Original Article

Ultra-widefield fundus fluorescein angiography in pediatric retinal vascular diseases

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Purpose: To describe the utility of RetCam ultra-wide-field fundus fluorescein angiography in pediatric retinal vascular diseases. **Methods:** A retrospective chart review was carried out in 43 eyes of 22 pediatric patients who were diagnosed or suspected to have a retinal vascular disease. Fluorescein angiography was carried out using the 130 degree lens of RetCam 3. Fluorescein angiography guided treatment (laser/cryotherapy) was carried out wherever required. **Results:** Diseases studied included - coats disease, familial exudative vitreoretinopathy, retinopathy of prematurity, congenital retinal folds, double optic nerve head, persistent fetal vasculature and incontinentia pigmenti. RetCam assisted fluorescein angiography was helpful in establishing a diagnosis in 4 patients (18%), in decision making regarding treatment in 18 patients (82%), in deciding need for retreatment in 5 patients (23%), helped in staging of disease in 5 patients (23%) and in detecting clinically subtle findings in 6 patients (27%). **Conclusion:** RetCam assisted FFA is extremely useful to document peripheral retinal vascular pathologies in pediatric patients and helps to take crucial therapeutic and retreatment decisions.

Key words: Fluorescein angiography, RetCam, retinal vascular diseases, retinopathy of prematurity, widefield imaging

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A large subset of pediatric vitreoretinal disorders is due to pathologies of the retinal vasculature. Vascular disorders of children include conditions like retinopathy of prematurity (ROP), familial exudative vitreoretinopathy (FEVR), Coats disease, persistent fetal vasculature, incontinentia pigmenti, Norrie disease and vasculitis.[1] Most of these disorders present with peripheral retinal vascular abnormalities. A proper assessment of many of these cases requires an examination under anesthesia. Additionally, these disorders can be better studied by fluorescein angiography. It is difficult to perform conventional fluorescein angiography in children as it requires good patient cooperation. Also, the field of view with most fundus cameras is limited; hence, the assessment and documentation of peripheral fundus abnormalities is met with difficulty.[2] Various modalities of widefield imaging have been described in children.[3-6] RetCam (Clarity Medical Systems, Inc.) is a widefield contact imaging device specifically developed for use in pediatric population. The latest version, RetCam 3, has option for fluorescein angiography and has been shown to be a useful tool for imaging vasculature in pediatric patients.[7-12] This study was conducted to further assess the utility of RetCam fluorescein angiography in patients with different types of pediatric vascular disorders.

Methods

This was a retrospective chart review carried out in 43 eyes of 22 pediatric patients in whom conventional fundus imaging and fluorescein angiography was not possible or in whom additional procedures like laser or cryotherapy were planned as a part of the management. The study was conducted at Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences. Patients were recruited from the retina and retinopathy of prematurity services of the hospital. The study adhered to the tenets of Declaration of Helsinki. Written informed consent was taken for performing RetCam imaging, fluorescein angiography, and expected interventions like laser or cryotherapy. Clearance from pediatrician was obtained in all small babies and patients with suspected systemic illness. RetCam imaging was carried out either under pediatrician monitoring (in babies <3 months) or under general anesthesia (in bigger children). Fundus photography (FP) and fundus fluorescein angiography (FFA) was done using RetCam 130º widefield lens. Intravenous sodium fluorescein (20%) was injected at a dose of 0.04 ml/kg or 7.7 mg/kg followed by an immediate saline flush.[13,14] Fluorescein angiography-guided treatment (laser/cryotherapy) was carried out wherever required. Follow-up visits were planned based on disease type, severity, and decision of the surgeon.

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Results

RetCam-guided imaging and FFA was carried out in 43 eyes of 22 patients. 15 cases were male and 7 were females. Their age ranged from 4 weeks to 10 years. We studied 6 cases of Coats disease, 5 cases of FEVR, 5 cases of ROP, 3 cases of congenital retinal folds, 1 case of double optic nerve head, 1 case of persistent fetal vasculature, and 1 case of incontinentia pigmenti. Table 1 summarizes the details of patients and the disease entities included in the study.

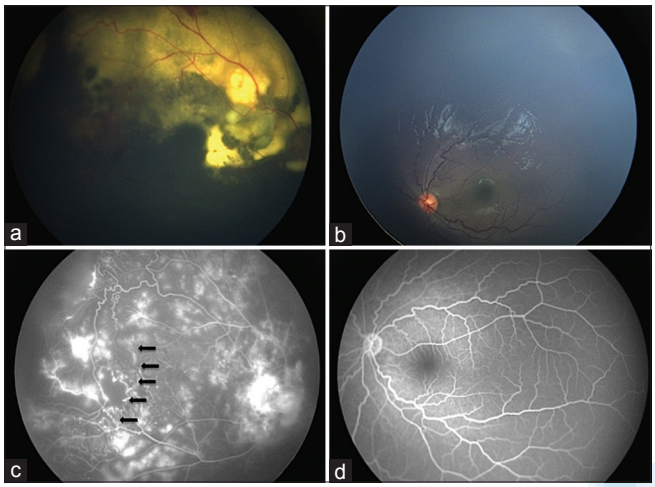

Figure 1: (a-d) A 5-year-old male patient with Coats disease. Right eye shows extensive lipid exudation (a), corresponding FFA image shows presence of numerous aneurysmal and telangiectactic changes along with capillary drop out areas in temporal retina (c, black arrows). No evidence of vascular abnormalities was noted in the fellow eye (b and d)

Of the 5 cases of Coats disease, 4 were males and 1 was a female patient. All cases were unilateral. FFA revealed telangiectatic and aneurysmal changes and areas of avascular retina. No evidence of significant vascular abnormalities was noted in the fellow eye of any patient. RetCam-assisted FFA was helpful to confirm the diagnosis, detect capillary nonperfusion areas and areas of vascular anomaly which required laser/cryotherapy. Additional follow-up RetCam fluorescein angiography of these cases was helpful in deciding adequacy of therapy/need for augmentation of therapy [Figs. 1-3].

All cases of FEVR had bilateral disease. Out of 10 eyes, 2 eyes had close funnel RD (stage 5), 5 eyes had stage 1, 2 eyes had stage 2, and 1 eye had stage 3 disease. RetCam-assisted FFA was useful in staging of the disease, to know the extent of avascular areas (for treatment), and to know the need for retreatment during follow-up [Figs. 4 and 5].

Of the total 10 eyes of ROP, 6 eyes had aggressive posterior ROP and 4 eyes had ROP sequelae. In case of APROP, RetCam-assisted FFA was extremely useful to identify the extent of retinal vascularization, to identify avascular loops, and to know the status of macular perfusion [Fig. 6].

In 2 patients with ROP sequelae, 1 eye of each patient had a total retinal detachment. The other eye of the first patient was found to have avascular retina in Zone 3 and in the second patient a floating venous loop was identified.[15]

Out of the 3 cases of congenital retinal folds, two cases had a family history of FEVR [Fig. 7]. In one patient, the cause of retinal fold was attributed to ROP. In these cases, RetCam FFA assisted in making a final diagnosis and ruling out any persistent disease activity.

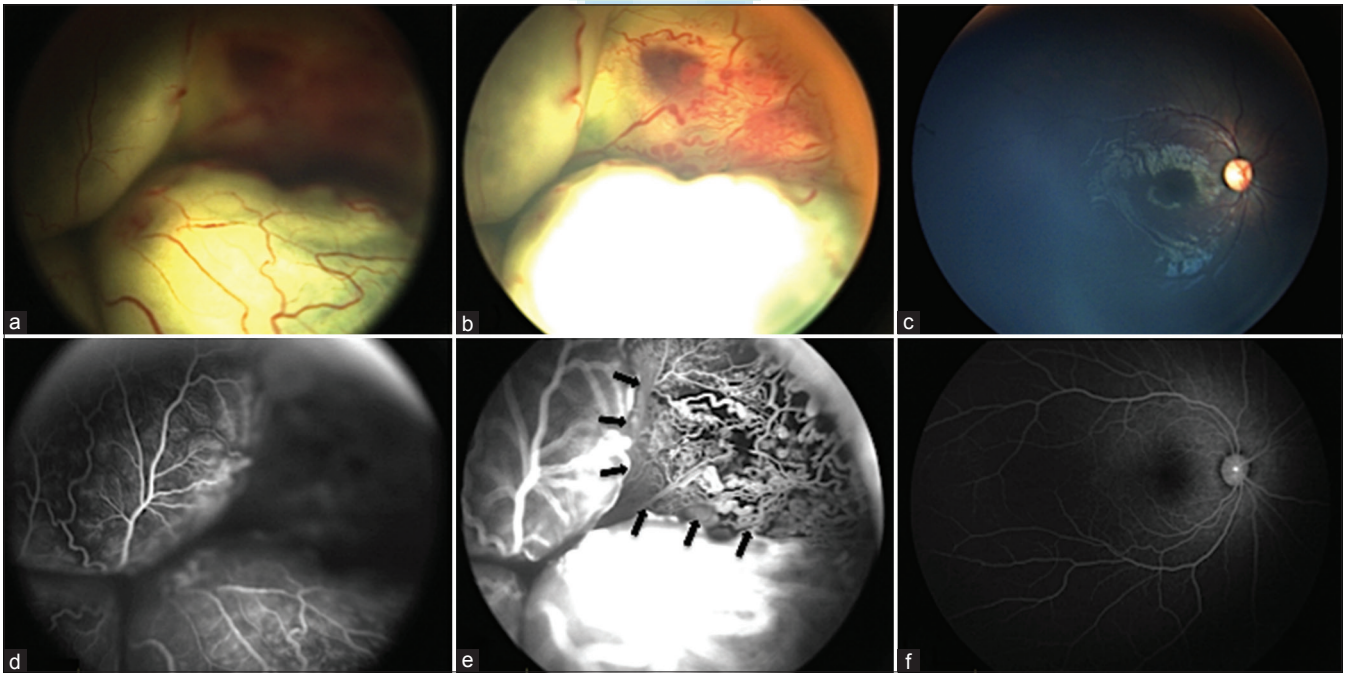

Figure 2: (a-f) A 1.5-year-old female patient who presented with leucocoria in the left eye. There was bullous retinal detachment with some peripheral vascular abnormalities in the left eye (a and b). FFA revealed presence of extensive telangiectasia and aneurysmal changes (d and e, black arrows). FFA of the right eye did not reveal any vascular abnormality (f). Diagnosis of Coats disease was confirmed in this case based on the FFA findings

Table 1: Demographic details of patients and the disease entities included in the study (RE - right eye, LE - left eye, BE - both eyes, APROP - aggressive posterior retinopathy of prematurity, FEVR - familial exudative vitreoretinopathy)

No	Age	Sex	Clinical diagnosis	RetCam FP/FFA features	Management
1	8 years	Male	Coats disease	RE - extensive subretinal exudation, temporal telangiectasia and aneurysmal changes and capillary dropout areas LE - within normal limits [Fig. 1]	Laser + Cryo
2	8 years	Male	Coats disease	RE - Lipid exudates temporal to fovea, temporal aneurysms and capillary dropout areas LE - within normal limits	Laser
3	3 years	Male	Coats disease	RE - small far peripheral non perfusion area, no telangiectasia or aneurysms LE - extensive lipid exudation with tractional retinal detachment involving macula	No intervention
4	1 year 6 months	Female	Exudative RD	RE - within normal limits LE - exudative RD, aneurysms and telangiectasia visible on FFA between bullous retinal detachment confirming the diagnosis of Coats disease [Fig. 2]	No intervention
5	7 years	Male	Coats disease	RE - aneurysms, few lipid exudates at fovea LE - within normal limits	Laser
6	6 years	Male	Cryo treated Coats disease	Cryo scars+, residual activity in superior retina [Fig. 3]	Laser
7	1.5 years	Female	FEVR	RE - close funnel retinal detachment LE - straightening of arcades, extensive neovascularization, peripheral avascularity [Fig. 5]	LE Laser (twice)
8	10 years	Male	FEVR	RE - close funnel retinal detachment LE - straightening of arcades, neovascularization at junction of vascular and avascular retina, peripheral avascularity	LE Laser (twice)
9	2 years	Male	FEVR	Bilateral temporal avascular retina, slight temporal vessel straightening [Fig. 4]	Observation
10	5 years	Male	FEVR	BE vessel straightening, neovascularization at junction of vascular and avascular retina	BE Laser
11	2 years	Male	FEVR	BE temporal avascularity, temporal vessel straightening	Observation
12	5 weeks	Male	APROP	Posterior zone 2 APROP, macular vascularization present, multiple avascular loops present	BE laser
13	5 weeks	Male	APROP	Posterior zone 2 APROP, macular vascularization present, multiple avascular loops present	BE laser
14	4 weeks	Female	APROP	Zone 1 APROP, macula not vascularized completely, avascular loops present [Fig. 6]	BE intravitreal anti-VEGF therapy
15	3 years	Female	ROP sequelae	RE temporal avascularity LE tractional retinal detachment (retinal fold)	RE laser LE no intervention
16	7 years	Male	ROP sequelae	RE temporal avascular retina, floating venous loop, vitreous hemorrhage, LE close funnel retinal detachment	RE Laser LE no intervention
17	6 years	Male	Congenital retinal fold	BE vascularized tractional retinal folds (FEVR)	No intervention
18	4 years	Male	Congenital retinal fold	BE retinal folds, LE total rhegmatogenous RD (history of prematurity, diagnosed as ROP sequelae)	RE no intervention LE Vitrectomy + Silicone oil tamponade
19	3 years	Male	Congenital retinal fold	BE vascularized tractional retinal folds (FEVR); FFA suggestive of FEVR in 2 siblings [Fig. 7]	No intervention
20	4 weeks	Female	RE anophthalmos LE double optic nerve head	LE double retinal circulation confirmed on FFA [Fig. 8]	No intervention
21	2 months	Female	Incontinentia pigmenti	BE temporal avascular retina (RE>LE)	BE laser (twice)
22	3 years	Male	LE posterior persistent fetal vasculature	RE within normal limits LE stellate fibrous membrane over disc with radiating folds. Staining on FFA. No peripheral vascular abnormalities.	Observation

One patient had clinical anophthalmos in one eye and evidence of double optic nerve head in the other eye. FFA clearly demonstrated evidence of two independent retinal circulations arising from each of the optic nerve heads [Fig. 8].

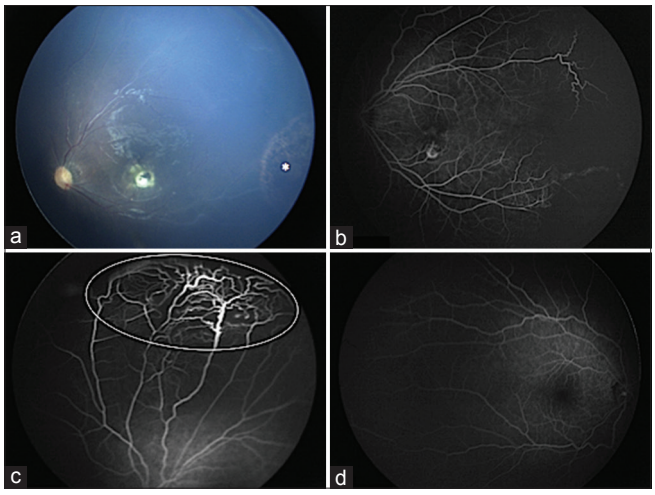

Figure 3: (a-d) A 6-year-old male child, diagnosed case of left eye Coats disease (previously cryotherapy treated). Right eye had a parafoveal lipid plaque and temporal cryotherapy scars (a, asterisk). FFA revealed parafoveal staining corresponding to the lipid plaque (b). Peripheral scans revealed the presence of localized area of telangiectasia and aneurysmal changes in the superior retina suggestive of residual activity (c, encircled area). Laser therapy was carried out selectively to this area. Right eye did not reveal any vascular abnormalities (d)

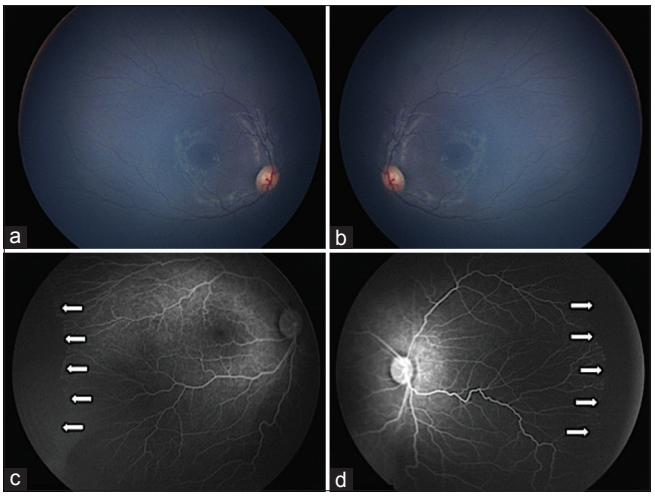

Figure 4: (a-d) A 2-year-old female patient with stage 1 FEVR. RetCam FFA in this case was useful to stage the disease, to know the extent of retinal avascularity (white arrows) and to rule out neovascularization

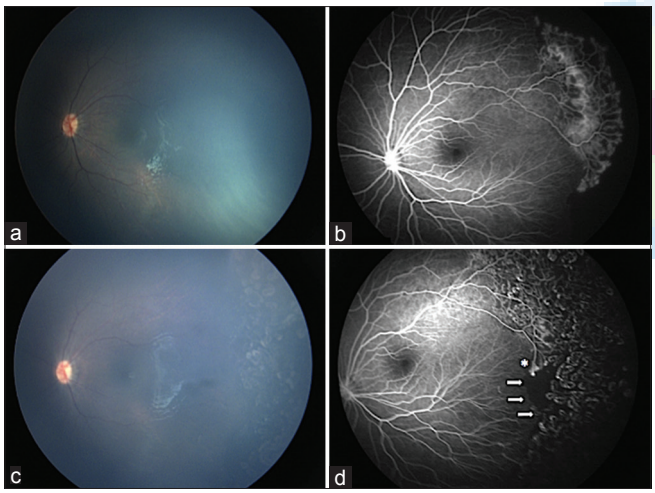

Figure 5: (a-d) A 3-year-old male patient with stage 2 FEVR with extensive retinal neovascularization in left eye (a and b). Right eye had close funnel retinal detachment. 8 weeks post laser fundus photo (c) and corresponding FFA image showing persistent small capillary dropout area (white arrows) with residual fine neovascularization (asterisk). Laser augmentation was done in this case

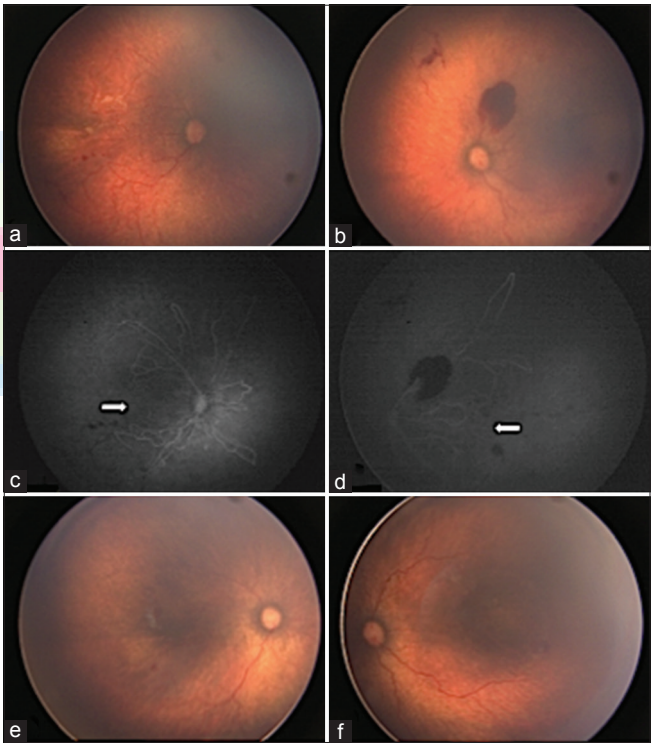

Figure 6: (a-f) A 29 weeks born preterm child examined at 33 weeks postconceptional age. Fundus examination (a and b) showed presence of ill-defined posterior pole disease (Zone 1 APROP). RetCam FFA revealed only part of zone 1 to be vascularized with incomplete vascularization of the macula (white arrows). Multiple avascular loops can also be noted (c and d). Intravitreal anti-VEGF therapy was planned in both eyes. At 4 weeks post-injection, macula appeared vascularized with retinal vasculature extending upto zone 2 (e and f)

FFA could detect bilateral temporal avascular retina in one case of incontinentia pigmenti. One case had unilateral posterior persistent fetal vasculature with a stellate fibrous membrane over disc with radiating folds. FFA showed staining of the membrane with absence of any peripheral vascular abnormalities.

Complications and difficulties encountered

None of the patients in the study developed anesthesia complications or allergic reactions to fluorescein injection like rash, respiratory distress, tachycardia, fever, and local injection site reactions. In 1 patient of APROP, who had extensive iris neovascularization, imaging of the late phases was met with difficulty due to leakage of the dye into the anterior chamber obscuring the fundus details.

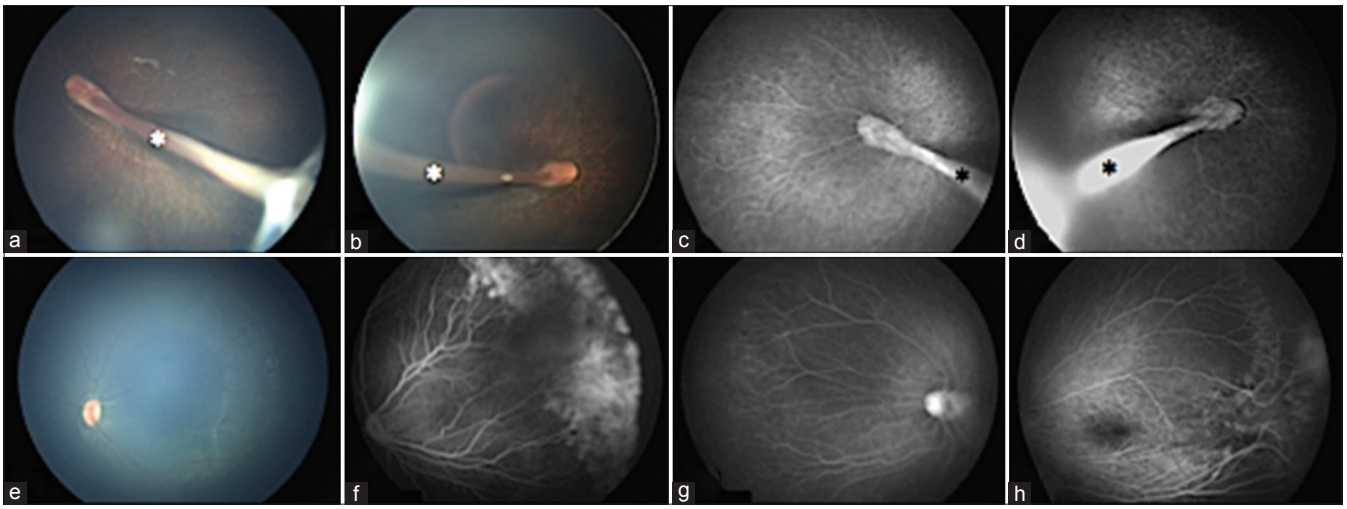

Figure 7: (a-h) A 3-year-old male child presenting with low vision and nystagmus. Both eyes had tractional retinal folds (a and b, white asterisks). The cause of these retinal folds was not certain. RetCam FFA revealed bilateral vascularized retinal folds (c and d, black asterisks). RetCam assisted FFA of 1.5-year-old (e and f) and 5-year- old (g and h) siblings showing features typical of FEVR

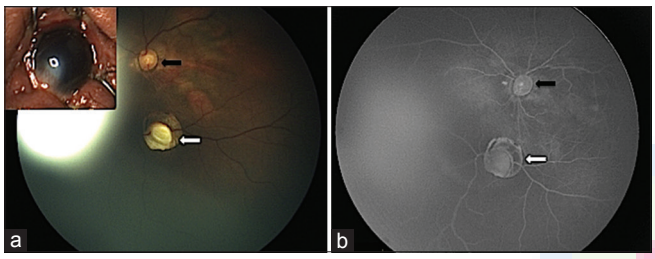

Figure 8: (a and b) A 4 weeks old female presenting with RE anophthalmos and LE congenital corneal opacity (a inset). Fundus examination of the left eye revealed evidence of double optic nerve head (a). The second optic nerve was colobomatous (white arrow). Retcam FFA confirmed the presence of double retinal circulation in the left eye arising from the two optic nerve heads

Treatment

Fluorescein angiography assisted laser treatment by Laser Indirect Ophthalmoscopy was carried out in 23 eyes immediately after performing angiography. Direct visualization of the FFA images on the RetCam screen helped the surgeon to precisely identify and treat the vascular abnormalities and avascular retina. In cases where the posterior segment neovascularization was extensive, the dye leaking into vitreous cavity caused a slight greenish haze but laser treatment could be successfully achieved in all cases.

Twelve patients received laser for the treatment of vascular abnormalities. One patient received cryotherapy. Three patients received retreatment with laser based on persistence of disease/avascular retina on FFA on follow-up. One eye received retreatment with cryotherapy.

In our study performing a RetCam assisted fluorescein angiography in addition to the clinical assessment helped in establishing a diagnosis in 4 patients (18%). The diagnosis of Coats was established in 1 case and FEVR was diagnosed in 3 cases. This technique helped in decision making regarding treatment in 18 patients (82%), and in deciding need for retreatment in 5 patients (23%). It helped in staging the disease in (FEVR, Coats and ROP) 5 patients (23%) and detecting clinically subtle findings in (e.g. small NVE, venous loop) in 6 patients (27%). Presence of two independent vascular arcades emanating from two disc-like structures helped in confirming a very rare diagnosis of double optic nerve head in 1 patient (5%). Table 2 summarizes the advantages gained by use of RetCam widefield fluorescein angiography over clinical findings and it's influence in changing management plan [Table 2].

Discussion

The purpose of this study was to evaluate the utility of RetCam FFA in the management of pediatric retinal vascular disorders. In this study, we intended to see if FFA would provide more details compared only to clinical examination or imaging only. RetCam-assisted FFA not only was able to confirm and corroborate with the clinical findings but also provided excellent details of the fundus pathology not appreciated on color photography alone.

Treatment in most of the adult retinal vascular diseases is guided by fluorescein angiography. Since conventional FFA including the Spectralis and Optos require patient cooperation, RetCam serves as an excellent tool to image the pediatric patients not comfortable with the conventional imaging.

In our retrospective study, a wide range of pediatric retinal vascular disorders were included. RetCam FFA enabled in establishing a diagnosis in 18% cases and defining treatment in 82% cases as discussed in detail in the results.

We did FFA only in selected cases of APROP where there was clinical confusion to decide management. In one of our cases, FFA helped to identify incomplete macular perfusion and hence was decided to carry out injection intravitreal anti-VEGF over laser procedure. Follow-up of this case showed vascularization progressing upto anterior zone 2. Also in 2 cases, FFA helped to identify all the areas of avascular loops. Identification and laser of these loops is essential for complete regression of the disease. Studies have also shown that FFA can be useful to detect vascular and macular abnormalities seen in cases of ROP and in eyes treated with intravitreal Bevacizumab.[16,17] Also, FFA images appear to be easier to interpret than RetCam

Table 2: Advantages gained by use of RetCam widefield fluorescein angiography over clinical findings

No	Advantages gained by using RetCam widefield FFA over clinical findings	Did FFA change management plan?
1	To identify the areas requiring treatment and to screen fellow eye	Yes
2	To identify the areas requiring treatment and to screen fellow eye	Yes
3	To screen fellow eye for any clinically invisible vascular abnormalities	No
4	To arrive at diagnosis of Coats disease	Yes
5	To identify the areas requiring treatment and to screen fellow eye	Yes
6	To treat residual areas of activity	Yes
7	To identify the areas requiring treatment and to guide in retreatment by identifying residual areas of avascularity and neovascularization.	Yes
8	To identify the areas requiring treatment and to guide in retreatment by identifying residual areas of avascularity and neovascularization.	Yes
9	FFA showed no evidence of retinal neovascularization and hence was decided for observation only with follow-up	Yes
10	To precisely identify areas requiring treatment	Yes
11	FFA showed no evidence of retinal neovascularization and hence was decided for observation only with follow-up	Yes
12	To identify the areas of avascular loops and avascular retina and guide in laser treatment (laser of avascular loops is essential for successful regression of disease in APROP and FFA clearly demonstrated these areas)	Yes
13	To identify the areas of avascular loops and avascular retina and guide in laser treatment	Yes
14	FFA clearly showed disease confined to Zone 1 with incomplete vascularization of macula. Hence decided for both eye intravitreal anti-VEGF therapy. Follow-up of this child showed vascularization developing upto anterior zone 2.	Yes
15	To identify the areas requiring laser treatment in right eye	Yes
16	To identify the probable source of vitreous hemorrhage and aid in treatment of peripheral avascular retina. A floating venous loop could be demonstrated only by FFA	Yes
17	To aid in diagnosis of FEVR (diagnosed primarily as persistent fetal vasculature).	Yes
18	To identify the cause of congenital retinal folds (ROP)	No
19	To ascertain the cause of congenital retinal folds (FEVR) as a part of family screening	No
20	To identify the presence of two independent retinal circulations arising from two discs.	Yes
21	To identify areas requiring treatment (areas of avascularity) and identification of early neovascularization and skip areas requiring retreatment.	Yes
22	To confirm the diagnosis and rule out peripheral vascular abnormalities	No

images, in cases of ROP with a high degree of reliability, even where trainee practitioners are involved.[18]

RetCam FFA was extremely useful in a female child with exudative detachment to make a diagnosis of Coats disease with certainty by revealing characteristic telangiectasia and capillary nonperfusion areas which could not be easily picked up clinically. The utility of FFA in a similar case has been reported previously by Koozekanani *et al*.[11] In other cases of Coats disease, FFA was useful for identification of areas requiring treatment, to guide in retreatment by identifying residual areas of avascularity and neovascularization. FFA guided treatment in early stages of Coats has been shown to result in good anatomic and visual outcomes by providing valuable information not provided by clinical examination alone.[12] In our series, widefield FFA using RetCam was extremely convenient to screen the fellow eyes. The occurrence of angiographic vascular abnormalities in a clinically normal appearing fellow eye has been shown in various studies.[19,20] Thus, it is preferable to thoroughly screen clinically normal appearing fellow eyes of Coats disease to look for subtle angiographic signs.

In cases of FEVR, manifestations range from asymptomatic disease to total retinal detachment. RetCam FFA in our patients was mainly useful to decide the need for treatment and retreatment. FFA helps to clearly identify variety of vascular abnormalities, which are not picked by clinical examination. It has also been noted previously that vascular leakage without clinical exudation can be detected only by angiography and early treatment before exudation is critical for favorable outcomes.[21]

Congenital retinal fold is a condition characterized by a vascular retinal fold extending from optic disc towards peripheral fundus. These folds are thought to result from insufficient retinal vascular development in conditions like FEVR, ROP, Norrie disease, and incontinentia pigmenti.[22] Unlike cases of persistent fetal vasculature, these cases tend to be bilateral. In our series, the cause of these folds could be attributable to FEVR and ROP.

Other few interesting pathologies picked up in our series of cases were a floating venous loop causing vitreous hemorrhage (the details of this case have been published in the same journal)[15] and double optic nerve head. True double optic nerve head is a rare entity. Similar to the previous reports on true double optic nerve head,[23] our case had two independent retinal circulations arising from the two discs. However, we

could not carry out MRI and other imaging modalities as the parents denied for further investigations.

The study has a few limitations. This was a retrospective study with a variable duration of follow-up. Also, we did not do a direct comparison between clinical examination based treatment and FFA guided treatment.

Conclusion

RetCam-assisted FFA is an extremely useful investigation in the management of pediatric retinal vascular diseases. Widefield angiographic images help to analyze and document subtle peripheral vascular pathologies that can be missed on clinical examination. RetCam FFA guides the surgeon in making crucial therapeutic and retreatment decisions.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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