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Longitudinal Examination of Fellow-Eye Vascular Anomalies in Coats' Disease With Widefield Fluorescein Angiography: A Multicenter Study

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Abstract

BACKGROUND AND OBJECTIVE: Retinovascular anomalies in the fellow eyes of patients with Coats' disease have been described, but the clinical significance is unknown, as well as whether these lesions progress over time.

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PATIENTS AND METHODS: This is an international, multi center, retrospective, observational cohort study of fellow-eye abnormalities on widefield fluorescein angiography in patients with Coats' disease.

RESULTS: Three hundred fifty eyes of 175 patients with Coats' disease were analyzed. A total of 33 patients (18.8%) demonstrated abnormal fellow-eye findings: 14 (42.4%) telangiectasias, 18 (54.5%) aneurysms, six (18.2%) segmental non-perfusion, six (18.2%) leakage, and two (6.0%) vascular tortuosity. All eyes were asymptomatic, and none of the lesions progressed over time. There was no association between fellow-eye findings with severity of Coats' disease ($P = .16$), patient age ($P = .16$), or presence of systemic vascular disease ($P = .16$).

CONCLUSIONS: The vascular abnormalities in fellow eyes of patients with Coats' disease did not progress over time. Observation is a reasonable initial management strategy.

INTRODUCTION

Coats' disease is an idiopathic, non-hereditary retinal vascular disease, classically characterized by unilateral retinal vascular telangiectasias and "light bulb" aneurysmal dilatations that can produce retinal exudation and edema with subsequent exudative retinal detachment.¹⁻³ The diagnosis is based on funduscopy examination, and fluorescein angiography (FA) provides valuable information.

Much of the pathologic retinal vasculature in Coats' disease is often located in the peripheral retina, which can be challenging to evaluate with conventional imaging, especially in a pediatric population. Fortunately, developments in imaging modalities, specifically widefield FA (WFA), are useful diagnostic adjuncts that have proven vital for diagnosis, surveillance, and treatment of Coats' disease.⁴

Although Coats' disease was initially considered a unilateral retinovascular disorder, vascular changes have been since been documented in the unaffected (fellow) eyes with various imaging modalities.⁵⁻⁷ However, little is known regarding the clinical significance of these abnormalities. This study investigates the longitudinal progression of fellow-eye findings using WFA, the presence of any associated factors for these findings, and their implications for Coats' disease screening and treatment.

PATIENTS AND METHODS

This is an international, multicenter, retrospective, observational cohort study of patients with Coats' disease who underwent WFA at 13 clinical sites between January 2007 and January 2018. The participating sites consisted of Massachusetts Eye and Ear Infirmary, Bascom Palmer Eye Institute, Associated Retinal Consultants, Weill Cornell Medical College, Retina & Vitreous of Texas, The University of Calgary, Shiley Eye Institute, John A. Moran Eye Center, Austin Retina Associates, Kellogg Eye Center, Great Ormond Street Hospital, Illinois Eye and Ear Infirmary, and New England Eye Center. The study protocol was approved by the respective institutional review boards and was performed in compliance with the Healthcare Insurance Portability and Accountability Act and the tenets put forth in the Declaration of Helsinki.

Inclusion criteria consisted of patients who underwent WFA between January 2007 and January 2018. The following patients were excluded from the study: those with non-WFA; those with systemic causes of Coats'-like retinopathies, such as muscular dystrophies; and those with a history of prematurity less than or equal to 36 weeks gestational age. Patients with WFA that solely captured the posterior pole were excluded from analyses. Patients with a single WFA session were included in the non-longitudinal analyses. For subjects meeting the inclusion criteria, the following demographic and clinical examination findings were recorded: baseline and final visual acuity (VA), age at diagnosis, gender, staging of the affected eye with Coats' disease, history of prematurity, presence of systemic vascular disease (hypertension, diabetes mellitus, or coronary artery disease), family history of retinovascular disease, and any treatments of the affected and fellow eye. Coats' disease stage³ was determined based on the review of the evaluating clinician's staging diagnosis in the assessment section, fundus photos, and WFA.

WFAs were obtained on FA systems in the office or utilized during examinations under anesthesia (California and Tx200; Optos, Marlborough, MA; or RetCam II and III; Natus Medical, Pleasanton, CA). Two independent readers evaluated all images (KWJ-M and YY). Initial and most recent follow-up WFAs were examined for the presence of telangiectasias, aneurysms, segmental non-perfusion, leakage, vascular tortuosity, and other vascular findings in the fellow eye. These parameters were chosen based on descriptions in previous Coats' fellow eye case reports and series. Progression was determined qualitatively via increased number of telangiectasias and aneurysms, increased areas of segmental nonperfusion, and increased leakage. Any discrepancies between the readers were adjudicated.

VAs were measured via Snellen, ETDRS, Allen optotypes, and Teller preferential looking, depending on the age of the child. These were converted to logarithm of the minimal angle of resolution (logMAR) units for analyses. As the majority of the population for Coats' disease consists of pediatric patients, vision was often recorded as "fix and follow" or "Central-Steady-Maintained (CSM);" these values were not included in the analysis. Microsoft Excel (Microsoft, Redmond, WA) and GraphPad Prism (GraphPad, San Diego, CA) were used for statistical analyses. Student's *t*-test was performed for comparisons between means. Fisher's exact or chi-square test was performed for frequency comparisons of categorical variables. Intergrader reliability was determined by Cohen's Kappa coefficient. All analyses were two-tailed with *P* values equal to or less than .05 considered significant.

RESULTS

Three hundred and fifty eyes of 175 patients with Coats' disease were analyzed (Table 1). Mean age at presentation was 10.4 years with a mean time of follow-up of 25.4 months (range: 1 month to 79 months). Eighty-six percent of patients were male and 14% were female. The mean VA of the fellow eyes was 20/22 in initial presentation and 20/20 on final presentation. The majority (61.7%) of patients with Coats' were classified as having stage 2b disease (retinal telangiectasia with exudation involving the fovea). The number of patients who had multiple WFA for longitudinal analyses totaled 103 (58.8%). There were

72 (41.1%) patients from the entire cohort and 13 (39%) patients with fellow-eye findings who received a single WFA. Ninety-one patients (52%) underwent imaging with RetCam cameras, and 84 (48%) with Optos imaging systems. One patient had a family history of an unspecified sectoral vascular disease in the father; otherwise, no patients had a family history of retinovascular disease. Treatment of the Coats' affected eye ranged from a combination of laser, intravitreal bevacizumab (Avastin; Genentech, South San Francisco, CA), intravitreal kenalog, cryotherapy, scleral buckling, and pars plana vitrectomy.

Fellow-Eye Findings

A total of 33 (18.8%) patients demonstrated fellow eye abnormalities. Intergrader reliability after the initial independent image grading was 0.799. Fellow eye findings consisted of 14 (42.4%) telangiectasias (Figure 1), 18 (54.5%) aneurysms (Figure 1), six (18.2%) segmental non-perfusion (Figure 2), six (18.2%) leakage (Figure 3), and two (6.0%) tortuosity of vessels (Figure 4). These fellow eye abnormalities were in the periphery, with the exception of tortuosity, and all remained unchanged during the follow-up period. Only one (3.0%) aneurysmal lesion was treated. The highest proportion of patients (51.5% of the 33 patients) with fellow-eye findings were characterized as having stage 2b disease in the affected eye with Coats' disease (Table 2).

Fellow Eye Findings and Associated Variables

We performed an exploratory analysis evaluating the univariate relationship between the presence of fellow-eye findings and severity of Coats' disease. Although the highest proportion of patients with fellow eye findings were characterized with stage 2b Coats' disease, the severity of Coats' disease was not associated with the presence of fellow-eye findings ($\chi^2 = 5.1$; $P = .16$). Four patients were documented to have had systemic vascular disease (hypertension (1), sickle cell trait (2), and bicuspid aortic valve (1)). There was no relationship between the presence of systemic vascular disease and the presence of fellow eye findings (Fisher's exact test; $P = .16$). Lastly, no age group demonstrated a disproportionate prevalence for fellow-eye findings ($\chi^2 = 6.6$; $P = .16$) (Table 3).

DISCUSSION

Coats' disease is a congenital, sporadic disease with characteristic retinovascular findings. Although classically unilateral, recent reports in the literature argue for bilateral vascular findings, asymmetric in appearance and of decreased severity in the fellow eye, in a proportion of patients.⁵⁻⁷ To the best of our knowledge, this is the largest cohort examining the presence of fellow-eye findings in Coats' patients and is the only study to examine whether these changes evolve over time.

In this study, we retrospectively reviewed the frequency of fellow-eye retinovascular findings in patients with Coats' disease using WFA, and the relationship of these findings with Coats' disease stage, patient age, and presence of systemic vascular disease. Additionally, we studied whether these fellow-eye findings progressed over time, by comparing the initial WFA and final WFA.

The key findings of this study were: 1) Fellow-eye findings were identified in nearly 20% of patients with Coats' disease; 2) Fellow-eye findings did not progress over time or result in visually significant changes; and 3) Fellow-eye findings were not associated with severity of Coats' disease, patient age, or presence of systemic vascular disease.

There are several important clinical implications of these data. First, fellow-eye findings should be examined carefully when evaluating patients with Coats' disease. A prevalence of 18.8% of vascular changes in the unaffected eye is a substantial number. Optical coherence tomography angiography has also demonstrated abnormal macular foveal avascular zone in fellow unaffected eyes of patients with unilateral Coats, which also supports that the retinovascular abnormality is not isolated to the unilateral affected eye.⁷ This study was a retrospective review of previously taken images, so we suspect that if physicians are purposely looking for these changes, that even more peripheral views and detailed fluorescein angiograms would be obtained, leading to potential detection of even more fellow-eye findings. Therefore, fellow-eye findings may possibly be considerably more prevalent compared to what we found in this study. Only a prospective study would be able to address this question with certainty.

Second, although these fellow-eye findings are potentially changing our understanding of Coats' disease, in the current study, they did not have any clinical implications. The lesions were subtle in most patients, and there was no progression of the vascular anomalies, at least during the follow-up period in this study. We cannot assert that these lesions never progress due to the limitations of the study design; however, we can reasonably infer that these lesions likely do not acutely progress and that observation is the most prudent initial management strategy. We also need to remember that we studied idiopathic Coats' disease, and excluded Coats'-like retinopathies that can be seen in some systemic diseases or in association with other bilateral vitreoretinopathies or retinal degenerations.⁸⁻¹¹ The latter presentations of bilateral Coats'-like retinopathies tend to be more symmetric and are different entities from what we studied.

The pathophysiologic implication of our findings is that Coats' disease may in fact be a bilateral disease with asymmetric severity. This raises the question of Coats' disease having a genetic predisposition or alterations, with phenotypic variability resulting from mosaicism, or environmental or developmental insults in one eye leading to asymmetric disease. As there is no established genetic marker for Coats' disease, our patients were all diagnosed clinically. However, Coats' disease can have a broad differential diagnosis, and the bilateral findings in this paper raise the possibility that there is a bilateral process of a similar clinical appearance at work, such as familial exudative vitreoretinopathy, Norrie disease, and retinoblastoma. To support our diagnosis of Coats' disease, the patients in this series did not exhibit any evidence of syndromic disease, had normal hearing, did not have family history supportive of familial vitreoretinopathies, and there were no concerns for or evidence of neoplastic processes. Furthermore, FA in Coats' disease is distinct from these other diagnoses, and all patients in our cohort had undergone angiographic confirmation by design of the study.

WFA provides essential diagnostic information for pediatric retinal vascular diseases and is essentially confirmatory for Coats' disease. However, there are reports demonstrating a high prevalence of peripheral vascular abnormalities on WFA that occur in adult eyes expected to have normal peripheral vasculature.^{12–14} The imaged eyes in these studies had presented for evaluation of the following conditions: epiretinal membrane, choroidal nevus, floaters, diabetes, and fellow eyes of patients with retinal vein occlusion and central serous retinopathy. In the study by Shah et al., peripheral findings were found in nearly 100% of eyes. These findings included right angle vessels (70.69%), terminal networks (77.59%), loss of capillary detail (98.28%), ground glass hyperfluorescence (87.93%), capillary nonperfusion (98.28%), and microaneurysms (41.38%).¹² Lu et al. reported findings of granular background fluorescence (100%), a mottled fluorescent band (43.6%), and vascular leakage (19.8%) in the periphery on WFA.¹⁴ In a 2016 study by Seo et al., telangiectasias (43.4%), microaneurysms (40.9%), and vascular leakage (58.3%) were observed in diabetic eyes (categorized as ranging from no diabetic change to early diabetic change).¹³ However, given the presence of systemic vascular disease in these patients, there may be occult vascular findings on FA that are not clinically apparent. In our cohort of patients, none had reported systemic diabetes. To summarize, rates of vascular changes in these studies relevant to our findings were leakage (approximately 20%), capillary non-perfusion (approximately 98%), telangiectasias (approximately 43%), and microaneurysms (approximately 40%). However, these studies were conducted in adult eyes, some with systemic vascular pathology (retinal vein occlusion, diabetes) that may result in occult fellow eye findings. In contrast, our study focuses on a predominantly pediatric cohort that you would not expect to find abnormal peripheral findings in presumed normal contralateral eyes. The above definitions of "telangiectasia" and "microaneurysms" are also likely different in morphology from what we are observing in this Coats' study, where we are focusing on identifying Coats' - like lesions. We attempted to avoid over categorizing peripheral vascular changes as pathologic findings by using these studies as reference points as well as employing two independent readers; however, it is still possible our results contain a cohort of "normal" peripheral findings that could falsely inflate our reported percentages of fellow-eye findings.

Other limitations of this study include its retrospective nature and inherent inconsistencies of imaging techniques and quality, which would only be possible in a controlled prospective study. Coats' disease is a relatively rare condition, with an estimated incidence of 0.09 cases per 100,000.¹⁵ Therefore, a prospective study to account for the majority of confounding variables would be relatively difficult to achieve. Furthermore, clinical diagnosis with FA is the standard for diagnosing Coats' disease; until our understanding of the pathophysiology of this disease improves, we are limited by these methods for definitive diagnosis. We also found no associations between the presence of systemic vascular disease and Coats' disease. Most patients followed for Coats' disease are younger and often lack systemic vascular pathology that typically manifests in older age. It is possible that there are relationships between systemic vascular factors and the presence of fellow-eye findings, which may become more apparent, as the patients age.

In conclusion, fellow eye findings were prevalent in our cohort of patients with Coats' disease. Although these lesions have not been shown to progress, we recommend close

examination of both the clinically affected eye and the fellow “unaffected” eye to identify these lesions and monitor for potential progression.

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Figure 1. Fundus image (left) and widefield fluorescein angiography (right) of the fellow unaffected eye in a patient with Coats' disease demonstrating aneurysms (yellow arrow) and telangiectasias (red arrow).

Figure 2. Widefield fluorescein angiography of the fellow unaffected eye in a patient with Coats' disease demonstrating peripheral non-perfusion (area between the yellow outline).

Figure 3. Fundus image (left) and widefield fluorescein angiography (right) of the fellow unaffected eye in a patient with Coat's disease demonstrating peripheral vascular leakage (yellow arrows).

Figure 4. Fundus image (left) and widefield fluorescein angiography (right) of the fellow unaffected eye in a patient with Coats' disease demonstrating retinal vascular tortuosity. The patient has no systemic cardiovascular disease after a thorough workup.

TABLE 1**Patient Demographics**

Mean Age at Presentation	10.4 years
Mean Time of Follow-Up	25.4 months (range: 1-79 months)
Gender	
Male	151 (86%)
Female	24 (14%)
Eye With Coats' Disease	
Right eye	88
Left eye	87
Mean logMAR Visual Acuity of Fellow Eye	
Initial presentation	0.045 (~20/22)
Final presentation	0.008 (~20/20)
Stage of Coats' Disease in Affected Eye	
1	8 (4.57%)
2a	35 (20%)
2b	108 (61.7%)
3a-1	5 (2.9%)
3a-2	7 (4%)
3b	9 (5.1%)
4	1 (0.6%)
5	2 (1.1%)

TABLE 2

Fellow-Eye Findings According to Stage of Coats' Disease

Stage	Abnormal Fellow Eyes n = 33	Normal Fellow Eyes n = 142
1	2 (6.06%)	6 (4.23%)
2a	11 (33.3%)	24 (16.9%)
2b	17 (51.51%)	91 (64.1%)
3a-1	0 (0%)	5 (3.5%)
3a-2	1 (3.03%)	6 (4.2%)
3b	2 (6.06%)	7 (4.9%)
4	0 (0%)	1 (0.7%)
5	0 (0%)	2 (1.4%)

TABLE 3

Fellow-Eye Findings According to Age Group

Age (Years)	Number of Fellow Eyes With Abnormal Findings
0-3	8
4-8	6
9-12	5
13-17	7
18+	7

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