Coats disease

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Abstract

Coats disease is an idiophatic disorder characterized by an abnormal development of retinal vessels (telangiectasia) with a progressive deposition of intraretinal or subretinal exudates, potentially leading to exudative retinal detachment. Coats disease is classically isolated, unilateral and affects mainly young males. The onset of the clinical symptoms usually occurs at early age, with an incidence peak between 6 and 8 years. The etiology of Coats disease remains almost unknown, even if reported associations with different genetic syndromes emphasize the hypothesis of a genetic component. The abnormal permeability of the capillary endothelial cells in the retina is thought to be the underlying histopathological mechanism. The advanced stages of Coats disease (total retinal detachment, leukocoria, painful glaucoma secondary to angle closure) are difficult to differentiate from retinoblastoma. The diagnostic methods include indirect ophthalmoscopy, fluorescein angiography, ultrasonography, fine-needle aspiration biopsy, CT scan and MR imaging. The treatment is directed towards closure of the abnormal leaking retinal vessels to facilitate the resolution of exudation and retinal detachment. Available treatments include laser therapy and cryotherapy in the early stages. More advanced cases require surgical techniques of retinal reattachment, such as scleral buckling, pars plana vitrectomy and removal of vitreous membrane. Stabilization of the disease course or clinical improvement can be currently achieved in 70% of the cases using a carefully selected therapy.

Keywords
Retina, exudative retinal detachment, Coats disease

Disease name and synonyms
- Coats disease
- Retinal telangiectasis
- Primary retinal telangiectasis
- Exudative retinopathy

Diagnosis criteria/ definition
Coats disease is a non-hereditary condition, which usually occurs unilaterally in young males, and is characterized by idiopathic retinal telangiectasia with intraretinal and/or subretinal exudation, exudative retinal detachment without appreciable retinal or vitreal traction (1).

In 1908, Coats described an entity characterized by unilateral vascular abnormalities and retinal exudation, which usually occurred in young males (2). In 1912, Leber reported a condition characterized by multiple retinal aneurysms associated with retinal degeneration that was usually unilateral in young males (3). These conditions subsequently came to be known as Coats disease and Leber miliary aneurysms, respectively. Although they shared many features, they were often considered to be two different entities in the first half of the twentieth century. In 1955, Reese elucidated similarities between Coats disease and Leber miliary aneurysms and proposed that they represented a spectrum of the same disease. He selected the term Coats disease to describe the combination of telangiectasia and exudative retinopathy (4).

Differential diagnosis

The differential diagnosis of Coats disease depends on the age of presentation. In children, Coats disease must be differentiated from all the other entities causing leukocoria, strabismus or intraocular masses, such as:
- Retinoblastoma,
- Persistent hyperplastic primary vitreous (PHPV)
- Retinopathy of prematurity (ROP)
- Toxocara granuloma
- Familial exudative vitreoretinopathy
- Retinal angiomatosis
- Congenital cataract
- Norrie disease
- incontinentia pigmenti
- Endophlthalmitis and pars planitis

In older children and adults, diseases that might be confused with early Coats disease include:
- Retinal vein occlusions
- Diabetic retinopathy
- Eales disease
- Vasculitis
- Juxtafoveal telangiectasia
- Arterial macroaneurysm
- Familial exudative retinopathy, primary vasoproliferative tumor
- Epiretinal membrane with vascular leakage
- Melanoma
- Choroidal and capillary hemangiomas
- Choroidal metastasis (5-6-7)

The principal aim and challenge of the differential diagnosis consist in excluding advanced retinoblastoma, which is also characterized by the triad of retinal detachment, dilated retinal vessel, and the appearance of a subretinal mass, requiring enucleation.
The advances in radiological imaging and ultrasonography enable an easier and more reliable differentiation between Coats disease and retinoblastoma (see section "Diagnostic methods"). Therefore, it is rare nowadays that enucleation is performed as a direct consequence of an erroneous diagnosis of retinoblastoma (8).

Frequency

Coats disease usually occurs in young boys with the onset of symptoms occurring mostly before age 20. Although the incidences peak is between 6 and 8 years, cases have been reported ranging from 4 months to the seventh decade. The frequency of Coats disease depends on the gender: a marked male preponderance of about 69% has been shown in the largest study of the disease, which included 855 patients.
The disease manifests unilaterally in 80% to 90% of the patients, without any evidence of racial, genetic or familial predisposition (5).

Clinical description

Opthalmoscopy reveals primarily localized foci of retinal telangiectasia, increased tortuosity, and aneurysmal dilatations in the retinal capillary bed. The temporal quadrants at the equator or periphery of the retina are more often affected, leading to a characteristic fluorescein angiography.
At this initial stage, the posterior pole of the retina may be spared and vision may be normal.
As disease progresses, the vascular abnormalities are associated with increasing amounts of yellow intraretinal and subretinal exudation. This massive exudation often leads to thickening of the retina and exudative retinal detachment. Central vision is usually affected by direct deposition of subfoveal hard exudates, clear exudative macular detachment, or cystoid macular edema. Some eyes develop retinal or choroidal neovascularization, which might result in hemorrhages (6-9).
The advanced stages of the disease include unilateral leukocoria, exotropia, loss of fixation, painful glaucoma secondary to angle closure.
Coats disease is isolated in the majority of cases, although association with facioscapulohumeral muscular dystrophy, Turner syndrome, Senior-Loken syndrome, and the ichthyosis hystrix variant of epidermal nevus syndrome have been reported. Coats disease has been also described in two reports of ocular abnormalities occurring in children born after *in vitro* fertilization (10). Coats disease associated with skeletal defects, movement disorder, epileptic seizures, leukodystrophic changes, and postnatal growth failure has been recently referred to as Coats plus syndrome (11).

Etiology

The etiology of Coats disease is still unknown, even if the reported associations with the above-mentioned genetic syndromes emphasize the hypothesis of a genetic component.

Supporting the evidence of a genetic etiology, Genkova et al. and Skuta et al. described a deletion of 13q 12.1 in a child with Coats disease and a pericentric inversion of chromosome 3 in an apparent Coats disease, respectively (12-13). Later, Black et al. reported a woman with an unilateral variant of Coats disease who gave birth to a son affected by Norrie disease (14). Both the mother and child carried a missense mutation within the NDP gene (cys96 to trp) on chromosome X p11.4. Subsequent analysis of the retinas of nine enucleated eyes from males with Coats disease demonstrated in one case a somatic mutation in the NDP gene that was not present in nonretinal tissue (15). This mutation was identical to that described by Black et al. These authors suggested that the development of telangiectasia in Coats disease is secondary to somatic mutation in the NDP gene, which result in a deficiency of norrin, the NDP-encoded protein, within the developing retina (14). This hypothesis is supported by the critical role that norrin plays in normal retinal vasculogenesis (14).

Histopatology

Histopathologic specimens from enucleated eyes, examined by electron microscopy, show loss of vascular endothelial cells and pericytes with subsequent mural disorganization of retinal capillaries (16). The endothelial cells show fenestrations and intraendothelial cell separation. Some vascular segments demonstrate thickening of the capillary wall secondary to deposition of basement membrane-type material and blood products with intact endothelium.

The degeneration of abnormal endothelial cells progresses to marked telangiectasia and lead to the formation of multiple saccular and fusiform aneurysms (17). These changes result in the loss of the blood-retinal barrier, causing abnormal vascular permeability, and consequent massive lipid exudation into the intraretinal and subretinal space. The exudate is composed of blood components rich in cholesterol crystals, cholesterol and pigment-laden macrophages, and contains also few erythrocytes and minimal hemosiderin (18). At the stage of massive retinal detachment, large amount of exudate containing cholesterol crystals and lipid-laden macrophages may be seen in the subretinal space. Gliosis develops in non-telangiectatic retinal regions. Fibrous submacular nodules appear in up to 50% of the cases. These nodules might represent exuberant proliferation and metaplasia of the retinal pigment epithelium (19).

The resulting chronic exudative retinal detachment leads eventually to secondary involvement of the anterior segment that include iris neovascularization with closure of the anterior chamber angle, subsequent painful neovascular glaucoma (ending in blindness and sometimes requiring enucleation), iris atrophy, and cataract.

Disease course and classification

The clinical course of Coats disease is variable, but nearly always progressive. Periods of acute exacerbation alternate with quiescent stages. Rare cases of spontaneous remission have been described (20).

The vast majority of cases, however, develop eventually massive subretinal exudation and retinal detachment. Secondary complications include rubeosis iridis, neovascular glaucoma, cataract, uveitis, and phthisis bulbi. The younger patients (less than 5 years of age) have a more dismal clinical course, while the patients older than 10 years have a less virulent natural course.

From a study recruiting a large sample of patients affected with Coats disease, the following evidences have emerged:

- the inferior temporal quadrant is the retinal zone more predominantly affected;
- there are poor visual outcome (20/200 or worst) risk factors such as: postequatorial, diffuse or superior location of telangiectasia and exudation, failed resolution of subretinal fluid after treatment, presence of retinal macrocysts;
- the principal enucleation risk factors are represented by an elevated intraocular pressure and iris vascularization (1).

In 1965, Gomez Morales classified Coats disease in five stages based on the severity of the abnormalities that resulted from the vascular changes (21).

- *Stage 1*: only focal exudates
- *Stage 2*: massive intraretinal exudation
- *Stage 3*: partial exudative retinal detachment
- *Stage 4*: total retinal detachment
- *Stage 5*: complications secondary to chronic retinal detachment (neovascular glaucoma)

On the basis of a large consecutive series of patients with Coats disease, Shields et al. have recently proposed a staging classification which might help in selecting treatment and predicting the ocular and visual outcomes of the disease (22):

- *Stage 1*: retinal telangiectasia only

- *Stage 2*: telangiectasia and exudation
  - A: extrafoveal exudation
  - B: foveal exudation
- *Stage 3*: exudative retinal detachment
  - A: subtotal detachment
    - 1 extrafoveal
    - 2 foveal
  - B total retinal detachment
- *Stage 4*: total retinal detachment and glaucoma
- *Stage 5*: advanced end-stage disease

Diagnostic methods

Birth history, medical and family history should help exclude other diseases (ROP, retinoblastoma, and other types of exudative retinopathy) (23-24).

Slit lamp biomicroscopy in Coats disease usually shows normal findings of anterior segment. This exam allows differentiation of Coats disease from congenital cataract and persistent hyperplastic primary vitreous.

In case of total retinal detachment, the retina in Coats disease displays telangiectasia and yellow subretinal fluid, whereas exophytic retinoblastoma is associated with a subretinal space full of gray-white material. Fundus examination with indirect ophthalmoscopy and detailed, large fundus drawing, fundus photography and fluorescein angiography are very helpful in differentiating Coats disease from retinoblastoma (25). In addition, differential diagnosis between Coats disease and retinoblastoma can be established by means of ultrasonography, CT scan, and MR imaging. Fine-needle aspiration biopsy used to be performed in differential diagnosis of Coats disease, but tends now to be replaced by the non-invasive methods.

Ocular ultrasonography (A scan and B scan) enables the detection of intraocular mass and/or calcification, which are characteristic features of exophitic retinoblastoma. In advanced stages of Coats disease, ultrasonography shows a linear echo typical of retinal detachment, and sometimes few prominent echoes due to the presence of subretinal cholesterolosis (23).

Ancillary tests are CT scan, MR imaging. CT scan is frequently required in the diagnosis of Coats disease, especially in the advanced stages of the disease. It is an extremely valuable diagnosis method because of its ability to detect intraocular calcification, to characterize intraocular morphology, to quantify subretinal densities, and to identify vascular structures in the abnormal tissue, using contrast enhancement (26). Over 90 % of advanced retinoblastomas show evidence of calcification on CT scan. Calcification in retinoblastoma usually is scattered, multifocal, and varies in size (27-28), whereas it is rarely seen in advanced Coats disease, and is usually focal, submacular and represents metaplastic changes in the retina pigment epithelium (19).

MR imaging studies can be very helpful in Coats disease because it provides multiplanar imaging with high contrast resolution that yields insights into the biochemical composition of the intraocular structure. The presence of proteinaceous subretinal fluid in Coats disease leads to the production by MR imaging of typical T1- and T2 weighed sequences, without the need of using radiation (29-30).

Although CT might be inferior to MR imaging in some aspects concerning the diagnosis of Coats disease, it has the advantages of being more performant in detecting calcifications, as well as requiring lower costs and shorter time.

Management and treatment

The rational behind the therapy is the obliteration of affected retinal vessels.

Laser photocoagulation and cryotherapy are commonly used to arrest further leakage of the telangiectatic vessels and to reverse the process by causing resorption of the former exudate. Laser photocoagulation is the treatment of choice in the early stages of Coats disease (31). Cryotherapy is more effective for lesions in the far periphery and in the presence of exudation (32-33).

Both techniques become less effective once the retina is detached and when more than two quadrants are affected. There is no universal recommendation for treatment in advanced Coats disease. In most cases, the natural course is likely to progress to glaucoma and phthisis. However, slightly fewer than half of untreated patients have been reported to show no disease progression (34). On the other hand, more than 7% of cases present with late recurrence (average of 10 years) of the telangiectasia and retinal exudation after successful treatment.

The proposed classification of Coats disease (22) can be helpful for selecting treatment and predicting the ocular and visual outcomes.

- *Stage 1 disease* (telangiectasia only): this stage can be managed by either periodic observations or laser photocoagulation. In this stage, there is a high probability that the eye can be saved, and the visual prognosis is usually favorable. However, stage 1 disease is uncommon in a clinical practice, and Coats disease is usually more advanced at the time of diagnosis.
- *Stage 2 disease* (telangiectasia and exudation): this stage is generally best managed by laser photocoagulation or

cryotherapy, depending on the extent of the disease and the preference of the ophthalmologist.

If the exudation is limited to one quadrant or located nasally, a reasonably good visual outcome can be expected. In stage 2A the visual prognosis is generally good, because the fovea is not involved by exudation. In stage 2B the visual prognosis is relatively good if the foveal exudation is not advanced, but if this stage is associated with a dense yellow gray nodule centered within the foveal exudation, the visual prognosis worsens.

- *Stage 3A disease* (subretinal retinal detachment): photocoagulation or cryotherapy can generally be useful in this stage. Even if the retinal detachment involves the fovea, it will resolve when the telangiectasia is eradicated. The subretinal fluid in the retinal detachment makes laser photocoagulation less effective than cryotherapy.
- *Stage 3B disease* (total retinal detachment): this stage can be managed with cryotherapy if the retinal detachment is shallow, but may require an attempt at surgical reattachment if the detachment is advanced and immediately posterior to the lens.
- *Stage 4 disease* (total retinal detachment with glaucoma): this stage often needs enucleation for the severe ocular pain.
- *Stage 5 disease*: at this stage, patients have generally a blind, but comfortable, eye and require no aggressive treatment.

Surgical treatment

Coats disease complicated by exudative retinal detachment requires pars plana vitrectomy to drain the subretinal fluid, thus allowing the treatment of pathologic vessels. In addition removal of tractional vitreous membranes, mostly invisible, can be required to reattach the retina. In this case removal of the epiretinal membrane and endocryocoagulation of the affected retina result in a complete resorption of subretinal fluid exudates (35).

Tasman has reported a scleral bucking procedure used to bring first the retina in apposition to the pigment epithelium, and then to drain the subretinal fluid, followed by endocoagulation or cryotherapy (32).

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