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Comparison of Visual Outcomes in Coats' Disease

A 20-Year Experience

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Purpose: To report differences in visual acuities among patients with Coats' disease who sought treatment at a tertiary care university-based practice.

Design: Single-center retrospective cohort study.

Participants: Patients with Coats' disease diagnosed clinically, angiographically, or both from 1995 through 2015.

Methods: Patients were divided into 2 groups based on date of presentation: decade 1 (1995–2005) and decade 2 (2006–2015).

Main Outcome Measures: Visual acuity (VA).

Results: Thirty-nine eyes of 39 patients were included with 19 eyes presenting in decade 1 and 20 eyes presenting in decade 2. Three patients demonstrated bilateral disease, but only the worse eye was included for analysis. Forty-seven percent of eyes in decade 1 demonstrated advanced stages of disease (stage 3B or worse) compared with 20% of eyes in decade 2. There was a trend for the mean initial presenting VA (±standard deviation) for decade 1 eyes to be worse (2.05±1.29 logarithm of the minimum angle of resolution [logMAR]) than for decade 2 eyes (1.45±0.99 logMAR; $P = 0.1$). From initial to final follow-up visit, mean VA also worsened for decade 1 eyes ($P = 0.03$), but remained stable for decade 2 eyes ($P = 1.0$). At the end of follow-up, there was a trend for mean VA for decade 1 eyes (2.28±1.17 logMAR) to be worse than for decade 2 eyes (1.60±1.15 logMAR; $P = 0.07$). Eight eyes were observed initially in decade 1 compared with 1 eye in decade 2, and only 1 of the observed eyes (in decade 2) developed painful glaucoma requiring enucleation. Decade 2 eyes had a higher average number of procedures per eye (6.5±4.9) compared with decade 1 eyes (1.4±1.7; $P < 0.001$).

Conclusions: The earlier presentation of disease in decade 2 suggests improvements in disease detection over time. Furthermore, there was a trend for eyes to have better final VA in this decade. This is due to a combination of factors, including earlier presentation of disease, fewer eyes being observed without treatment, and eyes, when treated, receiving a higher number of procedures. *Ophthalmology 2017;124:1368-1376 © 2017 by the American Academy of Ophthalmology*

Coats' disease is a sporadic and nonhereditary condition characterized as idiopathic retinal telangiectasia that may progress to retinal exudation and exudative retinal detachment in the absence of retinal or vitreous traction.[1] Severe complications of untreated Coats' disease can be devastating and include neovascular glaucoma and phthisis bulbi.[2]

Traditionally, Coats' disease has been diagnosed clinically with indirect ophthalmoscopy, and in eyes with early stages of disease, has been treated with laser photocoagulation or cryotherapy to the abnormal telangiectasic vessels.[1] In recent years, the advent of wide-field imaging and fluorescein angiography during examination under anesthesia has allowed earlier identification of peripheral vascular anomalies and areas of abnormal retinal perfusion in one or both eyes.[3–5] In cases where subretinal fluid prevents adequate ablative therapy, Coats' disease has been treated with intravitreal triamcinolone (IVT) or anti–vascular endothelial growth factor (VEGF) injections, or surgically with vitrectomy, subretinal fluid drainage, or both, with or without scleral buckle.[6–10]

Despite the introduction of new diagnostic methods and treatment strategies for Coats' disease in recent years, few studies have been published to describe how these new advances have affected patients' anatomic and visual outcomes. Herein, we studied the population of Coats' patients who were diagnosed and treated at a tertiary care academic vitreoretinal practice over a 20-year period to compare treatment approaches and outcomes over 2 distinct 10-year periods.

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Methods

This was a retrospective review of all consecutive patients aged 18 years or younger at presentation with Coats' disease treated by multiple vitreoretinal specialists (E.G.B., B.W.M., G.J.J., E.A.P., T.H.M., C.A.T., L.V., P.M.) at the Duke University Eye Center between January 1, 1995, and September 30, 2015, and who were followed up for at least 12 months. The study was designed in accordance with the tenets of the Declaration of Helsinki, was approved by the Duke University Institutional Review Board, and complied with the Health Insurance Portability and Accountability Act. Patients with a diagnosis code of exudative retinopathy (International Classification of Diseases, Ninth Revision, code 362.12) were identified using the Duke Enterprise Data Unified Content Explorer database. Patients were excluded if they did not have clinical evidence of Coats' disease, were treated at another institution, or had missing or incomplete records.

Patients were diagnosed clinically with Coats' disease based on the following criteria: presence of idiopathic retinal telangiectasia with or without intraretinal or subretinal exudation and with or without exudative retinal detachments. Demographic information, visual acuity (VA) at several time points (initial presentation, the 12- to 18-month follow-up, the intermediate period for decade 1, and the final follow-up) when available were recorded, and details of each examination were recorded. Pediatric patients usually were examined and treated under anesthesia. Fundus photography and fluorescein angiography were performed using a RetCam 2 (Clarity Medical Systems, Pleasanton, CA), Zeiss FF450 (Carl Zeiss Meditec, Okerkochen, Germany), or Optos 200Tx (Optos, Inc., Dunfermline, United Kingdom) imaging device at the discretion of the treating physician.

Eyes then were divided into 2 groups based on year of presentation: decade 1 (1995−2005) and decade 2 (2006−2015). Furthermore, eyes were divided into 5 stages of disease at the time of presentation as previously described by Shields et al.[11] Briefly, stages 1, 2A, 2B, 3A, 3B, 4, and 5 are defined as follows: stage 1 corresponds to eyes with retinal telangiectasia only; stage 2A refers to eyes with retinal telangiectasia and extrafoveal exudation; stage 2B denotes eyes with retinal telangiectasia and foveal exudation; stage 3A represents eyes with retinal telangiectasia, exudation, and subtotal retinal detachment; stage 3B describes eyes with retinal telangiectasia, exudation, and total retinal detachment; stage 4 eyes demonstrate retinal telangiectasia, exudation, total retinal detachment, and secondary glaucoma; and stage 5 eyes are defined as blind eyes with retinal telangiectasia, exudation, total retinal detachment, and anterior chamber involvement or phthisis (advanced end-stage disease).

Management methods included observation (defined as no treatment for posterior manifestations of Coats' disease; some patients in this group still underwent cataract or strabismus surgery); ablative therapies including cryotherapy, 532-nm laser, or both; vitreoretinal surgery, which included any combination of subretinal fluid drainage, scleral buckle, pars plana vitrectomy, epiretinal membrane removal, and intraocular gas or silicone oil tamponade; IVT injection; or enucleation. After 2008, off-label intravitreal bevacizumab (IVB; 1.25 mg or 0.625 mg; Genentech, Inc., South San Francisco, CA) was given to selected eyes based on treating physician preference. Anatomic disease resolution was defined as resolution of exudates, exudative subretinal fluid, or both. When possible, best-corrected VA was obtained at each clinical visit. Visual acuity was measured using Snellen or Early Treatment Diabetic Retinopathy Study charts. In young children who could not recognize the letters or numbers on Snellen or Early Treatment Diabetic Retinopathy Study charts, VA was measured using Allen pictures or HOTV charts. Snellen VA equivalent of 20/125 was selected as a cutoff to determine eyes that maintained functional vision at the end of follow-up.

Statistical Analysis

Snellen VA equivalent was converted to logarithm of the minimum angle of resolution (logMAR) units for analysis. Snellen acuities for counting fingers, hand movements, light perception, and no light perception (NLP) measured at 2 feet were approximated as described previously.[12] Snellen acuities for measurements made at other distances were extrapolated from those obtained at 2 feet. Only 1 eye from each patient was included in statistical analysis. In patients with bilateral involvement, the worse eye was included in statistical analysis. For paired analysis (comparison of same eyes at different time points), only eyes that had documented Snellen VA equivalent at both of the visits being compared were included. The Mann−Whitney U test and Kruskal−Wallis test were used to compare continuous variables between groups and among groups, whereas the Fisher exact test was used to compare categorical variables between groups. The Wilcoxon signed-rank test was used to compare paired data. A P value of 0.05 or less was considered statistically significant. Statistical analysis was performed using SAS software version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Baseline Characteristics of Study Participants

A total of 55 patients with complete medical records who were treated for Coats' disease at our institution were identified. A total of 16 patients were excluded: 14 had follow up less than 12 months and 2 were adults older than age 18 years at the time of presentation. Thirty-nine patients met inclusion criteria. Three patients demonstrated asymmetric bilateral disease at presentation (decade 1: stages 2B and 1 and stages 3B and 5; decade 2: stages 3A and 1). Only 1 eye from each patient was included in statistical analysis, and the better eye from patients with bilateral disease was excluded.

Baseline demographics and ocular characteristics of the final cohort of 39 eyes of 39 patients who met inclusion criteria are shown in Table 1 and are consistent with previously published reports.[1,13−19] There was no significant difference in baseline demographic characteristics between patients in the 2 decades. There was a trend for eyes in decade 1 to demonstrate more advanced stages of disease than those in decade 2: 47% of eyes in decade 1 demonstrated stage 3B to 5 disease (9 of 19 eyes) compared with 20% of eyes in decade 2 (4 of 20 eyes; $P = 0.1$).

Given the small number of eyes with advanced disease in decade 2, eyes from both decades were combined to examine the relationship between stage of disease and presenting VA. Eyes with more advanced stages of disease presented with worse initial VA ± standard deviation (SD; stage 2A, 0.12±0.13 logMAR [n = 4]; stage 2B, 0.87±0.48 logMAR [n = 5]; stage 3A, 1.78±1.03 logMAR [n = 15]; stage 3B, 2.95±0.21 logMAR [n = 7]; stage 4, 3.20 logMAR [n = 1]; stage 5, 3.20 logMAR [n = 1]; $P = 0.001$). Correspondingly, there was a trend for eyes in decade 1 to demonstrate worse VA than eyes in decade 2 ($P = 0.1$).

Table 1. Patient Demographics and Baseline Ocular Characteristics

Variable	Decade 1	Decade 2	P Value
Total no. of patients	19	20	
Age (mos)			
Mean ± SD	78.1±63.7	95.2±73.3	0.5
Range	1–221	5–224	
Gender, no. (%)			
Male	16 (84.2)	17 (85.0)	1.0
Female	3 (15.8)	3 (15.0)	1.0
Race, no (%)			
White	13 (68.4)	10 (50.0)	0.3
Black	5 (26.3)	4 (20.0)	0.7
Asian	0	2 (10.0)	0.5
Hispanic	0	1 (5.0)	1.0
Not reported	1 (5.3)	3 (15.0)	0.6
Eye laterality, no. (%)			
Right eye	10 (52.6)	12 (60.0)	1.0
Left eye	9 (47.4)	8 (40.0)	1.0
Stage of disease at presentation, no. (%)			
1	0	0	N/A
2A	2 (10.5)	2 (10.0)	1.0
2B	3 (15.8)	4 (20.0)	1.0
3A	5 (26.3)	10 (50.0)	0.2
3B	7 (36.8)	4 (20.0)	0.3
4	1 (5.3)	0	0.5
5	1 (5.3)	0	0.5
Combined stages of disease, no. (%)			
Stages 1 to 3A	10 (52.6)	16 (80.0)	0.1
Stages 3B to 5	9 (47.4)	4 (20.0)	0.1
Best-corrected visual acuity (logMAR) at presentation by stage, mean ± SD (no.)			
2A	0.05±0.07 (2)	0.20±0.14 (2)	0.4
2B	0.95±0.38 (3)	0.75±0.78 (2)	1.0
3A	2.00±1.45 (5)	1.69±0.83 (10)	0.7
3B	2.95±0.23 (6)	2.90 (1)	N/A
4	3.20 (1)	0	N/A
5	3.20 (1)	0	N/A
P value	0.05*	0.07	
All stages	2.05±1.29 (18)	1.45±0.99 (15)	0.1

logMAR = logarithm of the minimum angle of resolution; N/A = not applicable; SD = standard deviation.
*Statistically significant.

Outcomes by Decade of Treatment

Nineteen eyes presented in decade 1 and 20 eyes presented in decade 2. As expected, the mean ± SD follow-up was longer for decade 1 eyes (110.9±74.2 months) than for decade 2 eyes (46.2±28.9 months; $P = 0.01$).

Visual Acuity Outcomes. Average VA at presentation and end of follow-up were compared for each of the 2 groups, as shown in Table 2. This analysis examined only eyes that had VA documented at both initial and final follow-up visits (16 eyes in decade 1 and 14 eyes in decade 2). Mean VA worsened from initial to final visit for decade 1 eyes ($P = 0.03$). As shown in Figure 1, VA in decade 1 stayed the same for 3 eyes, improved for 2 eyes, and worsened for 11 eyes. Only 2 of the 16 eyes (13%) maintained VA of 20/125 or better by the final follow-up, whereas 8 eyes (50%) had maintained or progressed to NLP VA. In contrast, mean initial and final VA for decade 2 eyes remained stable ($P = 1.0$). Specifically, VA in this decade remained stable for 1 eye, improved for 8 eyes, and worsened for 5 eyes. Five of 14 eyes (36%) maintained VA of 20/125 or better, whereas 1 eye (7%) had progressed to NLP VA at the end of follow-up. Overall, there was a trend of better mean final VA in decade 2 (1.60±1.15 logMAR) than in decade 1 (2.28±1.17 logMAR; $P = 0.07$).

To determine if the difference in length of follow-up between decades 1 and 2 influenced the final visual outcomes, VA at an intermediate period of follow-up for decade 1 also was examined. The mean intermediate follow-up period was 38.2±10.9 months (range, 14–61 months). Mean VA in decade 1 again worsened from initial to intermediate follow-up (2.27±1.15 logMAR; $P = 0.02$), and there was no difference in mean VA between intermediate and final follow-up ($P = 0.9$). Visual acuity for eyes in decade 1 at the final visit was stable for 13 eyes, improved for 1 eye, and worsened for 2 eyes compared with the intermediate follow-up period. Two of the 16 eyes (13%) maintained VA of 20/125 or better and 8 eyes (50%) maintained or progressed to NLP VA by this intermediate period of follow-up. Given the comparable follow-up periods between intermediate follow-up in decade 1 and final follow-up in decade 2, mean VA for these 2 groups were then compared. Overall, there was a trend of better mean final VA in decade 2 (1.60±1.15 logMAR) than mean intermediate VA in decade 1 (2.27±1.15 logMAR; $P = 0.07$).

Next, VA at a common time point (12–18 months of follow-up) in both decades was examined. Visual acuity during this window of follow-up was available only for 13 eyes in decade 1 and 10 eyes in decade 2. There was no significant difference in mean VA in decade 1 from initial visit (1.84±1.24 logMAR) to the 12- to 18-month follow-up (2.12±1.17 logMAR; $P = 0.3$). Similarly, there was no significant difference in mean VA in decade 2 from presentation (1.68±0.95 logMAR) to the 12- to 18-month follow-up (1.55±0.93 logMAR; $P = 0.6$). Additionally, mean 12- to 18-month VA in decade 2 was not statistically different from mean 12- to 18-month VA in decade 1 ($P = 0.2$).

Globe Salvage and Anatomic Outcomes. Although more eyes were managed with observation alone in decade 1 (n = 8) compared with decade 2 (n = 1), the globe salvage rates did not differ in the 2 decades. Only 1 observed eye was enucleated because of uncontrolled pain after progression to angle-closure glaucoma, and this eye had stage 3B disease and had presented in decade 2. Before enucleation, this eye had been treated with transscleral diode cyclophotocoagulation with inadequate intraocular pressure relief. None of the observed eyes in decade 1 demonstrated glaucoma and none had to be enucleated.

In addition to the 1 stage 3B eye in decade 2 that was enucleated after progression to uncontrolled painful glaucoma, 12 other eyes across both decades demonstrated stage 3B or worse disease. Of these, 2 eyes (with stages 3B and 5 disease) in decade 1 and 1 eye (with stage 3B disease) in decade 2 were enucleated at presentation because of concern about retinoblastoma, although pathologic examination eventually showed Coats' disease. Despite poor visual outcomes, the globe was salvaged in the other 9 eyes with stage 3B disease or worse. The 1 stage 4 eye was observed without treatment for posterior segment manifestations of Coat's disease, but underwent cataract extraction without intraocular lens placement for angle-closure glaucoma in the setting of total retrolental retinal detachment. The glaucoma resolved after cataract surgery.

Table 2. Visual Acuity Measured at Presentation and Final Follow-up for All Eyes, Eyes in Decades 1 and 2, and by Stage of Disease

	Overall				Decade 1				Decade 2			
Stage	*No.*	*Initial Visual Acuity*	*Final Visual Acuity*	*P Value*	*No.*	*Initial Visual Acuity*	*Final Visual Acuity*	*P Value*	*No.*	*Initial Visual Acuity*	*Final Visual Acuity*	*P Value*
All stages	30	1.73±1.15	1.96±1.19	0.2	16	1.90±1.29	2.28±1.17	0.03*	14	1.53±0.97	1.60±1.15	1.0
2A	3	0.06±0.06	0.93±1.45	0.8	2	0.05±0.07	1.39±1.71	0.5	1	0.10	0	N/A
2B	5	0.87±0.48	0.90±0.72	1.0	3	0.95±0.38	0.90±0.46	0.9	2	0.75±0.78	0.91±1.29	1.0
3A	15	1.78±1.03	1.98±1.08	0.5	5	1.96±1.45	2.41±1.11	0.1	10	1.69±0.83	1.77±1.06	1.0
3B	6	2.90±0.19	3.10±0.16	0.1	5	2.90±0.21	3.14±0.13	0.1	1	2.90	2.90	N/A
4	1	3.20	3.20	N/A	1	3.20	3.20	N/A	0	N/A	N/A	N/A
5	0	N/A	N/A	N/A	0	N/A	N/A	N/A	0	N/A	N/A	N/A

N/A = not applicable.
Visual acuity (VA) measured in logarithm of the minimum angle of resolution (logMAR) units. Data are mean ± standard deviation unless otherwise indicated. *P* values from Wilcoxon signed-rank test for comparison of mean VA at initial and final follow-up visits. Only eyes that had documented VA at both the initial and final visits were included in this analysis.
*Statistically significant.

As expected, none of the observed-only eyes showed anatomic resolution of disease. Of the eyes that received therapeutic interventions, exudation with or without subretinal fluid resolved in 5 of 10 eyes (50%) in decade 1 and in 11 of 18 eyes (61%) in decade 2. Two of the eyes in decade 2 that did not show anatomic resolution of disease were still being treated at the end of the study (1 eye had follow-up of 19 months, whereas the other had follow-up of 12 months by the end of the study). One eye in decade 2 (with stage 3A disease) developed phthisis despite treatment with vitreoretinal surgery and ablation.

Treatment Differences between the First and Second Decade of the Study

We also analyzed if there was a difference in the number of procedures per eye in both groups that could explain the difference in

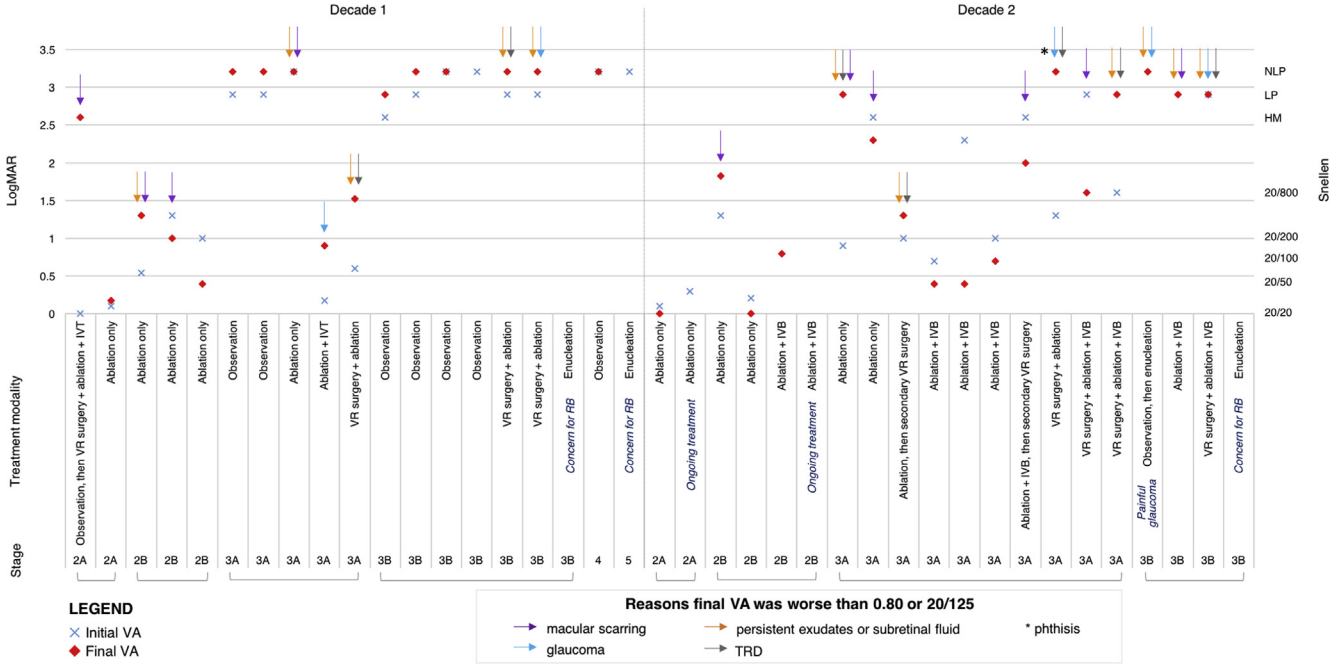

Figure 1. Scatterplot showing initial and final visual acuity (VA) measurements in logarithm of the minimum angle of resolution (logMAR) units in each eye by decade of presentation. The VA by Snellen equivalent is marked on the right axis. Eyes that presented in decade 1 are listed on the left, and eyes that presented in decade 2 are listed on the right. Visual acuity on presentation is plotted as a blue cross, whereas VA at the end of follow-up is plotted as a red diamond. Reasons for final VA worse than 0.80 logMAR or 20/125 despite treatment are denoted as arrows. Persistent exudates, subretinal fluid, or both are denoted as orange arrows, macular scarring is denoted as purple arrows, tractional retinal detachment (TRD) is denoted as gray arrows, and glaucoma is denoted as light blue arrows. The 1 eye that developed phthisis is marked with an asterisk. Two eyes in decade 2 were still undergoing treatment by the end of follow-up because of persistent exudates. Three eyes were enucleated because of concern for retinoblastoma (RB). HM = hand movements; IVB = intravitreal bevacizumab; IVT = intravitreal triamcinolone; LP = light perception; NLP = no light perception; VR = vitreoretinal.

VAs between groups. Eyes that presented in decade 2 underwent a higher average number of procedures per patient (mean ± SD, 6.5±4.9) compared with eyes that presented in decade 1 (mean ± SD, 1.4±1.7; $P < 0.001$). After removing eyes that were observed only or had been enucleated, the difference between the number of procedures between the 2 groups remained significant (7.1±4.8 in decade 2 vs. 2.4±1.8 in decade 1; $P = 0.003$).

Comparison of Eyes Treated with and without Intravitreal Bevacizumab over Both Decades

Intravitreal bevacizumab was introduced after 2008 and was used in eyes with stage 2B disease and greater. As shown in Figure 1, of the stage 2B eyes, 2 of 5 eyes treated with ablation only had final VA of 20/125 or better. Reasons for VA worse than 20/125 included failure to achieve anatomic resolution and macular scarring. One of 2 stage 2B eyes treated with ablation and IVB also achieved VA of 20/125 or better. The remainder stage 2B eye treated with ablation and IVB was still undergoing treatment at the end of the study (length of follow-up, 12 months) because of unresolved exudation and telangiectasia.

Only 3 of the 15 stage 3A eyes (20%) had final VA of 20/125 or better, and all 3 eyes had undergone ablation and IVB therapy. Another stage 3A eye that had been treated primarily with ablation and IVB therapy later demonstrated nonclearing vitreous hemorrhage requiring secondary vitreoretinal surgery, and this eye's final VA was worse than 20/125 in the setting of macular scarring (Table 3). The rest of the stage 3A eyes were observed (n = 2), underwent ablation only (n = 3), underwent ablation only initially followed by secondary vitreoretinal surgery for tractional retinal detachment (TRD; n = 1), underwent ablation with IVT (n = 1), and underwent primary vitreoretinal surgery with ablation (n = 2) or primary vitreoretinal surgery with ablation and IVB (n = 2). Reasons for VA worse than 20/125 in these eyes included failure of anatomic improvement, macular scarring, TRD, and glaucoma. Phthisis developed in 1 eye. The decision to perform vitreoretinal surgery as primary therapy in stage 3A eyes was dependent on the extent of retinal detachment. Eyes with 2 quadrants or fewer of retinal detachment were treated with ablation only or ablation with IVB without vitreoretinal surgery, whereas those with more extensive retinal detachment also underwent vitreoretinal surgery. See Table 3 for details of individual eyes that underwent vitreoretinal surgery.

Stage 3B eyes had poor final visual outcomes ranging from light perception to NLP regardless of treatment method. Treated eyes received vitreoretinal surgery with ablation (n = 2), ablation with IVB (n = 1), or vitreoretinal surgery with ablation and IVB (n = 1). Reasons for poor VA included failure to achieve anatomic improvement, macular scarring, TRD, and glaucoma. Five of 11 stage 3B eyes (45%) were observed, and 1 of the observed eyes demonstrated glaucoma and eye pain requiring enucleation.

Development of Tractional Retinal Detachment, Macular Scarring, and Glaucoma

Because of previous reports that IVB could induce TRD and macular fibrosis,[20] we examined differences in rates of TRD and macular scarring among all eyes that were treated with and without IVB. This analysis of TRD and macular scarring development did not exclude eyes with VA of 20/125 or better as in the prior analysis (Fig 1). We found no difference in TRD development among eyes that underwent primary therapy with ablation only (3 of 11 eyes) versus ablation with IVB (0 of 7 eyes) or among eyes that underwent primary vitreoretinal surgery with ablation (3 of 4 eyes) versus primary vitreoretinal surgery with ablation and IVB (2 of 3 eyes). There was also no difference between TRD development in primary ablation-only groups treated in decade 1 (0 of 4 eyes) versus in decade 2 (3 of 7 eyes) or in primary vitreoretinal surgery with ablation groups treated in decade 1 (2 of 3 eyes) versus in decade 2 (1 of 1 eye). Eyes treated with IVB all sought treatment in decade 2, so a comparison across decades was not performed.

We then analyzed the difference in rate of macular scarring between eyes that had received IVB therapy versus those that had not. We found no difference among eyes that underwent primary therapy of ablation only (6 of 11 eyes) versus ablation with IVB (2 of 7 eyes) or among eyes that underwent primary vitreoretinal surgery with ablation (1 of 1 eye) versus primary vitreoretinal surgery with ablation and IVB (3 of 3 eyes). There was only 1 eye in the primary vitreoretinal surgery with ablation group because the other eyes in this group had severe pathologic features precluding assessment for macular scarring. There was also no difference between macular scarring development in primary ablation-only groups treated in decade 1 (3 of 4 eyes) versus those treated in decade 2 (3 of 7 eyes) or in primary vitreoretinal surgery and ablation groups treated in decade 1 (1 of 1 eye) versus those treated in decade 2 (0 eyes).

Secondary glaucoma was found at presentation for the stage 4 eye in decade 1. After lensectomy, the angle-closure glaucoma resolved in this eye. Glaucoma developed after presentation in 2 eyes in decade 1 and 3 eyes in decade 2. Only 1 of the 5 eyes (1 observed stage 3B eye in decade 2) required enucleation because of painful glaucoma that remained uncontrolled despite transscleral diode photocoagulation. Glaucoma in the other 4 eyes was controlled with ocular hypotensive drops (decade 1, 1 stage 3A eye treated with ablation and IVT and 1 stage 3B eye treated with vitreoretinal surgery and ablation; decade 2, 1 stage 3A eye treated with vitreoretinal surgery and ablation) or ocular hypotensive drops with IVB (1 stage 3B eye treated with vitreoretinal surgery, ablation, and IVB in decade 2).

Discussion

Coats' disease presents numerous challenges in the management and preservation of VA across the disease spectrum. Our study demonstrated differences in ocular characteristics, treatment approach, and outcomes spanning 2 different decades in a university-based Coats' disease population. In this study, eyes that presented in decade 1 were more likely to show advanced stages of disease compared with eyes that presented in decade 2, which suggests earlier recognition and detection of disease over time. This could be related to improvements in visual screenings in schools and the general pediatrics office. The American Academy of Pediatrics and the United States Preventative Services Task Force have advocated for screenings for visual impairment in children at a young age,[21,22] and automated devices that take less time per child and allow the screening of an uncooperative child have become more available and easier to use over time.[23,24]

Table 3. Vitreoretinal Surgical Methods by Decade of Presentation and Whether Surgery Was Conducted to Address Primary or Secondary Ocular Manifestations of Coats' Disease

Decade of Presentation	Stage	Other Treatments	Initial Visual Acuity	Final Visual Acuity	Vitreoretinal Surgery	Surgery for Primary or Secondary Manifestations of Coats' Disease	
1	2A	Ablation and IVT	20/20	HM	PPV with MP	Primary	
1	3A	Ablation	20/80	6/200	SRF drainage	Primary	
2	3A	Ablation	20/400	NLP	PPV with MP and gas, then PPV with MP and SO	Primary	
2	3A	Ablation	20/200	20/400	PPV with MP	Secondary	TRD
2	3A	Ablation and IVB	LP	20/800	PPV with MP	Primary	
2	3A	Ablation and IVB	20/800	LP	SB, PPV with MP, retinectomy and SO, then PPV with SO removal	Primary	
2	3A	Ablation and IVB	HM	CF @ 2 ft	PPV	Secondary	Nonclearing vitreous hemorrhage
1	3B	Ablation	LP	NLP	SRF drainage	Primary	
1	3B	Ablation	LP	NLP	SRF drainage	Primary	
2	3B	Ablation and IVB	LP	LP	SRF drainage	Primary	

CF = counting fingers; HM = hand movements; IVB = intravitreal bevacizumab; IVT = intravitreal triamcinolone; LP = light perception; NLP = no light perception; MP = membrane peel; PPV = pars plana vitrectomy; SB = scleral buckle; SO = silicone oil; SRF = subretinal fluid; TRD = tractional retinal detachment; VA = visual acuity.
Only patients who received treatment at Duke were included in the study.

Furthermore, ultrawide-field imaging, which was designed originally for use in pediatric patients, has made examination of the peripheral retina in children more accessible in pediatric ophthalmology clinics.[25]

Correspondingly, the initial VA for eyes that presented in decade 1 trended toward being worse than that of eyes that presented in decade 2. These data are consistent with those of previous reports[11,13,17,19,26,27] showing that eyes with early-stage Coats' disease have better presenting VA compared with eyes with more advanced disease stages. Presenting VA was worse in eyes with stage 2B disease, coincident with foveal exudates, and is especially poor in eyes with total exudative retinal detachment for which the average VA was light perception for stage 3B or NLP for stage 4 and 5 disease and which did not improve despite treatment.

Over time, mean VA in decade 1 worsened from initial to final follow-up, whereas mean VA in decade 2 remained stable. Moreover, from presentation to final follow-up, VA in decade 1 worsened for most eyes, whereas VA in decade 2 improved for most eyes. Because Coats' disease is a progressive disease and the difference in length of follow-up could have influenced final VA, mean VA at different time points also were compared. Mean VA in decade 1 at an intermediate period of follow-up (intended to mimic the average time to final follow-up for decade 2) also was worse when compared with that at presentation. However, at a common time point (12−18 months of follow-up), mean VA in both decades did not differ significantly from that at presentation. Taken together, this suggests that mean VA did not change significantly from presentation to the 12- to 18-month follow-up for either decade, but became worse for decade 1 at an average of 38 months of follow-up, and this difference persisted until final follow-up (mean, 111 months). In contrast, mean VA for decade 2 did not differ significantly at different time points, including final follow-up (mean, 46 months). Given the trends toward more advanced stage of disease at presentation and worse presenting VA, as well as worsening of VA over the length of follow-up in decade 1, it is not surprising that there was also a trend toward worse final visual outcomes in eyes in this decade compared with those that had presented in decade 2.

More eyes were observed without treatment in the first decade (n = 8) compared with the second decade (n = 1), which may reflect either the practice pattern of some in our group at that time or the more aggressive approach to treatment as imaging and surgical technology improved in decade 2. Without treatment, Coats' disease, with rare exception,[28–32] progresses and causes VA loss.[11,19] In our study, 1 stage 2A eye in decade 1 that was observed initially showed worsening of disease. Despite treatment after disease progression, the eye had poor visual outcome. For the other 8 observed eyes, 2 had stage 3A disease and 6 had stage 3B or worse disease at presentation, and as previously reported, observation was thought to be a reasonable option as long as the patient was comfortable, because treatment for advanced disease often is challenging and may not lead to improved visual outcomes.[11,33] However, other authors have advocated treatment of eyes with advanced disease to prevent painful glaucoma requiring enucleation.[11,27] In the present report, of the 6 observed eyes with stage 3B or worse disease, 1 (17%) required enucleation because of uncontrolled glaucoma causing a painful eye. This rate is similar to that of the study by Shields et al,[11] in which 3 of 16 eyes (19%) with stages 3B and 5 disease that were observed demonstrated painful glaucoma and required enucleation. However, Silodor et al[27] reported that 4 of the 6 eyes (67%) with total retinal detachment that were observed progressed to painful neovascular glaucoma requiring enucleation.

Among eyes that were treated, eyes in decade 2 were treated with a higher number of procedures than eyes in

decade 1. We suspect the shift away from observation and toward increasing numbers of treatments in the decade 2 group reflects increasing evidence showing the benefits of aggressive repetitive treatments to achieve anatomic resolution of disease.[11,34]

Although most stage 2B eyes treated with ablation only (4 of 5 eyes) showed good anatomic outcomes, only 40% (2 of 5) showed good visual outcomes (≥20/125 VA). Macular scarring accounted for poor visual outcomes in the 3 eyes treated with ablation only. Meanwhile, the 1 stage 2B eye that completed treatment with ablation and IVB achieved anatomic resolution and maintained final VA better than 20/125. It has been reported previously that prolonged macular exudation can develop into macular fibrosis leading to visual loss.[17] Shields et al[11] similarly noted that visual prognosis usually is limited when a dense yellow-gray nodule is centered within the foveal exudation or when there is late subretinal fibrosis at the fovea. Given the small sample size, it is not possible to determine if IVB had a role in preventing prolonged macular exudation and consequently scarring in stage 2B eyes.

There are higher levels of VEGF in eyes with Coats disease.[35,36] Accordingly, one might hypothesize that anti-VEGF treatment would be effective to manage the VEGF-induced exudation and sequelae in this condition. In our study, IVB was introduced in decade 2 and seemed to have had a positive impact in some stage 3A eyes. Intravitreal bevacizumab in conjunction with ablation with or without vitreoretinal surgery was associated with anatomic resolution in 5 of the 6 stage 3A eyes and with final VA of 20/125 or better in 3 of the 6 stage 3A eyes. The eyes with final VA of 20/125 or better were also 3 of the 4 eyes treated with ablation and IVB without primary vitreoretinal surgery. Because stage 3A eyes that were treated with ablation and IVB without primary vitreoretinal surgery usually had 2 or fewer quadrants of retinal detachment, this observation may suggest that the advantage of using IVB may be most apparent in stage 3A eyes with limited quadrants of retinal detachment because VA potential is good after treatment. In contrast, only 2 of the 6 stage 3A eyes treated with ablation with or without vitreoretinal surgery and without IVB showed anatomic resolution, 1 eye demonstrated phthisis, and all 6 eyes showed unfavorable visual outcomes.

Similar to our report, other studies have demonstrated that adjunctive anti-VEGF therapy may be beneficial in eyes with stage 3A disease or better. Sein et al[37] showed that 100% globe salvage and reasonable visual outcomes were achieved in the 26 patients with stages 2A and 3A disease treated with laser and IVB (presenting VA was not reported, but final VA was 20/20 for both stage 2A eyes and ranged from 20/20 to counting fingers at less than 1 foot for the 24 stage 3A eyes). Additionally, in a retrospective consecutive interventional study, Lin et al[38] reported that 6 stage 2B eyes (treated with ablation only, n = 2; treated with ablation and anti-VEGF, n = 3; or treated with ablation, anti-VEGF, and IVT, n = 1), 1 stage 3A eye (treated with ablation and anti-VEGF), and 1 stage 3B eye (treated with ablation only) showed anatomic improvement, but 1 stage 3B eye (treated with ablation and anti-VEGF) did not show anatomic improvement.

In the current report, only 2 stage 3B eyes were treated with ablation and anti-VEGF therapy with or without vitreoretinal surgery. Both eyes showed poor anatomic and visual outcomes. Given the small number of eyes in this group, it was not possible to conclude if anti-VEGF was beneficial in the treatment of stage 3B eyes. However, other studies have shown that anatomic resolution was possible in stage 3B eyes treated with anti-VEGF and other therapies. For example, in another retrospective case series, although treatment failed in 2 eyes (both stage 3B) of 10 patients treated with ablation only, all 10 patients matched by macular appearance, quadrants of subretinal fluid, and quadrants of telangiectasia (stages ranged from 2B to 3B) treated with ablation and IVB achieved anatomic resolution.[9] Meanwhile, Zheng and Jiang[39] reported that although all eyes in their study responded to treatment with complete or partial resolution of telangiectasia, subretinal fluid, and exudation, average VA improved for the 14 pediatric patients (stages 2 to 3B), but not for the 5 adult patients (stages 3A and 3B) treated with IVB with or without other therapies. Furthermore, in a retrospective review of 24 children with exudative retinal detachment (not differentiated between stage 3A or 3B) associated with Coats' disease who were treated with large-spot diode laser and IVB, Villegas et al[40] showed that all 24 patients achieved resolution of exudative retinal detachment, vascular telangiectasia, and anatomic improvement. Like our study, most of these reports are limited by small sample sizes, lack of adequate control groups, and nonstandardization of the number of treatment sessions, but taken together, there is evidence to suggest treatment benefit of adding IVB for eyes with all stages of disease, but particularly for eyes with stage 3A or worse disease.

Although anti-VEGF therapy has been shown to have favorable results in the previously mentioned studies, the long-term effects of anti-VEGF therapy in children remain unknown. Ramasubramanian and Shields[20] first reported the risk of incident TRD with adjunctive IVB. Of the 8 patients with Coats disease who were treated with ablation and IVB, 4 demonstrated vitreous fibrosis, whereas 3 demonstrated TRD. Other studies also have cautioned that patients treated with IVB in conjunction with other treatments may be at increased risk of vitreoretinal fibrosis and TRD.[8,39,41] In our study, we compared eyes that underwent ablation with or without vitreoretinal surgery with IVB as compared with similar treatment groups without IVB and did not find a difference in TRD or macular scarring rates among the groups. However, it is important to note that the small sample size limits the power of detecting differences across groups. Similarly, Ferrone[42] showed that in the absence of anti-VEGF use, TRD developed after ablative therapy in 5 Coats' disease eyes with total exudative detachment. Interestingly, Daruich et al[43] recently reported that TRD and macular fibrosis developed at a higher rate in patients with extramacular fibrosis and questioned whether the higher rate of TRD found in Ramasubramanian and Shields' report could be because the eyes studied had advanced (stage 3B) disease.

The strengths of this study include available anatomic and visual outcomes over a long follow-up. Limitations of

this study include its retrospective nature, diverse group of treating specialists, small number of participants because of the rarity of the disease, and variable length of follow-up. Moreover, given the retrospective nature of the study, best-corrected VA measurements in children by Snellen charts, Early Treatment Diabetic Retinopathy Study charts, Allen pictures, or HOTV charts were not standardized across eyes or visits. Additionally, patients were managed with a wide variety of methods, thus further decreasing the number of participants in each study group. The limited study power in individual treatment groups precluded statistically meaningful comparisons among treatment groups.

Based on the results from this study and a review of the literature, eyes with stage 2A or more advanced disease should be treated promptly to prevent disease progression and worsening of VA. Stage 2A and 2B eyes that were treated with ablation to full resolution of exudates showed good visual outcomes when macular scarring did not develop. In this study, some stage 3A eyes with 2 or fewer quadrants of retinal detachment also responded to ablation with IVB with anatomic resolution and good visual outcomes, but given the small sample size, a prospective study with larger sample size is needed to determine treatment efficacy definitively. Advanced-stage eyes should still receive treatment to prevent progression to painful uncontrolled glaucoma requiring enucleation.

In conclusion, this study demonstrated the evolution of practice patterns for management of Coats' disease at a single institution over the past 2 decades. In the second decade of the study, fewer eyes presented with advanced stages of disease, fewer eyes were observed without treatment, and eyes were treated with a higher mean number of procedures. Additionally, fewer eyes had NLP VA at the final follow-up in decade 2 compared with both the intermediate and final follow-ups in decade 1. The results of this study also suggest that adding IVB therapy may benefit vision in stage 3A eyes with 2 or fewer quadrants of retinal detachment; further prospective studies to answer this specific question are needed. Although the globe salvage rate was high, the data from this report and those described in the literature also highlight the need for better treatments for advanced-stage Coats' disease.

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Abbreviations and Acronyms:
HIPAA = Health Insurance Portability and Accountability Act; **IVB** = intravitreal bevacizumab; **IVT** = intravitreal triamcinolone; **logMAR** = logarithm of the minimum angle of resolution; **NLP** = no light perception; **SD** = standard deviation; **TRD** = tractional retinal detachment; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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