

Coats' disease – Prognostic factors for globe and vision salvage in children, a long-term experience

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Purpose: Coats' disease is associated with poor outcomes, and there are limited studies on long-term outcomes of Coats' disease. The purpose of our study is to identify various predictive factors to help in prognosticating the treatment outcomes in advanced Coats' disease in children. **Methods:** This is a retrospective case series from a single tertiary eye care center of children (<18 years) diagnosed with coat's disease. Sixty-seven patients with Coat's disease were identified from the medical records from 2009 to 2020. Patients' demographic data, clinical presentation, stage, extent of involvement, detailed treatment history, clinical sequelae post-treatment (including complications and anatomical and functional outcomes) were noted. Binary logistic regression was performed to correlate the predictive factors for anatomical and functional improvement. **Results:** Of the 67 patients, 51 eyes of 51 patients were included in the study. The male to female proportion was 2.2. Mean age at presentation was 4.98 ± 3.55 years (range: 2 months–15 years). Mean duration of follow-up was 31.53 ± 26.38 months. Overall, our globe salvage rate was 92.2%. We found that vitreoretinal fibrosis ($P < 0.001$), subretinal gliosis ($P < 0.001$), vitreous hemorrhage ($P = 0.02$), tractional or combined retinal detachment ($P < 0.001$), foveal scar ($P < 0.006$), and cataract ($P < 0.001$) to be important factors to affect the outcome. **Conclusion:** Advanced stage of presentation (stage 3B and above), diffuse involvement, cataract, vitreoretinal fibrosis (preretinal and subretinal), vitreous hemorrhage, tractional or combined retinal detachment, and anterior hyaloid proliferation are poor prognostic factors for globe salvage in advanced disease. Subretinal gliotic nodule or scar and lack of visual rehabilitation suggest poor functional outcomes.

Key words: Coats' disease, globe salvage, outcomes, prognosis

Coats' disease is an idiopathic nonhereditary progressive retinopathy characterized by retinal vascular telangiectasias and aneurysms. It is associated with exudation with or without intraretinal and subretinal fluid.^[1-4] Shields *et al.*^[5] classified Coats' disease into five stages. Daruich *et al.*^[6] further classified stage 2B into 2B1 and 2B2 based on the absence and presence of subfoveal gliotic nodule, respectively.

Initially, photocoagulation and enucleation were the only treatment modalities used to treat Coats' disease.^[7] Treatment modalities have evolved over time; currently, management depends on the stage of the disease.^[8] Despite aggressive management, advanced Coats' disease is associated with poor outcomes, especially in our subset of the population, probably due to late presentation as mentioned by Rishi *et al.*^[9] Studies on long-term outcomes and predictive factors are limited.^[10-13] The purpose of our study is to identify various predictive factors to help in prognosticating treatment outcomes in advanced Coats' disease in children.

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Methods

This is a retrospective case series from a single tertiary eye care center of children (<18 years) diagnosed with Coat's disease. Approval was obtained from the institutional review board and the research adhered to the tenets of the Declaration of Helsinki.

Of the 67 patients whose medical records were reviewed from 2009 to 2020, 51 patients were included in the study; 16 were excluded for lack of adequate follow-up or other reasons. Patients' demographic data, clinical presentation, stage, extent of involvement, treatment history, complications, anatomical and functional outcome, and recurrence were noted. Baseline visual acuity (VA) was not available for 16 children in the preverbal age group. Visual acuity was measured using Allen's picture cards or Snellen's visual acuity charts.

Patients with stage 2A and 2B disease were treated with 532-nm green laser photocoagulation [Fig. 1]. Patients with stage 3A, 3B, and 4 disease underwent one or more of the

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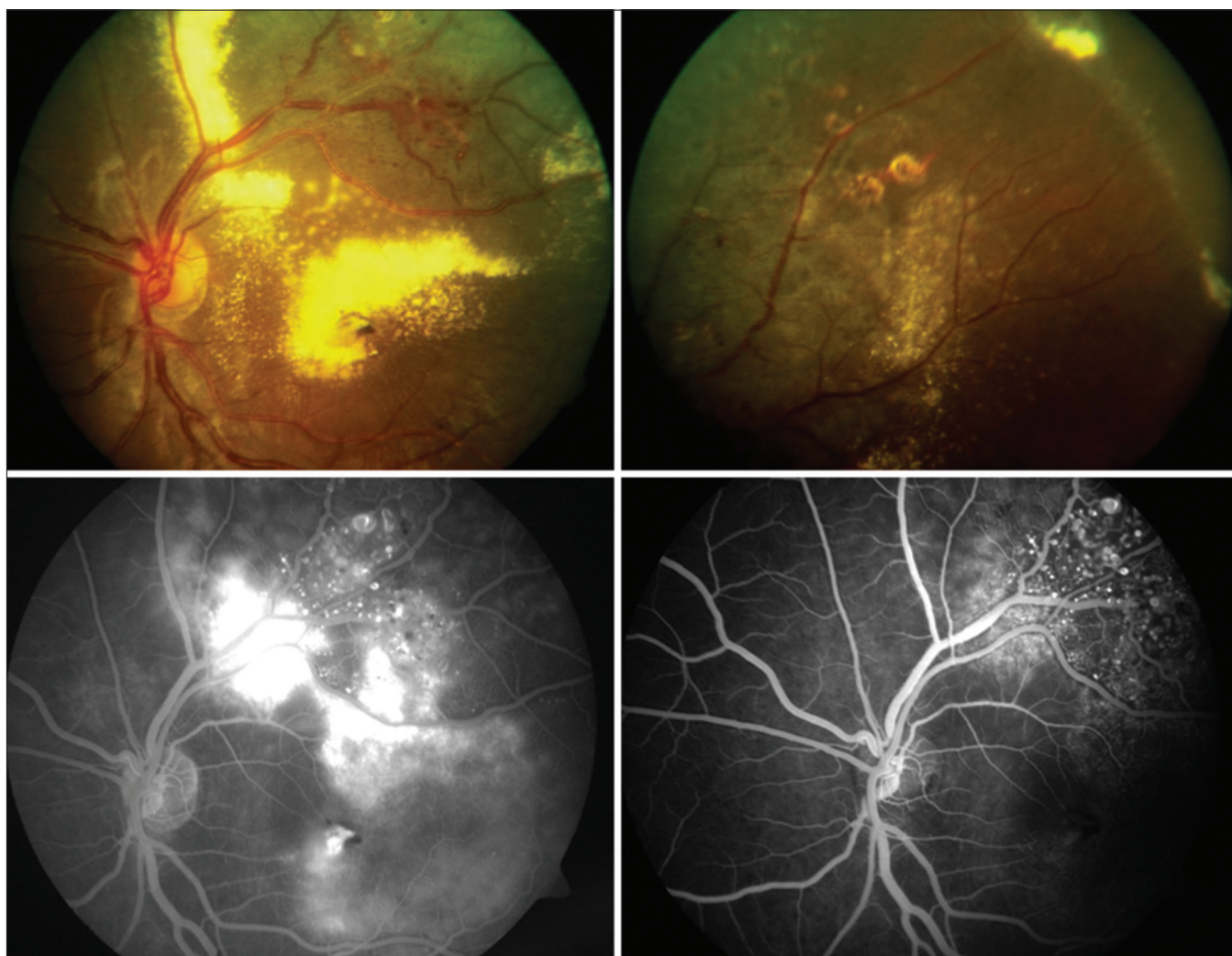


Figure 1: Color fundus photo and fluorescein angiography images of a child with stage 2B Coats' disease showing hard exudates and telangiectatic vessels with typical light-bulb appearance on FA

Table 1: Stage-wise demographics and quadrant distribution

	Female (x) Male (y)	Mean Age In years; (Range)	No of eyes	1 quadrant	2 quadrants	3 quadrants	4 quadrants	Diffuse (3/4 quadrants)
Stage 2A	1 (x)	6	1 (2%)	-	1 (100%)	-	-	-
Stage 2B	2 (x) 2 (y)	5.7 (2-10)	4 (7.8%)	2 (50%)	1 (25%)	1 (25%)	-	1 (25%)
Stage 3A	3 (x) 10 (y)	6.9 (1-15)	13 (25.5%)	2 (15.4%)	5 (38.5%)	4 (30.7%)	2 (15.4%)	6 (46.1%)
Stage 3B	7 (x) 19 (y)	3.8 (0.2-15)	26 (51%)	-	-	-	26 (100%)	26 (100%)
Stage 4	3 (x) 4 (y)	4.1 (0.9-11)	7 (13.7%)	-	-	-	7 (100%)	7 (100%)

Table 2: Stage-wise treatment modalities

	Laser	Cryotherapy	SRFD	IVTA	Ozurdex	Anti-VEGF	Lensectomy	Vitrectomy	Buckling
Stage 2A (1)	1 (100%)	0	0	0	0	0	0	0	0
Stage 2B (4)	4 (100%)	1 (25%)	0	0	0	0	0	0	0
Stage 3A (13)	13 (100%)	1 (7.69%)	2 (15.38%)	0	0	2 (15.38%)	0	0	0
Stage 3B (26)	22 (84.61%)	4 (15.38%)	16 (61.53%)	14 (53.84%)	3 (11.53%)	4 (15.38%)	10 (38.46%)	3 (11.53%)	3 (11.53%)
Stage 4 (7)	4 (57.14%)	0	5 (71.4%)	2 (28.57%)	3 (42.86%)	7 (100%)	2 (28.57%)	1 (14.29%)	1 (14.29%)

following: transconjunctival subretinal fluid drainage (SRFD) assisted with balanced salt solution injection, intravitreal

steroid, or anti-VEGF injections. Indications of draining subretinal fluid were in eyes with stage 3A disease, where

Table 3: Treatment details of each eye in advanced stages, i.e., stage 3B and stage 4

Stage	SRF drainage	Laser sessions	Cryotherapy	Ozurdex	IVTA	Antivegf	Vitrectomy	Total no. of treatment
3B	1	1	0	0	1	0	0	3
3B	1	4	1	0	1	0	1	8
3B	1	2	1	0	2	0	0	6
3B	0	2	0	0	1	0	0	3
3B	1	1	1	0	1	0	0	4
3B	0	2	0	0	1	0	0	3
3B	3	5	0	0	2	1	1	12
3B	1	3	0	0	0	0	0	4
3B	0	2	0	0	1	1	0	4
3B	1	0	0	0	0	1	0	2
3B	1	2	0	0	1	0	0	4
3B	1	2	0	0	2	0	0	5
3B	1	2	4	0	0	2	0	9
3B	2	2	0	0	2	0	0	6
3B	1	6	0	2	0	0	0	9
3B	0	1	0	0	0	0	0	1
3B	0	0	0	0	0	0	0	0
3B	1	2	0	0	1	0	0	4
3B	0	0	0	0	0	0	0	0
3B	0	0	0	0	0	0	1	1
3B	0	3	0	1	0	0	0	4
3B	1	3	0	0	0	0	0	4
3B	0	1	0	0	1	0	0	2
3B	1	1	0	1	0	0	0	3
3B	2	1	0	0	3	0	0	6
3B	0	1	0	0	0	0	0	1
4	2	0	0	0	1	2	0	5
4	2	10	0	1	1	1	1	16
4	1	3	0	0	0	1	0	5
4	0	0	0	0	0	1	0	1
4	2	1	0	1	0	1	0	5
4	1	0	0	0	0	1	0	2
4	0	2	0	1	0	1	0	4

exudative RD was involving the fovea; in stage 3B and 4, where total bullous RD precluded the visualization and treatment of telangiectatic vessels, retina was behind the lens, or retina was very bullous, and the disc was not visible. The technique of SRFD employed was transconjunctival tangential entry into the subretinal space at the point of highest bulboisity, generally in the inferotemporal or inferonasal quadrant, by using a 26-G needle connected to a 2-cc syringe without plunger and bevel of the needle facing the RPE while simultaneously injecting saline using a 30-G needle through the pars plana, 3.5 mm from limbus, to compensate for the hypotony during SRFD. Cryotherapy using the double freeze–thaw technique was reserved for patients with extreme peripheral lesions. Stage 4 patients additionally received intracameral anti-VEGF injections. Patients with stage 3B and above disease were considered as advanced Coats' disease.

The data was entered on Microsoft[®] Excel and statistical analysis was performed using SPSS (Chicago, USA) software. Continuous variables were expressed as mean (range). We used the logarithm of the minimal angle of resolution scale for the

analysis of visual acuity, and Student's *t* test to compare the VA at presentation and final visit. Binary logistic regression was performed to correlate the predictive factors for anatomical and functional improvement, and *P* < 0.05 was considered as statistically significant. Odds ratio was calculated and expressed as OR along with the 95% confidence interval (CI).

Results

Of the 51 patients included in the study, there were 35 males (68.6%) and 16 females (31.4%). All the cases had unilateral disease. Mean age at presentation was 4.98 ± 3.55 years (range: 2 months–15 years). Mean logMAR visual acuity at presentation was 1.93 ± 1.24 (range: 6/9 to PL+). Stage-wise and quadrant-wise disease distribution is summarized in Table 1. Mean duration of follow-up was 31.53 ± 26.38 months (range: 6–112 months).

Management

Laser photocoagulation was performed in 44 (86.3%) eyes. Laser photocoagulation alone was performed in 16 eyes (31.4%), laser along with SRFD was performed in 20 eyes (39.2%), and

Table 4: Factors predicting anatomical and functional improvement

Variables	Functional outcome (Reference: Improvement)			Anatomical Stage (Reference: Improvement)		
	OR	95% CI	P+	OR	95% CI	P+
Age	0.96	(0.82, 1.13)	0.65	1.01	(0.86, 1.18)	0.88
Gender	0.76	(0.22, 2.63)	0.67	1.33	(0.40, 4.36)	0.63
Squint	0.88	(0.27, 2.85)	0.84	0.64	(0.21, 1.96)	0.43
Number of transscleral drainage session	1.70	(0.70, 4.12)	0.24	1.06	(0.51, 2.23)	0.85
Number of laser sessions	0.79	(0.57, 1.11)	0.19	0.55	(0.34, 0.89)	0.01*
Number of Ozurdex	2.68	(0.34, 20.91)	0.34	1.52	(0.37, 6.27)	0.55
Number of intravitreal triamcinolone	4.31	(1.00, 18.61)	0.05	1.92	(0.83, 4.43)	0.12
Number of Anti-VEGF	2.08	(0.60, 7.14)	0.24	1.20	(0.46, 3.12)	0.70
Lensectomy	0.32	(0.06, 1.66)	0.17	0.18	(0.04, 0.80)	0.02*
Vitrectomy	2.13	(0.27, 16.63)	0.47	2.64	(0.25, 27.25)	0.41
Cataract	0.09	(0.01, 0.47)	0.004*	0.07	(0.02, 0.29)	<0.001*
Residual telangiectasia	0.22	(0.06, 0.80)	0.02*	0.19	(0.05, 0.65)	0.008*
Residual hard exudates	0.19	(0.04, 0.78)	0.02*	NA	NA	NA
Foveal scar	7.65	(0.89, 65.31)	0.03*	10	(0.90, 52.47)	0.006*
Vitreoretinal fibrosis	0.06	(0.01, 0.28)	<0.001*	0.07	(0.01, 0.30)	<0.001*
Sub retinal gliosis	0.11	(0.02, 0.48)	0.003*	0.05	(0.01, 0.23)	<0.001*
Vitreous hemorrhage	0.19	(0.03, 0.96)	0.04*	0.23	(0.06, 0.84)	0.02*
Tractional or combined retinal detachment	0.03	(0.004, 0.25)	0.04*	0.02	(0.05, 0.12)	<0.001*

Table 5: Stage-wise outcomes in advanced disease

	Stage 3A (n=13)	Stage 3B (n=26)	Stage 4 (n=7)
Globe salvage	13 (100%)	24 (92.3%)	5 (71.4%)
Telangiectasia resolution	13 (100%)	20 (76.9%)	3 (42.8%)
Complete	11 (84.6%)	16 (61.5%)	2 (28.5%)
Partial	2 (15.4%)	4 (15.3%)	1 (14.3%)
SRF resolution	13 (100%)	15 (57.7%)	3 (42.8%)
Complete	11 (84.6%)	10 (38.5%)	1 (14.3%)
Partial	2 (15.4%)	5 (19.2%)	2 (28.5%)
Functional improvement	10 (77%)	3 (11.5%)	1 (14.3%)
Final PL+	13 (100%)	18 (69.2%)	2 (28.6%)
Final PL-	0 (0.0%)	8 (30.8%)	5 (71.4%)
Diffuse involvement (3 or 4 quadrants)	6 (46.1%)	26 (100%)	7 (100%)
Cataract	0 (0.0%)	16 (61.5%)	6 (85.7%)
Vitreoretinal fibrosis	0 (0.0%)	22 (84.6%)	7 (100%)
Subretinal gliosis	0 (0.0%)	20 (76.9%)	3 (42.8%)
Vitreous hemorrhage	1 (7.7%)	9 (34.6%)	6 (85.7%)
Tractional RD	0 (0.0%)	17 (65.3%)	5 (71.4%)
Combined RD	0 (0.0%)	7 (26.9%)	0 (0.0%)

laser along with SRFD and intravitreal steroid/anti-VEGF was given in 17 eyes (33.3%). Cryotherapy was performed in 6 (11.8%) cases along with laser photocoagulation. SRFD was performed in 23 (45.1%) eyes. Intravitreal steroids were administered in 21 (41.2%) eyes (triamcinolone acetate in 15 eyes, dexamethasone implant in 5 eyes, and both in 1 eye). Intravitreal anti-VEGF was administered in 13 (25.5%) eyes. Stage-wise treatment details are mentioned in Tables 2 and 3.

Of the 22 eyes that developed cataract, 12 eyes were treated with intravitreal steroids prior to the development of cataract. Lensectomy was performed in 12 eyes, while it was deferred in the rest due to extensive vitreoretinal fibrosis and gliosis or

NVG. Vitrectomy was performed in 3 eyes for taut posterior hyaloid with TRD. Scleral buckling was performed in 3 eyes with peripheral vitreoretinal fibrosis causing TRD. One case underwent combined scleral buckling and vitrectomy for taut posterior hyaloid with peripheral VR fibrosis and TRD. The remaining eyes with TRD did not undergo surgical intervention due to extensive fibrosis not amenable to treatment. Stage-wise treatment summary is mentioned in Tables 2 and 3.

Anatomical outcome

Overall, our globe salvage rate was 92.2%. None of the eyes required enucleation. At final visit, resolution of telangiectasia was seen in 1 eye (100%) vs. 4 eyes (100%) vs.

13 eyes (100%) vs. 20 eyes (77%) vs. 3 eyes (43%) of stage 2A, 2B, 3A, 3B, and 4, respectively. SRF resolution was seen in 13 eyes (100%) of stage 3A, 15 eyes (58%) of stage 3B, and 3 eyes (43%) of stage 4 disease. Average number of treatment sessions were 6.7 (range: 3–16) in eyes with stage 3B and 4 which attained anatomical success. Vitreoretinal fibrosis was seen in 29 eyes (56.9%), and subretinal gliosis was seen in 25

eyes (49%) [Table 4]. Vitreous hemorrhage (VH) was seen in 16 (31.3%) eyes. Foveal scarring was seen in 39 eyes (76.5%), and retinal macrocyst was seen in 3 (5.9%) eyes. Anterior chamber cholesterolosis was seen in 3 eyes (5.8%). One eye of stage 3B (1.9%) developed NVG. Of the 7 eyes with CRD, 2 eyes developed anterior hyaloid proliferation and 1 eye developed a macular hole.

Table 6: Stage-wise functional outcome

Stage	Functional improvement	Eyes with logMAR better than 1.0 at final visit	Eyes with PL present at final visit
Stage 2A (n=1)	1 (100%)	1 (100%)	1 (100%)
Stage 2B1 (n=2)	2 (100%)	2 (100%)	2 (100%)
Stage 2B2 (n=2)	2 (100%)	0	2 (100%)
Stage 3A (n=13)	10 (76.9%)	7 (53.8%)	13 (100%)
Stage 3B (n=26)	3 (11.5%)	0	17 (65.4%)
Stage 4 (n=7)	1 (14%)	1 (14%)	2 (28.5%)

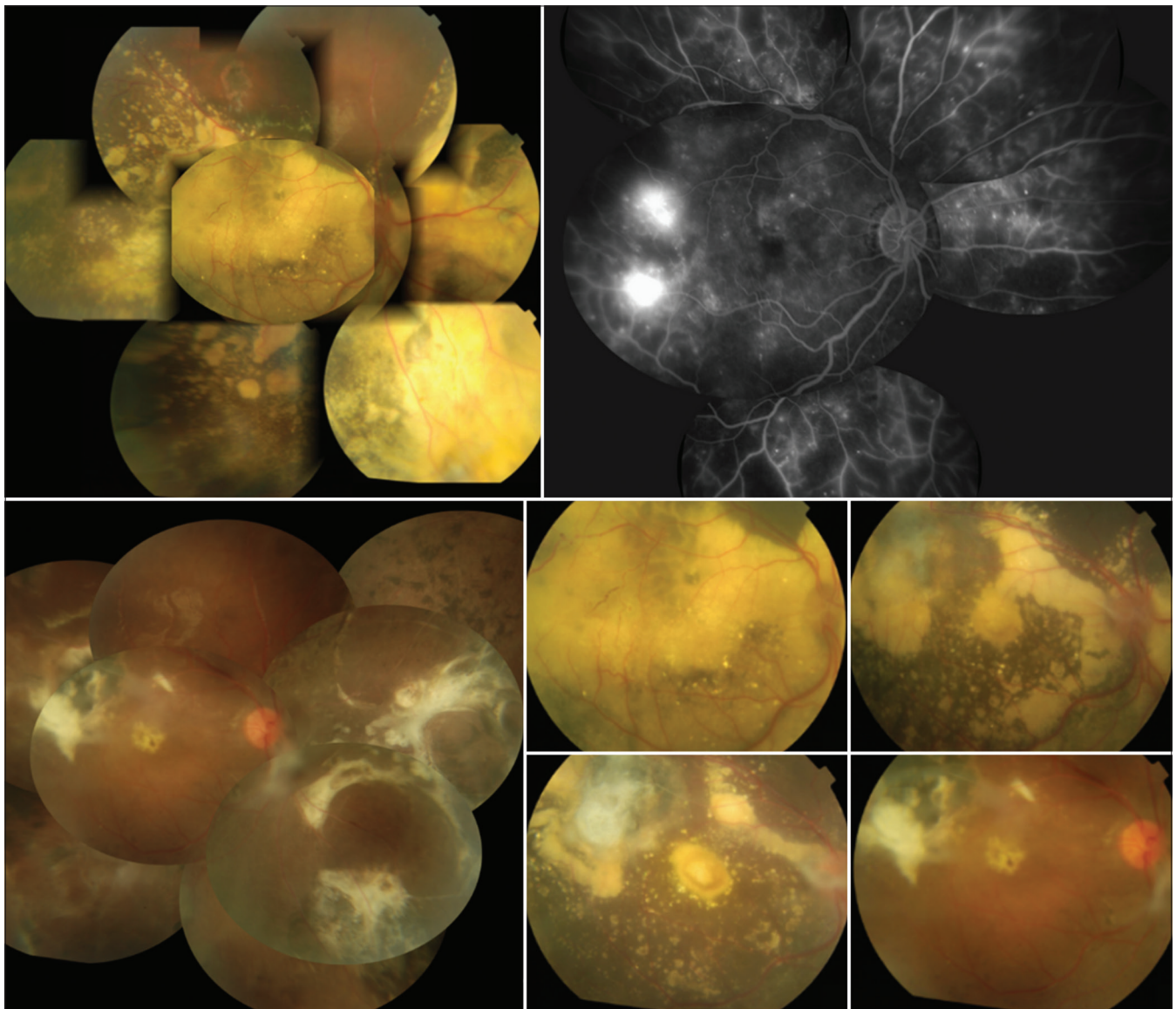


Figure 2: Montage color fundus photos and FA of a child with stage 3A Coats' disease showing extensive exudation and telangiectasia, pre and post treatment. Post-treatment resolution of exudation with subretinal and subfoveal gliosis and pigmentary changes can be noted

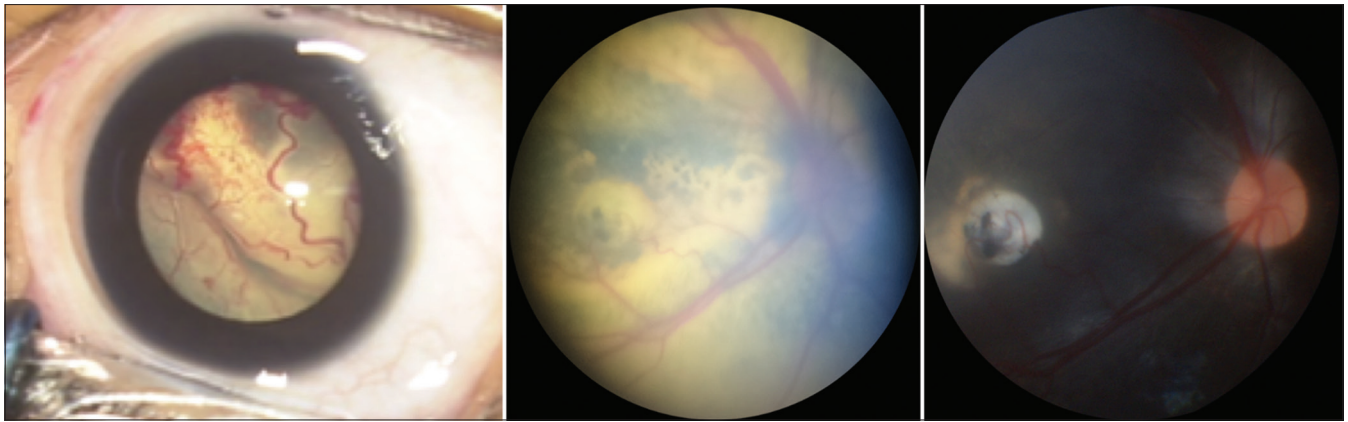


Figure 3: Color photograph of a child with stage 3B Coats' disease with total RD and retina behind the lens. Post treatment, retinal detachment settled and exudation gradually resolved, leaving behind a gliotic nodule

Four eyes (7.8%) progressed to phthisis bulbi of which 2 belonged to stage 3B and 2 belonged to stage 4. Recurrence of disease after complete regression was noted in 6 (11.8%) cases (5 eyes: 3B, 1 eye: 3A). Factors predicting anatomical and functional improvement are summarized in Table 4, and stage-wise outcomes are shown in Table 5.

By logistic regression, factors significantly associated with anatomical improvement were localized disease, eyes with clear lens at presentation and during follow-up, eyes requiring lesser number of laser photocoagulation sessions, complete regression of telangiectasia and absence of vitreoretinal fibrosis, subretinal gliosis, VH, and TRD/CRD.

Functional outcome

The mean final best-corrected visual acuity (BCVA) was logMAR 1.95 ± 1.08 (range: 6/6 to No PL). Visual acuity improved in 19 (37.3%) eyes. Perception of light (PL) was preserved in 37 (72.5%) eyes. Stage-wise results of functional outcomes are summarized in Table 6. Presence of subfoveal gliotic nodule, that is, stage 2B2 at presentation was associated with a poor functional outcome.

Factors associated with functional improvement included localized disease, clear lens at presentation and during follow-up, complete resolution of hard exudates and telangiectasia, absence of vitreoretinal fibrosis, subretinal gliosis, VH, and TRD/CRD.

Discussion

Various studies have shown that stage, age, visual acuity, and number of quadrants involved at presentation impact the prognosis in Coats' disease.^[14-17] In addition, from our study, we found vitreoretinal fibrosis ($P < 0.001$), subretinal gliosis ($P < 0.001$), vitreous hemorrhage ($P = 0.02$), tractional or combined retinal detachment ($P < 0.001$), foveal scar ($P < 0.006$) and cataract ($P < 0.001$) to be other important factors that affect the outcome.

Our results are comparable to those published earlier in terms of treatment outcomes [Figs. 2 and 3]. Complete resolution of SRF in a study by Shields *et al.*^[14] was 48% vs. 0%, while our study showed 38% vs. 14% in stage 3B and 4 disease. In terms of complete resolution of telangiectasia, Shields *et al.*^[14] reported 50% vs. 0%, while in our study, it was slightly higher

with 61% and 28% for stages 3B and 4, respectively. Globe salvage rate in a study by Scheffler *et al.*^[18] was 94%, while in our study, it was 92%.

Vitreoretinal fibrosis was noted in 29 (56.9%) eyes in our study: 84.6% of stage 3B and in 100% of stage 4 eyes. Of those eyes with vitreoretinal fibrosis, 86% further developed TRD/CRD. Thus, vitreoretinal fibrosis can be a very important prognostic indicator of anatomical resolution. It can develop either early or late in the course. It can occur in the natural course of the disease, as also supported by Zheng *et al.*,^[19] or worsen during the course of treatment.^[9] Adeniran *et al.*^[20] in their pooled analysis found no role of anti-VEGF or laser photocoagulation in the causation of fibrosis or TRD. A recent Korean study by Kang *et al.*^[21] found vitreoretinal fibrosis in 32% of children with Coats' disease at presentation, while its progression was noted in 67% during the course. In a study by Daruich *et al.*,^[22] 41% of the eyes developed extramacular fibrosis of which 71.4% had stage $\geq 3A$. Liang *et al.*^[23] reported an incidence of 75.9% of fibrosis in stage 3B eyes. Whether early surgical management of vitreoretinal fibrosis is beneficial requires further research. We performed vitrectomy in a 9-month-old child with stage 4 disease who developed taut posterior hyaloid with vitreoretinal fibrosis. At follow-up at 62 months, BCVA improved to logMAR 1.0 and complete anatomical regression was achieved.

Vitreous hemorrhage is another rare finding noted in Coats' disease and was noted in 16 eyes (31.4%) in our study. It was noted in 3B and 4 eyes of younger children, with a mean age of 3.41 ± 1.89 years. Of the various long-term studies on Coats' disease that we reviewed, it was reported to be 4% (14/307) by Rishi *et al.*,^[9] 3% (3/124) by Shields *et al.*,^[5] 12% (2/16) by Li *et al.*,^[11] and 2% (1/39) by Ong *et al.*^[10] As suggested by Rishi *et al.*,^[9] Indian eyes may have a higher incidence of VH, although further studies are required to understand the mechanism. In our series, 8% (4 cases) had VH at presentation, which is similar to that reported in the literature. Post treatment, stage 4 eyes with NVI (6 eyes, 11.7%) developed VH. This could have been due to bleeding from NVI, NVD, and/or anterior hyaloid proliferation. Another 2 eyes (3.9%) developed PVD-induced VH post treatment, 1 eye (1.9%) developed VH post cryotherapy, and 1 eye (1.9%) developed bleed from pars plicata due to iatrogenic trauma during simultaneous saline injection along with SRF drainage in bullous detachment. Two eyes (3.9%) developed VH post trauma while playing.

Cataract was seen in 22 eyes (43.1%) with advanced disease (3B and 4), of which 10 (45%) eyes had not received any intravitreal steroid injection. Our findings show a strong association between cataract and anatomical/functional outcome. Daruich *et al.*^[24] also concluded that cataract is seen in advanced stages and worsens the visual outcome. Chronic exudation and inflammation may contribute to cataract formation.

We would like to propose the following factors to be considered in the management of advanced Coat's disease from our experience.

Poor prognostic factors in globe salvage:

1. All four quadrants/diffuse involvement
2. Development of cataract
3. Vitreoretinal fibrosis (preretinal and subretinal gliosis)
4. Vitreous hemorrhage
5. Tractional or combined retinal detachment.

Poor prognostic factors in vision salvage:

Structural:

1. Subfoveal gliotic nodule or pigmentary scar
2. Cataract.

Functional:

1. Lack of visual rehabilitation (by intraocular lens/contact lens)
2. Poor adherence to patching and amblyopia therapy.

As suggested by Ong *et al.*,^[10] aggressive repetitive treatments can help achieve anatomic resolution of disease compared to observation alone.

Limitations of our study include retrospective nature of the study and variable duration of follow-up, which was compensated by excluding patients with less than 6 months follow-up. We could not assess visual rehabilitation and adherence to patching due to the retrospective nature of the study.

Conclusion

Advanced stage of presentation, diffuse involvement, cataract, vitreoretinal fibrosis, vitreous hemorrhage, tractional or combined retinal detachment, and anterior hyaloid proliferation are poor prognostic factors for globe salvage in advanced disease. Subfoveal gliotic nodule and lack of visual rehabilitation suggest poor functional outcome.

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Conflicts of interest

There are no conflicts of interest.

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