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Case Series

Optical coherence tomography angiography and multimodal imaging in the management of coats' disease

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ABSTRACT

Purpose: To illustrate the spectrum of clinical and imaging features in patients with unilateral Coats' disease at baseline and in response to treatment with laser, intravitreal bevacizumab, and regional steroids.
Observations: Telangiectasias, macular exudates, and vascular leakage were present in all 3 patients included in this series. After treatment with laser and bevacizumab, OCT angiography findings included an anomalous foveal vascular loop and chorioretinal anastomoses. Choroidal flow voids appeared to improve after intravitreal bevaziumab and laser treatment in 2 patients with OCT angiography obtained at follow up. A-scan axial lengths in affected eyes were 1.5–1.8 mm smaller than fellow eyes.
Conclusions and importance: OCT angiography is a non-invasive tool that can be a useful adjunct to multimodal imaging studies in the management of Coats' disease. Improved vascular density following anti-VEGF injection suggests a possible role of the choroidal vasculature in this retinal vascular pathology.

1. Introduction

Coats' disease is an idiopathic, non-hereditary condition defined by telangiectasias of the small-to medium-sized retinal vessels, causing intra- and sub-retinal exudation in the absence of vitreoretinal traction[1,2] It affects males in their first two decades of life and may present with xanthocoria or strabismus. A predominantly unilateral disease (95–100%), subtle angiographic contralateral findings occur in 50–78% of cases.[1–3] The pathophysiology of Coats' disease involves plasma protein leakage through a compromised blood retinal barrier, secondary to abnormal pericytes and damaged vascular endothelial tissue. Aneurysmal dilation of vessels and telangiectasia formation occurs.[1,4] In early Coats' disease, preventing disease progression involves destroying abnormal vessels using cryotherapy, laser, anti-vascular endothelial growth factor (VEGF) injections, and/or regional steroids.[4,5]

Coats' disease presents heterogeneously and often requires multiple imaging modalities to confirm diagnosis and monitor treatment response. Fundus photography, fundus fluorescein angiography (FFA), optical coherence tomography (OCT), and recently, OCT angiography (OCTA), have revolutionized the approach to managing Coats' disease.[3,5] While FFA shows small areas of vascular leakage throughout the fundus, OCTA non-invasively delineates flow patterns at various retinal and choroidal layers.[2,6]

The purpose of this series is to report the spectrum of imaging features in patients with Coats' disease, at baseline and in response to treatment. We used Spectralis HRA+OCTA (Heidelberg Engineering, Heidelberg, Germany) in three children with Coats' disease. We add to the general body of literature and show that changes in flow voids following treatment may be difficult to assess using OCTA technology.

2. Methods

Three non-consecutive cases of Coats' disease undergoing examination under anesthesia with multimodal imaging including Spectralis HRA+OCTA (Heidelberg, Heidelberg Spectalis, Germany) were retrospectively reviewed. OCTA slabs were selected for superficial vascular plexus [retinal nerve fiber layer to internal limiting membrane], deep vascular plexus [inner plexiform layer to outer plexiform layer], choriocapillaris [Bruch's membrane to 10 μm below], and choroid [10 to 60 μm below Bruch's membrane]. Segmentation was automated but individually reviewed to correlate for structural changes. Smooth segmentation was selected, and projection artifacts were removed. Standard OCTA contrast settings were selected 1:2 for the retinal slabs and 1:4 for the choroidal slabs.

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3. Findings

3.1. Case 1

A 9-year-old male presented with two years of decreased vision in the right eye. Snellen visual acuity was 20/30 in the right eye and 20/25 in the left eye. The intraocular pressure was 12 in the right eye and 14 in the left eye. The axial length by A-scan was 22.3 mm and 24.0 mm in the right and left eyes, respectively. Indirect ophthalmoscopy revealed a ridge of exudates and telangiectatic vessels in the right eye. The left eye was normal. FFA revealed extensive late leakage of temporal telangiectatic vessels with peripheral nonperfusion (**Fig. 1A**). The patient was diagnosed with Coats' disease. An examination under anesthesia (EUA) performed after 3 months showed stable posterior segment and fluorescein angiography findings. OCTA at this time point demonstrated irregular vascular flow around the foveal avascular zone (FAZ), choriocapillaris, and choroid (**Fig. 1B**).

The patient underwent treatment with intravitreal bevacizumab (Avastin, Genentech, USA), subtenon's triamcinolone acetonide (TA), and diode laser to the areas of nonperfusion. EUA 6 weeks later showed persistent crescentic lipid exudation. FFA highlighted light bulb telangiectasias and peripheral vascular leakage. OCT showed hard exudates without macular edema (**Fig. 1C**). An OCTA performed 6 weeks following initial treatment showed relatively stable retinal blood flow in the macula, with possible improvement of flow voids in the choriocapillaris, and choroid (**Fig. 1D**).

3.2. Case 2

A 5-year old male presented with a two-day history of subjective vision loss in the right eye. Visual acuity was 20/40 in the right eye and 20/30 in the left eye. Intraocular pressure was 17 and 12, in the right and left eyes, respectively. Fundus examination revealed peripheral exudation and telangiectatic vessels in the right eye. The left eye was normal. EUA two weeks later revealed echographic axial lengths of 20.8 mm and 22.3 mm in the right and left eyes, respectively. In the right eye, there were multiple areas of exudation, with a small area of exudative elevation temporally. FFA showed peripheral telangiectasias with incomplete peripheral perfusion and late leakage (**Fig. 2A**). Macular OCT was without macular edema. The patient was treated with intravitreal bevacizumab and indirect diode laser to the avascular retina.

By 3 months, the patient developed anisometropia and severe vision loss in the right eye. Visual acuity was 4/200 with a +4.00 sphere. The patient had a worsened examination, with thickening and exudation. EUA two weeks later confirmed clinic findings. OCT showed new intreretinal fluid and exudates at the level of the outer plexiform layer (OPL). FFA showed persistent peripheral non-perfusion and leakage (**Fig. 2B**). The patient received intravitreal bevacizumab, subtenon's TA, and diode laser to the avascular retina. Treatment was repeated 6- and 12- weeks later. At 8 months, OCT showed improved edema. OCTA had patchy flow voids in the choriocapillaris and choroid (**Fig. 2C**). Shadowing of the retinal slabs by exudates precluded a meaningful interpretation of the SVP and DVP architecture. Possible improvement in the choriocapillaris and choroidal vascular density was noted five weeks after an intravitreal bevacizumab was given (**Fig. 2D**).

3.3. Case 3

A 2-year-old male presented with two months of left ocular deviation. Presenting visual acuity using Allen optotypes was 20/60 and 20/400 in the right and left eyes, respectively. Intraocular pressures were 19 bilaterally. Pupils were symmetrically round and reactive. Left exotropia was confirmed. The right eye was normal. The left eye fundus had subretinal exudates in the macula and extending inferiorly, consistent with Coats' disease. EUA two days later showed echographic axial lengths of 23.3 mm and 21.5 mm in the right and left eye, respectively. FFA showed central blocking, peripheral leakage, and peripheral telangiectasias (**Fig. 3A**). Treatment with intravitreal bevacizumab, subtenon's TA, and diode laser was given. Bevacizumab and laser were repeated at 2 months.

Imaging at 5 months illustrated the development of a macular star, inferior lipid exudation, characteristic fibrotic nodules, retinal pigment epithelium excrescences, and peripheral telangiectasias with increased leakage. OCTA showed a superficial vascular anomaly in the foveal

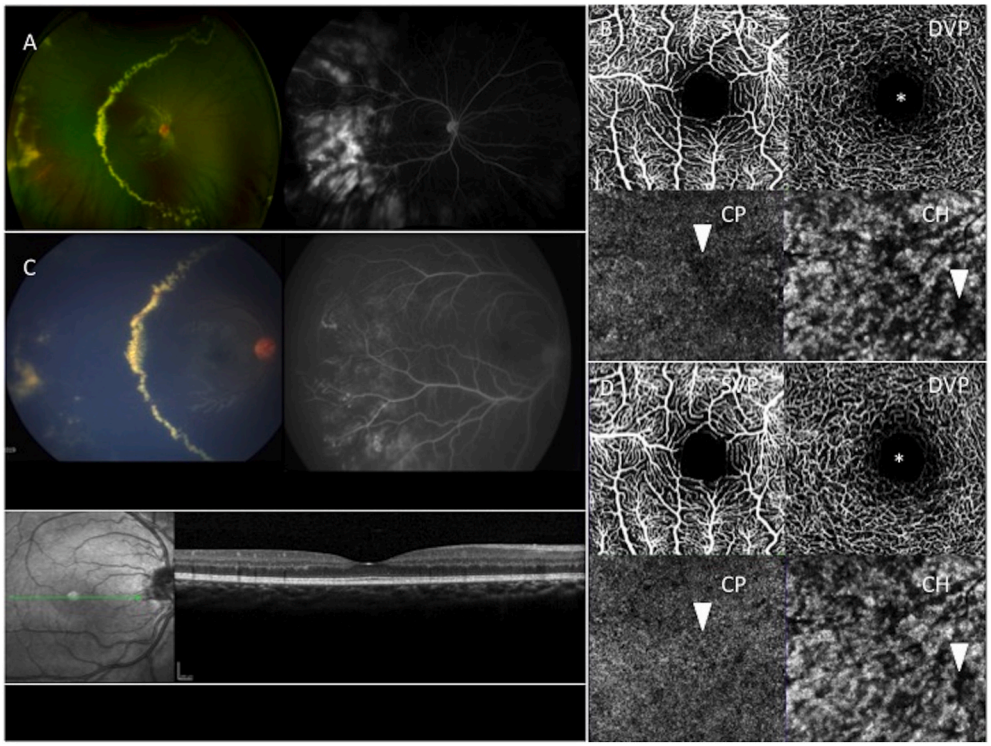

Fig. 1. Multimodal imaging of a patient with Coats' disease, at baseline **(A)**, 3 months **(B)**, and 4 months **(C, D)**. **A**. Optos photography and fluorescein angiography (Optos, UK) showed a line of exudates in the temporal periphery (left panel) with associated vascular leakage on fluorescein angiography (right panel). **B.** Three months later at EUA, OCTA (Heidelberg Spectralis, Germany) of the superficial vascular plexus [SVP], deep vascular plexus [DVP], choriocapillaris [CP], and choroid [CH]. The border of the foveal avascular zone (asterisk) and patchy areas of the choriocapillaris and choroid (white arrowhead) have relatively reduced flow density. Intravitreal bevacizumab and subtenon's triamcinolone acetonide were given. **C.** The next month, fundus photographs and fluorescein angiography (Retcam II, Clarity Medical Systems, California) at EUA showed persistent lipid exudation and telangiectasias (left panel) and vascular leakage and peripheral nonperfusion (right panel). OCT (bottom panel) was normal without macular edema. **D.** OCTA at that same EUA showed a stable foveal avascular zone (white asterisk) and possible diminished flow voids in the choriocapillaris and choroid (white arrowheads) compared to one month prior.

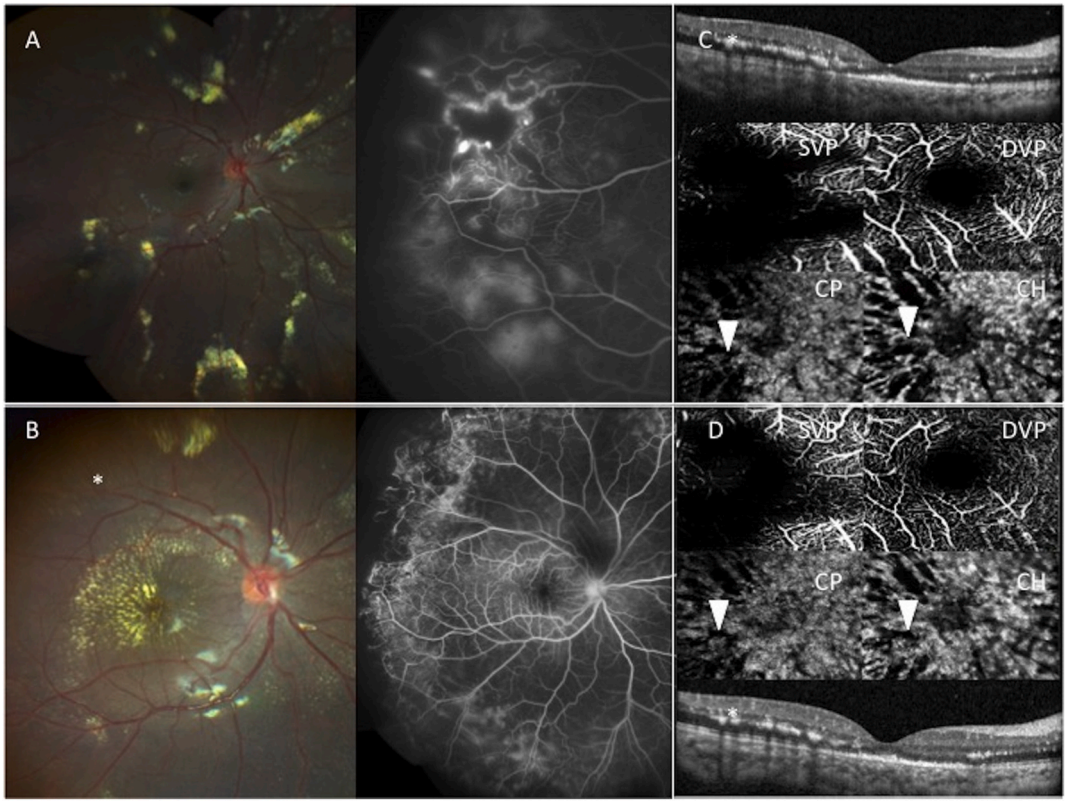

Fig. 2. Multimodal imaging of a patient with Coats's disease, at baseline **(A)**, 5 months **(B)**, 8 months **(C)**, and 9 months (D). **A.** Photography (Retcam II, California) at presentation showed scattered hard exudates (left panel), and fluorescein angiography showed telangiectasias, vascular leakage, and peripheral non-perfusion (right panel). **B.** Five months after intravitreal bevacizumab, subtenon's triamcinolone acetonide, and diode laser, there were increased hard exudates (left panel) and improved vascular leakage on fluorescein angiography (right panel). **C.** At 8 months, there were exudates concentrated in the outer plexiform layer on OCT (Heidelberg, Gerrmany) (top panel), as well as patchy flow voids across slabs on OCTA (bottom panels). There was some shadowing from the exudates on the retinal slabs (SVP, DVP). **D.** Apparent improvement in vascular flow on OCTA slabs (CP, CH) (white arrowheads), despite a stable structural OCT (bottom panel) was seen 5 weeks after interval treatment with intravitreal bevacizumab.

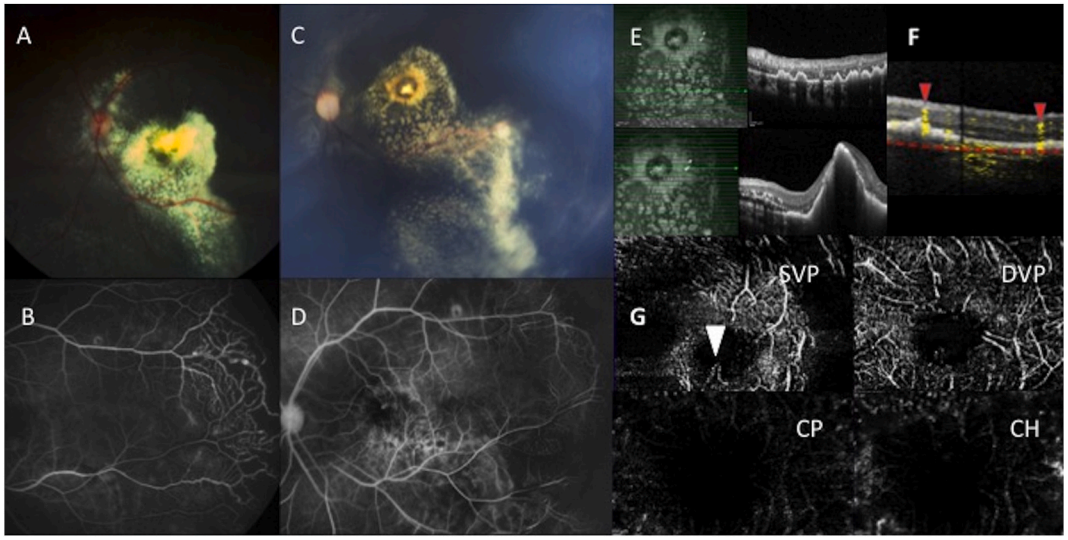

Fig. 3. Multimodal imaging of a patient with Coats's disease, at baseline **(A,B)** and 5 months **(B–G)**. **A.** Fundus photograph (Retcam II, California) showed extensive exudation at baseline. **B.** Fluorescein angiography showed telangiectasias, vascular leakage, and peripheral non-perfusion. Treatment was administered with intravitreal bevacizumab, subtenon's triamcinolone, and diode laser. **C.** Five months later, fundus photograph showed a central scar and exudates. **D.** Corresponding fluorescein showed increased staining and reduced leakage. **E.** Structural OCT (Heidelberg, Germany) revealed a fibrotic nodule (left top panel) and retinal pigment epithelial excrescences (left bottom panel). **F.** OCTA showed chorioretinal anastomoses (red arrowheads), corresponding to **(G)** an abnormal vascular loop (red arrowheads) within the FAZ on SVP, and reduced apparent flow in the deeper slabs (CP, CH). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

avascular zone, correlating with an area of chorioretinal anastomosis in the area of macular fibrosis. Poor flow in the choroid and choriocapillaris were seen deep to the atrophic outer retinal layers (**Fig. 3B**). There was no follow up OCTA for comparison.

4. Discussion

This study highlights the utility of correlating OCTA with other imaging modalities in the treatment monitoring of Coats' disease. A number of studies have looked at the use of multimodal imaging in the comprehensive management of Coats' disease. Rabiolo et al. reported that, in a prospective cohort of 11 patients with Coats' disease, the presence of any abnormality was identified in all cases, using ultra wide field fundus color photography and fluorescein angiography. Spectral-domain OCT (SD-OCT) was useful in identifying abnormal findings of subretinal nodules, ILM wrinkling, exudates, intraretinal fluid, macular atrophy, among other findings, in over 77% of affected eyes.[3] Similarly, FFA in all 3 of our cases showed the level of peripheral non-perfusion and vascular leakage, and fundus photographs illustrated the pattern of exudates over time. OCT was useful in identifying key features of Coats' disease in our series, including the presence of macular edema, macular scar, retinal pigment epithelium excrescences, and fibrotic nodules. OCT was pivotal in assessing structural changes at baseline and following treatment at each stage of follow up.

We presented 3 cases in which OCTA provided a more comprehensive clinical picture of the disease process to aid in management decisions. Even in patients without posterior findings, OCTA may have advantages over other modalities in visualizing pathology in Coats' disease. Similarly to findings described by Muakkassa et al.,[2] one of our patients (case 3) showed an anomalous superficial vessel within the FAZ, which was not seen on the corresponding FFA. In this same patient, there was evidence of chorioretinal anastomoses on OCTA corresponding to an area of macular fibrosis. This has been described in association with type 3 neovascularization.[3,7] Case 1 also lacked visible posterior pathology on photographs, FFA, and OCT, but demonstrated poor vascular flow at the border of the FAZ and within the choriocapillaris and choroid on OCTA. Consistent with our findings, Schwartz et al. previously showed that OCTA in the affected eye of Coats' disease patients is associated with a decreased vascular density and enlarged FAZ.[8] These assessments suggest an important role of OCTA use to supplement more traditional modalities during the management of Coats' disease.

OCTA noninvasively adds useful information about vascular flow in areas of atrophy and occlusion. Hautz et al. advocated for the use of OCTA in conjunction with, but not as a substitute to, FFA and OCT. The authors found that FFA provides more information about dynamic flow and leakage in smaller vessels of the central and peripheral retina, when compared to OCTA.[6] In agreement with these authors, our experience is that OCTA offers useful information when combined with photographs and FFA findings. Coordinated use with other imaging modalities may help overcome limitations of using a single imaging modality.

There is limited information in the literature about OCTA as a tool to monitor treatment response in Coats' disease. We propose that macular flow density on OCT angiography may be utilized in the monitoring of Coats' disease following treatment. Two of our patients (cases 1, 2) had follow up imaging after intravitreal bevacizumab and laser treatment for active disease. In agreement with the findings of Cennamo et al. and Hautz et al., the retinal vascular flow patterns were not convincingly different following anti-VEGF treatment.[6,9] However, the choroidal vascular density appeared increased following anti-VEGF therapy, according to the selected slabs. As OCTA studies have shown that anti-VEGF agents result in decreased choroidal density, presumably due to pharmacological vasoconstriction,[10] the relative improvement in choroidal slabs on our OCTA figures may be the results of artifact or may imply a possible role of choroidal vasculature in pathology of Coats' disease patients. While the mechanism of the choroidal involvement remains unknown, we propose that studies with indocyanine green angiography may help understand if an abnormal developmental relationship exists between retinal and choroidal vasculature in Coats' disease.

Our findings are subject to inherent limitations, particularly relating to the nature of OCTA artifacts. Thus, systematic investigations on a larger scale are necessary in order to confirm the results of this study. In a cross-sectional study of 75 patients with diabetic retinopathy, retinal artery occlusion, retinal vein occlusion, or wet age-related macular degeneration, Enders et al. determined that various artifacts might impact the interpretation of OCTA results. Projection artifact, defined by the incorrect display of more superficial vascular structures onto the deeper slabs, was ubiquitous in this study and was identified most commonly in the deep retina and avascular layers. Segmentation, motion, and masking artifacts were seen in 43–55 % in that study.[11] As such, generally speaking, side-by-side comparisons of OCTA slabs across different time points, as in our series, must be interpreted with caution. Consistent with conclusions of Rabiolo et al.,[3] the presence of retinal pigment epithelial excrescences and fibrosis seen in case 3 of our series may challenge the interpretation of flow voids in the deep layers of OCTA due to the effect of masking.

Baseline axial length measurements in eyes affected by Coats' disease in our series were consistently smaller by 1.5–1.8 mm on A-scan, compared to the normal fellow eye. These eyes were non-phthisical and had fair baseline vision (20/25-20/400). These observations correspond with those of Galluzzi et al., who concluded that globes affected by Coats' disease have a smaller relative volume. The authors postulated that this is related to a disruption of growth factor release essential to normal retinal vascular development.[12] While it is unclear how this information should be applied clinically, its use a prognostic sign in Coats' disease has potential for study.

5. Conclusion

OCTA is a non-invasive tool that can act as a useful adjunct to multimodal imaging in the management of Coats' disease. Alterations in choroidal flow on OCTA following treatment with anti-VEGF and laser in these patients may imply a role of the choroidal vasculature in disease pathology. OCTA may not provide meaningful information regarding changes in retinal vascular flow density following treatment with anti-VEGF in Coats' disease patients.

Patient consent

This case series does not contain any personal information that could lead to the identification of the patients.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

CRediT authorship contribution statement

Noy Ashkenazy: Investigation, Conceptualization, Writing – review & editing. **Dhariana Acon:** Investigation, Writing – review & editing. **Meghana Kalavar:** Investigation, Writing – review & editing. **Audina M. Berrocal:** Writing – review & editing, Supervision.

Declaration of competing interest

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