times within the same session (double or triple freeze/thaw therapy). Therapeutic interval of 4 to 6 weeks is preferred to evaluate therapy response. Previous studies confirm that cryotherapy increases epiretinal membrane formation and vitreoretinal traction. However, cryotherapy remains an effective method to achieve elimination of subretinal exudation, telangiectasis, and microvascular ablation in Coats' retinopathy.^{8,9} Laser photocoagulation is indicated in patients with simple exudation, but no retinal detachment. It utilizes conventional green or yellow laser with long duration (0.1-0.5s) to achieve effective closure of the vessels. Therapeutic interval of at least 3 months between two sessions is needed as the resolution occurs slowly.^{5,8}

In cases of Coats' disease with total retinal detachment, cryotherapy and laser photocoagulation are not recommended. Surgical reattachment, including pars plana vitrectomy procedures, may be useful in cases with significant epiretinal traction from preretinal membranes or proliferative vitreoretinopathy. However, vitrectomy possess technical difficulty and higher risk of complications. Major complication of vitrectomy is iatrogenic retinal break which may lead to persistent total exudative retinal detachment. Enucleation may also necessary in several cases of Coats' disease.

Vascular endothelial growth factor (VEGF) levels of patients with Coats' disease are markedly elevated. Previous studies confirm that intravitreal injection of anti-VEGF agents (bevacizumab and ranibizumab) lead to the regression of abnormal vessels and effective to reduce macular edema, subretinal fluid and exudation. Intraocular injections can cause seeding of extraocular tissue in several retinoblastoma cases. Therefore, anti-VEGF agents

should only be used if the diagnosis of Coats' disease is confirmed and retinoblastoma is ruled out.^{3,5,9} Intravitreal corticosteroids are useful to suppress inflammation and attenuate vascular leakage and leukostasis. It causes a decrease exudates in the central retinal thickness with subsequent improvement in visual acuity. Combined therapy with cryotherapy or laser photocoagulation may have long-term beneficial effects to control the disease. However, complications with the use of steroids are common, such as development of cataract and glaucoma.^{5,7,8}

CONCLUSION

Coats' disease is a disease of the retina that affects children, especially boys. At an advanced stage this disease can cause blindness. The challenge faced is a difficult initial diagnosis, because the child is not yet aware of the visual complaints in one eye. Therefore, periodic eye examinations in children need to be done.

Coats' disease has several similarities with other diseases, one of which is retinoblastoma. Therefore, a detailed examination is needed to make a diagnosis of this disease. Several imaging tests should be performed to confirm a diagnosis before making a decision to manage the disease.

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