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A 10-Year Retrospective Review of Juvenile Coats Disease Treated with Adjuvant Intravitreal Bevacizumab Injections

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ABSTRACT

Background: This study will analyse the visual outcomes of patients with juvenile Coats disease who were treated with adjuvant intravitreal bevacizumab injections, compared to a cohort who received conventional treatment without adjuvant therapy.

Methods: Retrospective data was obtained from <18-year-old children with Coats disease known to the Queensland Children's Hospital ophthalmology department between 1st January 2014 to 1st June 2024. After inclusion and exclusion criterion were applied, there were 18 participants (19 eyes) remaining in the study (9 in the adjuvant cohort; 10 in the conventional cohort). The conventional cohort was treated with conventional therapy (cryotherapy +/- laser photocoagulation +/- additional surgery). The adjuvant cohort was treated with conventional and adjuvant therapy (intravitreal bevacizumab injections).

Results: The adjuvant and conventional cohorts both showed visual acuity (VA) improvement from baseline to disease resolution (logMAR -0.07 vs -0.13) (p=.461). Four eyes (40%) in the conventional cohort required additional surgery (e.g. vitrectomy, enucleation), whereas none had surgery in the adjuvant cohort (p=.049) over an average follow-up of 52.7 and 39.3 months respectively. Although time to disease resolution was similar, the conventional cohort (4 eyes; 40.0%) had significantly more disease recurrence in comparison to the adjuvant cohort (1 eye; 11.1%) (p=.039). The adjuvant group also had a longer mean time to disease recurrence (19.2 months) compared to the conventional group (13.4 months) (p=.044). There were no reported cases of tractional vitreoretinopathy following intravitreal bevacizumab with laser photocoagulation.

Conclusions: Adjuvant intravitreal bevacizumab injections, when combined with laser photocoagulation, constitute a safe and effective treatment modality for juvenile Coats disease. This combined approach is associated with a reduced incidence of disease recurrence and a prolonged duration of disease quiescence.

Keywords: Coats disease; Anti-vascular endothelial growth factor injections

INTRODUCTION

Coats disease is a rare idiopathic nonhereditary progressive retinopathy characterised by retinal telangiectasias and aneurysms [1-4]. Presentation is often unilateral and affects mainly young male children [5]. Risk factors for poor visual outcomes include younger age and more advanced disease at presentation, with various management regimens available depending on the stage of disease [3,4]. Conventional treatment in Coats disease includes laser photocoagulation and cryotherapy, however the introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections has become more commonplace within the past decade [3]. Raised intraocular VEGF levels is associated with Coats disease, with He et al reporting on the first case of Coats disease which responded to intravitreal injection of bevacizumab in 2010.6 Intravitreal anti-VEGF injections however are thought to pose an increased risk of vitreoretinal fibrosis and tractional retinal detachment [5]. Current literature analysing the utility of these agents have been limited to case reports or small case series [3]. In 2017, Li et al reported that conventional therapy with adjuvant intravitreal anti-VEGF injections was effective in treating severe Coats disease with exudative retinal detachment [7]. While a 2023 systematic review by Bai et al concluded that anti-VEGF drugs provide an effective and relatively safe treatment strategy for Coats disease, there were no cohort studies available for analysis [8]. Previous retrospective studies comparing conventional and adjuvant therapy have also been limited by a lack of available optical coherence tomography (OCT) and fundus fluorescein angiography (FFA) imaging for monitoring [9]. This study will therefore analyse the cohort visual outcomes of patients with juvenile Coats disease who were treated with adjuvant intravitreal anti-VEGF injections (bevacizumab), compared to a cohort who received conventional treatment without adjuvant therapy. These results will help in supporting the role of intravitreal anti-VEGF injections in the management of juvenile Coats disease.

METHODS

Study design, population and settings

Retrospective data was obtained from patients with Coats disease who were known to the ophthalmology department at the Queensland Children's Hospital, a tertiary Australian paediatric public hospital, between 1st January 2014 to 1st June 2024. These participants were identified by the procedural coding for 'exudative vitreoretinopathy' or 'Coats disease' and was collected by Queensland Children's Hospital medical records department., in which 71 participants (73 eyes) were identified during this period. Participants were recruited via convenience sampling through these procedural codes. Inclusion criteria included participants aged <18-years-old and had clinically confirmed treatment naïve Coats disease, with diagnosis made by a paediatric ophthalmologist. Exclusion criteria included participants who were >18 years old, had previously treated Coats disease from other services (e.g. private rooms, interstate) with missing clinical information, or undiagnosed exudative vitreoretinopathy were excluded. The conventional cohort was defined as juvenile Coats disease treated with conventional therapy only (cryotherapy ± laser photocoagulation ± additional surgery) during the initial treatment phase, whereas the adjuvant cohort was defined as juvenile Coats disease treated with conventional and adjuvant therapy (intravitreal anti-VEGF injections) during the initial treatment phase. In this study, initial treatment phase was defined as the time between date of diagnosis until date of disease resolution. Additional surgery was defined as surgical procedures that were not cryotherapy or laser coagulation, such as vitrectomy, lensectomy and/or

enucleation. The demographic information, clinical characteristics and visual outcomes were collected via the integrated electronic medical record (iEMR). After inclusion and exclusion criterion were applied, there were 18 participants (19 eyes) remaining in the study: 9 in the adjuvant cohort and 10 in the conventional cohort. Ethics approval for the study was granted by the Institutional Human Research Ethics Committee (HREC/24/QCHQ/112609). This study adhered to the principles outlined in the Declaration of Helsinki. All aspects of the study were kept confidential and only researchers in this study had authorised access.

Study measures

Demographic information collected included age at diagnosis, birth sex, ethnicity, Aboriginal or Torres Strait Islander status and geographic locality. Clinical characteristics collected included initial baseline visual acuity (VA), disease laterality, baseline disease stage, ancillary testing including optical coherence tomography (OCT; Topcon Triton), fluorescein fundus angiography (FFA), and total treatments received within the initial treatment phase. Cryotherapy was performed using triple freeze-thaw technique. Laser photocoagulation was done using either Argon green (514nm) or diode laser (810nm) indirect ophthalmoscopy. The adjuvant intravitreal anti-VEGF injection used was bevacizumab (1.25mg/0.05mL). Eyes were staged according to the Coats disease classification system proposed by Shields et al: stage 1 (retinal telangiectasia), stage 2a and 2b (retinal telangiectasia plus extrafoveal exudation or foveal exudation), stage 3a and 3b (subtotal or total exudative retinal detachment), stage 4 (retinal detachment plus secondary glaucoma) and stage 5 (advanced end-stage disease) [5]. Visual outcomes such as final VA, change in VA, days to disease resolution, days to disease recurrence, disease recurrence treatment and follow-up duration were also collected. For patients who had preverbal limitations, a VA of central, steady and maintained (CSM) were recorded as logMAR 0.3 [10]. For patients who had enucleation, a VA was recorded as no light perception (NPL; logMAR 3). The final VA was defined as the VA measured on the date of disease resolution. Days to disease resolution was defined as the days between date of initial treatment until the date when stable quiescence disease was identified which required no further active treatment. Disease recurrences were then monitored once initial disease resolution had occurred. Disease recurrence was defined as resurfacing of disease manifestations (e.g. retinal telangiectasia, exudate) that required active treatment based on ophthalmological opinion. Follow-up duration was defined as the number of months from the date of diagnosis to the earliest of the following: date of discharge, transfer to adult services, lost to follow-up or most recent review.

Data analyses

The collected data was analysed using IBM SPSS Statistics version 27. Descriptive statistics was generated for population demographics. Chi-square test, independent T-test and univariate analysis of variance were applied where relevant comparing the adjuvant and conventional cohort. A multivariate analysis was performed on final VA with initial VA, disease stage, foveal involving disease, year and age at presentation and gender as confounding variables. A two-sided p value <0.05 was considered statistically significant.

RESULTS

Demographic characteristics

The demographic characteristics were comparable between the adjuvant and conventional cohorts. Among the 19 eyes reviewed, the mean age at presentation was similar between the adjuvant cohort (6.8 years; range, 2-13 years) and the conventional cohort (7.2 years; range, 0-14 years). The adjuvant cohort tended to present more recently,

with a median year of presentation in 2020 (range, 2016-2023), compared to 2018 (range, 2014-2023) in the conventional cohort; however, this difference was not statistically significant. The majority of patients in both cohorts were male, Caucasian, and had unilateral ocular involvement. The reasons for referral were also similar amongst the cohorts, with Coats disease and retinal detachment being the primary indications for ophthalmology referral (Table 1).

Table 1: Demographic characteristics (mean age at presentation, birth sex, laterality, eye, ethnicity) and reason for referral of juvenile Coats disease in the adjuvant cohort and conventional cohort.

Demographic characteristics		**Adjuvant (n=9)**	**Conventional (n=10)**	**p-value**
Mean year seen (range)		2020 (2016-2023)	2018 (2014-2023)	0.852
Mean age at presentation (years)		6.8 years	7.2 years	0.332
Birth sex	**Female**	1 (11.1%)	3 (30.0%)	0.313
	Male	8 (88.9%)	7 (70.0%)	
Laterality	**Unilateral**	9 (100.0%)	8 (80.0%)	0.366
	Bilateral	0 (0.0%)	2 (20.0%)	
Eye	**Right**	6 (66.7%)	3 (30.0%)	0.11
	Left	3 (33.3%)	7 (70.0%)	
Ethnicity	**Caucasian**	6 (66.7%)	9 (90.0%)	0.213
	Non-Caucasian	3 (33.3%)	1 (10.0%)	
Reason for referral	**Coats disease**	3 (33.3%)	3 (30.0%)	0.772
	Exotropia	1 (11.1%)	1 (10.0%)	
	Leukocoria	1 (11.1%)	1 (10.0%)	
	Retinal detachment	1 (11.1%)	3 (33.3%)	
	Other	3 (33.3%)	2 (20.0%)	

Clinical characteristics

The mean initial baseline VA was slightly worse in the adjuvant cohort (logMAR 1.11; range 0.3-2.3) compared to the conventional cohort (logMAR 1.06; range 0.3-3.0), although this difference was not statistically significant. According to Shield's classification system, all eyes in both cohorts presented with either Stage 2 or Stage 3 disease. Approximately 70% of eyes in each cohort demonstrated foveal involvement.

Ancillary testing with OCT and/or fundus fluorescein angiography (FFA) was performed more frequently in the adjuvant cohort during diagnosis. Specifically, diagnostic OCT was obtained in 88.9% (n=8) of eyes in the adjuvant cohort versus 40.0% (n=4) in the conventional cohort (p=.027), while FFA was performed in 100% (n=9) of adjuvant cases compared to 70.0% (n=7) in the conventional cohort (p=.043).

Two eyes in each cohort underwent both cryotherapy and laser photocoagulation. However, a significantly greater proportion of eyes in the adjuvant cohort (77.8%, n=7) were treated with laser photocoagulation alone, compared to the conventional cohort (40.0%, n=4) (p=.033). Notably, 40.0% (n=4) of eyes in the conventional cohort required additional surgical intervention, whereas no eyes in the adjuvant cohort underwent additional surgery (p=.049). Of these four eyes in the conventional cohort, two were enucleated due to initial concerns for retinoblastoma, and two underwent vitrectomy for exudative retinal detachment. In the adjuvant cohort, the mean number of intravitreal anti-VEGF (bevacizumab) injections administered per eye during the initial treatment phase was 2.4 (range 1-6) (Table 2).

Table 2: Clinical characteristics (mean initial baseline VA, ancillary testing, Shields disease stage, conventional treatment) of juvenile Coats disease in the adjuvant cohort and conventional cohort.

Clinical characteristics		**Adjuvant (n=9)**	**Conventional (n=10)**	**p-value**
Mean initial baseline VA (logMAR)		1.11	1.06	0.457
Ancillary tests	**OCT**	8 (88.9%)	4 (40.0%)	**0.027**
	FFA	9 (100.0%)	7 (70.0%)	**0.043**
Disease stage (Shields)	**1**	0 (0.0%)	0 (0.0%)	0.515
	2A	1 (11.1%)	2 (20.0%)	
	2B	4 (44.4%)	4 (40.0%)	
	3A	3 (33.3%)	1 (10.0%)	
	3B	1 (11.1%)	3 (30.0%)	
	4	0 (0.0%)	0 (0.0%)	
	5	0 (0.0%)	0 (0.0%)	
Fovea involving disease		6 (66.7%)	7 (70.0%)	0.876
Conventional treatment received	**Cryotherapy + laser**	2 (22.2%)	2 (20.0%)	0.906
	Laser only	7 (77.8%)	4 (40.0%)	**0.033**
	Additional surgery	0 (0.0%)	4 (40.0%)	**0.049**

Visual outcomes

There was a wide range in mean time to disease resolution in both groups, which was not statistically significant between the adjuvant cohort (11.2 months; range 4.1-13.8 months) and the conventional cohort (7.1 months; range 0–24.6 months) (p=.294). The mean final VA was similar between the conventional cohort (logMAR 1.19; range 0-3) and the adjuvant cohort (logMAR 1.13; range 0-2.7) (p=.460). Both cohorts demonstrated an overall mean improvement in VA from baseline, with no significant difference between the cohorts. Final VA could not be obtained for two eyes in the adjuvant cohort due to loss to follow-up or ongoing active treatment at the time of data collection. On average, the adjuvant cohort had a shorter follow-up duration (39.3 months) compared to the conventional cohort (52.7 months) (p=.060) however this was not statistically significant, and the majority of patients were still undergoing ophthalmology review at the time of data collection (Table 3). Among the nine eyes in the adjuvant cohort, no cases of tractional vitreoretinopathy were reported following intravitreal bevacizumab injections with an average follow-up period of 39.3 months (Table 3).

At the most recent follow-up, four eyes (40.0%) in the conventional cohort had experienced disease recurrence, compared to one eye (11.1%) in the adjuvant cohort (p=.039). The adjuvant group had a longer mean time to disease recurrence (19.2 months) than the conventional group (13.4 months) (p=.044). Among eyes with recurrent disease, the single eye (100%) in the adjuvant cohort was treated with a secondary intravitreal ranibizumab injection. For recurrent disease in the conventional cohort, three eyes (66.7%) received further laser photocoagulation, while one eye (33.3%) was treated with an orbital floor steroid injection (Table 3).

There was no statistical significance on final VA outcome when a multivariate analysis was performed based on cohort, initial baseline VA, disease stage, foveal involving disease, year of presentation, age of presentation and gender (Figure 1). Patients who had worse initial baseline VA and more advanced disease stage tended to have worse final VA although these were both not statistically significant.

Table 3: Visual outcomes (mean time to resolution, mean final and change in VA, mean follow-up time, follow-up outcome) and recurrent disease outcomes for juvenile Coats disease in the adjuvant cohort and conventional cohort.

Visual outcomes		Adjuvant (n=9)	Conventional (n=10)	p-value
Mean time to resolution (months)		11.2	7.1	0.294
Mean final VA (logMAR)		1.13	1.19	0.46
Mean change in VA (logMAR)		-0.07	-0.13	0.461
Mean follow-up time (months)		39.3	52.7	0.06
Follow-up outcome	**Discharged**	1 (11.1%)	2 (20.0%)	0.848
	Lost to follow-up	1 (11.1%)	1 (10.0%)	
	Ongoing review	6 (66.7%)	5 (50.0%)	
	Private practice	0 (0.0%)	1 (10.0%)	
	Transfer to adults	1 (11.1%)	1 (10.0%)	
Disease recurrence?		1 (11.1%)	3 (33.3%)	**0.039**
Mean time to recurrence (months)		19.2	13.4	**0.044**

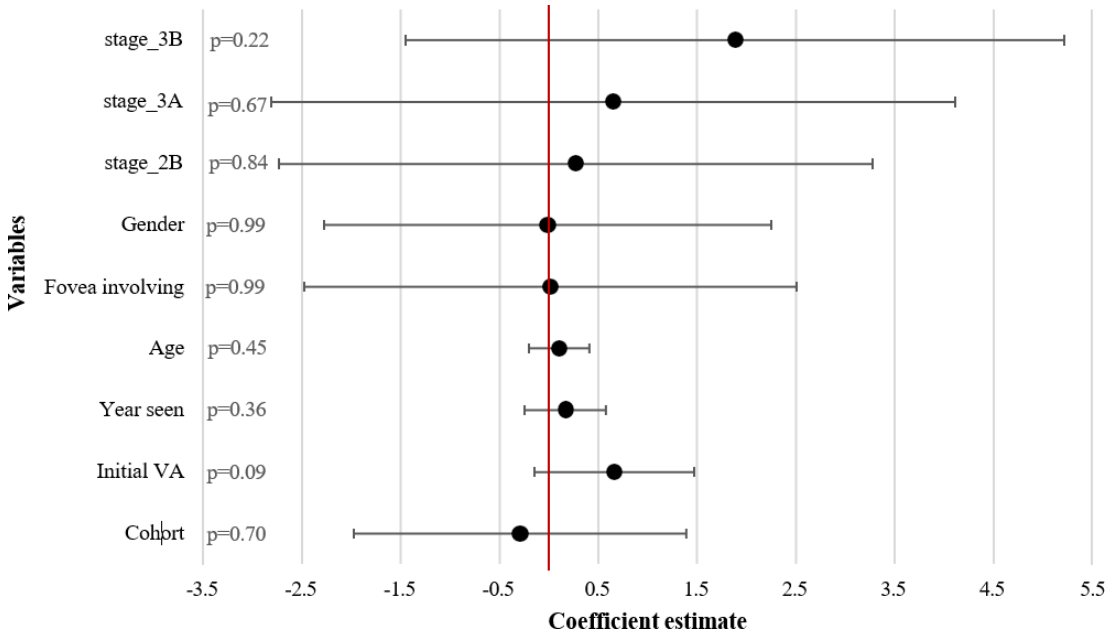

Figure 1: Multivariate analysis of mean final visual acuity (VA) on confounding variables (disease stage, gender, fovea involving disease, age, year seen, initial VA and cohort). A higher coefficient estimate correlates to worse logMAR vision. R-squared 0.609.

DISCUSSION

Consistent with current literature, this study confirms that Coats disease more commonly affects males during the first decade of life, is typically unilateral, and may initially present with leukocoria or retinal detachment. Although the adjuvant and conventional cohorts had comparable baseline VA and disease stage, the use of laser photocoagulation was significantly higher in the adjuvant group. All additional surgical interventions, such as enucleation or vitrectomy, occurred exclusively within the conventional cohort. While both groups demonstrated a mean improvement in final VA, the adjuvant cohort showed a statistically lower incidence of disease recurrence

(11.1% vs. 33.3%) and a longer duration of quiescent disease (19.2 months vs. 13.4 months). Previous studies have reported the use of intravitreal anti-VEGF injections primarily in advanced Coats disease, where conventional laser photocoagulation and cryotherapy have traditionally been less effective [7]. However, the positive outcomes observed in this study highlight the potential role of intravitreal bevacizumab injection therapy as part of initial treatment for juvenile Coats disease, regardless of disease stage.

The goal of treatment in Coats disease is to eradicate telangiectasia and preserve visual function [5,9,11,12]. In this study, all eyes in the adjuvant cohort received laser photocoagulation, whereas in the conventional cohort 60% had laser photocoagulation and the 40% had surgery alone (enucleation or vitrectomy). This is similar to current literature over the past decade, with laser photocoagulation being the primary treatment in 33-92% of cases [9,12-14]. A 30-year retrospective review comparing the clinical outcomes of Coats disease treated with conventional therapy and adjuvant therapy with a mean follow-up period of 24.9 months found no statistical difference in VA improvement between the two groups, which was similar in our study.9 In our study, the mean final VA outcome was similar in the adjuvant (logMAR 1.13) and conventional (logMAR 1.19) cohorts. The adjuvant and conventional cohorts also showed comparable improvements in VA from baseline (ΔlogMAR -0.07 vs -0.13) respectively.

While visual acuity is often the primary outcome measure in reported studies, it may not be an accurate marker in the paediatric population due to pre-verbal or non-verbal limitations. The complications from Coats disease are often secondary to chronic retinal detachment, and may lead to a painful blind eye requiring enucleation [3]. Disease resolution and disease recurrence are therefore important factors to consider. In our study, the adjuvant and conventional cohorts had similar times to disease resolution (11.2 months vs 7.1 months respectively) (p=.294). This is in contrast to a 2021 retrospective chart review by Oli et al, who reported faster resolution of exudates in the cohort treated with adjuvant intravitreal therapy (anti-VEGF or steroids) in comparison to the cohort treated with conventional therapy only [9]. A large cohort study analysing the age of Coats disease onset reported that younger patients (aged less than 3-years) often presented with more advanced stage disease, greater extent of exudation and subretinal fluid, and were more likely to require enucleation [15]. Goals to consider in Coats disease management should therefore not only focus on reducing exudative disease but also aim to maintain functional anatomy in the form of a non-phthisical and non-painful eye.

In our study, the adjuvant cohort had statistically less disease recurrence than the conventional cohort (11.1% vs 33.3%). A 2005 study by Tasman and Schienbaum analysed thirteen eyes with Coats disease treated with laser photocoagulation and/or cryotherapy between the years 1966 and 1997, and reported a similar 33% disease recurrence rate, with an average of three recurrences.16 Case reports and cohort studies reporting on adjuvant anti-VEGF injections and Coats disease recurrence are currently limited by minimal follow-up periods [17-19]. In our study, the follow-up durations of the conventional and adjuvant cohorts were both much longer in comparison to current literature. In 2014, Villegas et al retrospectively reviewed 24 children with advanced Coats disease who were treated with intravitreal bevacizumab and laser vascular ablation, and found no disease recurrence over a mean patient follow-up of 22.4 months [18]. Contrastingly in 2018, Zhang et al reviewed 28

adult and paediatric patients with Coats disease treated with intravitreal anti-VEGF injections (ranibizumab or conbercept) combined with laser therapy, and reported 7% disease recurrence over a mean follow-up period of 24.3 months [19]. In our study, we reported a slightly higher incidence of disease recurrence of 11.1% (n=1) in the adjuvant cohort however this was over a significantly longer mean follow-up period of 39.3 months. Importantly, this incidence was statistically less than the conventional cohort in our study, where 33.3% (n=3) experienced disease recurrence over a mean follow-up period of 52.7 months. Ongoing and longer follow-up is therefore necessary in treated Coats disease regardless of treatment modality and future studies should explore this.

Intravitreal anti-VEGF injections have been reported to decrease subretinal exudates, telangiectasia, macular oedema and improve clinical outcomes in Coats disease [8]. A 2019 review of Coats disease over 45 years showed a positive trend in management and outcomes, with greater use of laser photocoagulation and intravitreal injections leading to improved disease resolution and less globe removal [20]. There is however fear of vitreoretinal fibrosis and tractional retinal detachment following intravitreal anti-VEGF injections [7,21,22]. Our study had no reported cases of tractional vitreoretinopathy following adjuvant intravitreal bevacizumab injections. A 2012 retrospective analysis of Coats disease treated with adjuvant intravitreal bevacizumab reported vitreoretinal fibrosis in four patients, three of whom exhibited evidence of tractional retinal elevation [22]. In contrast, a 2016 retrospective review by Daruich et al analysing 69 patients with Coats disease found that treatment with anti-VEGF therapy was not associated with the development of extramacular fibrosis [23]. These patients however only had cryotherapy alongside their anti-VEGF therapy with no laser photocoagulation, which differs to our study where all eyes in the adjuvant group had received at least laser photocoagulation [22]. This was similarly identified by Adeniran et al who reported a significant association of cryotherapy and tractional retinal detachment following anti-VEGF therapy [11]. Laser photocoagulation may therefore offset the accelerated fibrosis and posterior hyaloidal contraction related to anti-VEGF therapy and should be considered whenever adjuvant intravitreal bevacizumab injection is used.

In our study, there was a statistical difference in additional surgery incidence amongst the two cohorts, with only the conventional cohort undergoing some form of additional surgical intervention bedsides from laser photocoagulation and cryotherapy. While enucleation in Coats disease is generally indicated for a painful blind eye related to chronic retinal detachment sequalae, two eyes in this study had enucleation due to initial concerns of retinoblastoma. These patients presented with advanced Stage 3B disease and were both under 5 years of age. This contrasts with the only stage 3B disease in the adjuvant cohort, who was 12 years of age, and did not undergo enucleation. Although retinoblastoma is the most common paediatric intraocular malignancy, it is often the most common misdiagnosis leading to enucleation in Coats disease.3 Differentiating advanced Coats disease from retinoblastoma especially in young children therefore remains a diagnostic challenge as a false misdiagnosis of the latter can delay lifesaving treatment. A 2020 retrospective review of radiological imaging assessment found that a larger eye size, vitreous seeding and sharp-V-shaped retinal detachment were almost exclusively present in retinoblastoma, and less so in Coats disease [24]. Future research on the relevance of magnetic resonance imaging

in diagnosing Coats disease in young children with advanced disease should be considered as this may allow for more globe salvage.

The strengths of this study include longitudinal data with long follow-up durations collected from a major tertiary Australian paediatric hospital that is the largest in the state. Given the retrospective nature of this study, treatment regimens and review periods did not follow a standardised protocol and were heavily based upon clinician preference. Clinical information was reliant on accurate clinician documentation in the patient's iEMR. VA assumptions were made for children with preverbal limitations and/or had enucleation, therefore overall VA outcomes may not be truly representative and is a similar limitation faced in past literature. The final VA outcome at disease resolution state could not be obtained from two eyes in the adjuvant cohort (one = lost to follow-up; one = still having ongoing treatment) therefore the mean changes in VA may not be truly representative of the entire adjuvant cohort. The multivariate analysis was also limited by a small sample size therefore future cohort studies with more participants may yield different effects.

Regardless, this study highlights the positive role that intravitreal anti-VEGF injections (bevacizumab) has on juvenile Coats disease, particularly on reducing disease recurrence. Modern management goals should therefore focus on disease stabilisation with laser photocoagulation and adjuvant intravitreal anti-VEGF injections, optimising visual function, and reducing disease recurrence and requirement for secondary enucleation.

CONCLUSION

Adjuvant intravitreal bevacizumab injections, when combined with laser photocoagulation, constitute a safe and effective treatment modality for juvenile Coats disease. This combined approach is associated with a reduced incidence of disease recurrence and a prolonged duration of disease quiescence. Further studies are needed to evaluate the role of intravitreal bevacizumab injections in a gold standard treatment regimen for juvenile Coats disease.

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