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Original Research Article

Role of fundus fluorescein angiography in identifying the unexplained visual loss due to macular edema in peripheral retinal diseases

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ABSTRACT

Aim: Aim of our study is to identify the peripheral retinal diseases in patients which is responsible for macular oedema causing visual loss in various age group of patients.

Materials and Methods: In this retrospective study 30 patients of macular oedema presented to our department between January 2020 to December 2021 were examined in detail. Proper history taking, BCVA, slit lamp examination, fundus examination with indirect ophthalmoscopy, fundus fluorescein angiography (FFA), OCT to quantify macular oedema and documentation done in all cases. Patients were managed with pan retinal photo coagulation, intra vitreal steroids and anti vegf were given to treat macular oedema.

Results: BCVA, fundus examination, FFA and OCT done in all cases, most of the patients showed good outcome with anti vegf, steroid injections and pan retinal photo coagulation, but reoccurrence of macular oedema noted in few cases after one year in cases where the cause of macular edema was not detected even after FFA.

Conclusion: Peripheral examination of fundus is very important to diagnose these conditions, FFA has major role in studying the peripheral retina particularly in conditions where the clinical presentation is not apparent.

1. Introduction

Macular oedema leading to visual loss could be due to involvement of central retinal diseases or peripheral retinal diseases. Identifying the peripheral disease which is causing macular oedema requires proper work up to manage the macular oedema, if not properly identified it is very difficult to treat macular oedema, persisting macular oedema can lead to permanent loss of vision. Various investigation modalities are available today to identify the peripheral retinal diseases which are clinically very difficult to identify with indirect ophthalmoscopy. Fundus fluorescein angiography and peripheral OCT are available today to confirm the diagnosis. We have done a Retrospective study where various patients presented with unexplained visual loss, particularly in middle age individuals.

Today we have many imaging technologies which help in detailed evaluation and documentation of peripheral retinal diseases. Ultra wide field imaging is one which helps in identifying the central as well as peripheral retinal lesions, it covers 200 degrees of peripheral lesions which are difficult to diagnose, unrecognised retinal lesions are visible which helps in proper diagnosis and management. [1] Due to its high cost, usage of UWF fundus camera is limited.

Traditional camera with 70 degrees' eccentricity requires patients to move the eyes in extreme gazes for the visualisation of the peripheral retinal lesions. In our study we have diagnosed peripheral retinal diseases with

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traditional camera only.

Anatomically and functionally there is difference between central retina and functional retina, there is difference in thickness of retina, peripheral retina is thin compared to central retina, photo receptors density, cones dominate in central area where as rods in peripheral area, functionally the central retina provides sharp image whereas peripheral retina provides movement of the objects.

In our study we tried to study the association of macular perfusion status with the peripheral retinal disorders. Peripheral retinal ischaemia is detected by the Fundus Fluorescein Angiography (FFA). Retinal Ischaemia releases VEGF in eyes which leads to break down of blood retinal barriers, increased vascular permeability and causes retinal oedema. Peripheral retinal ischaemia is detected with FFA helps in treating the peripheral retinal disease to reduce the macular oedema, treating macular oedema with anti VEGF injections only will not help in reducing macular oedema, the main disease need to targeted to solve the central visual problem.[2]

2. Materials and Methods

All 30 patients who presented with unexplained cause of macular edema where examined in detail, Proper history taking, BCVA, slit lamp examination, fundus examination with indirect ophthalmoscopy, Fundus Fluorescein Angiography (FFA), OCT to quantify macular oedema and documentation done in all cases. Patients were managed with different management options like pan retinal photo coagulation and anti vegf and steroid injections were given to treat macular oedema.

2.1. Inclusion criteria

Patients of all age groups and both sex without any previous ocular disorders & history of trauma were included in this study.

2.2. Exclusion criteria

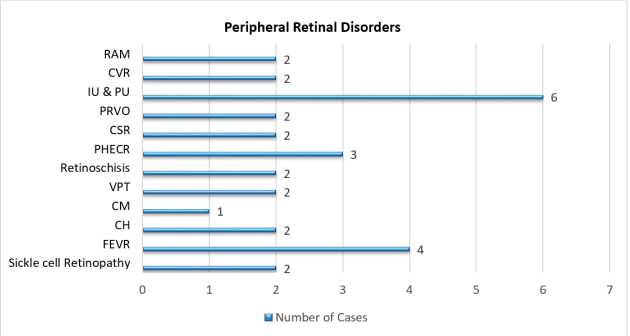
Patients with systemic disease like diabetes etc were excluded.

2.3. Procedure

All patients underwent FFA after clearance from physician. FFA images were taken in all quadrants till periphery, traditional fundus camera used to take the images of both central, mid, near and far peripheral retina. 3ml of 25% concentration dye used in all patients.

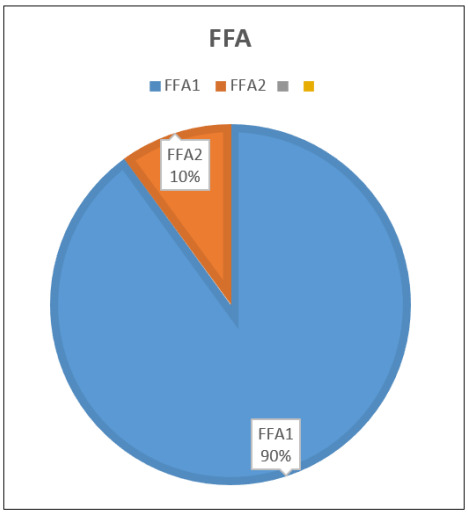
3. Result

FFA helped in detecting the cause of macular edema in 90% of the cases, treatment was successful in 90% of cases where cause of the vision impairment was detected. In few



Graph 1: Bar chart showing the number of peripheralretinal disorders

patients that is 10% of patients the cause was not revealed so the diagnosis was not confirmed, treatment in these cases was not effective, even though the macular edema resolved, after sometime rebound phenomenon was there, some cases were refractory to the treatment and ended with chronic structural changes in macula which lead to the visual and anatomical loss of macular morphology. FFA is definitely standard diagnostic tool in our study, 10% of cases where FFA did not help in diagnosis other investigations were tried like OCT, still the diagnosis was not confirmed in those cases, may be the macular edema in these cases was due to idiopathic cause or hereditary cystoid macular dystrophy.



Graph 2: Pie chart showing role of FFA in detecting the cause of macular edema

Relapse was noted in two to three cases, in these cases additional PRP done with repeated intra vitreal injections to maintain the vision, one or two cases developed tractional bands with elevation of retina, managed with vitrectomy and silicone oil tamponade.

Table 1:

Gender		
Male patients	19	
Female patients	11	
Management of Patients		
PRP	27	
NO PRP	3	
PRP Plus Anti Vegf Injections	27	
Only Anti Vegf Injections	3	
No of intra vitreal anti vegf injections given in patients		
3 injections with interval of one month	16	
2 injections with interval of one month	7	
One injection of anti vegf	3	
Repeated injections more than 3	4	
Management with steroids		
No of patients received	6	
No of injections given	2	
Vision recovery		
BCVA	6/12 to 6/9	10
BCVA	6/18 to 6/24	7
BCVA	6/24 to 6/36	5
BCVA	6/36 to 6/60	3
BCVA	6/60	2
BCVA	CF 3 TO 4 mts	3

4. Discussion

We want to describe each case in detail to know the role of FFA in our study, we could diagnose all the 30 cases with our traditional FFA camera and treated with anti VEGF injections, pan retinal photo coagulation if required we also injected intra vitreal / peri ocular steroids and advised oral steroids after physician clearance.

Two middle aged male patients presented with decreased distant vision in both eyes with gradual progressive loss of vision, on clinical examination there was macular oedema, only macular thickening noted in both the patients, peripheral fundus examination did not reveal any retinal changes, FFA done in both the patients, one patient showed characteristic peripheral sea fan neovascularisation with non-perfusion area in the temporal periphery and the other patient showed sun burst sign which is again characteristic feature of sickle cell anaemia. Sun burst sign is the early feature of the disease, hyper fluorescence is due to staining of the chorio retinal scar and surrounding hypo fluorescence is due to capillary drop out near the scar. PRPC and anti VEGF injections given, BCVA before treatment was 6/60 in BE, after three injections and PRPC, patient BCVA was 6/12 in BE. Second patient BCVA was 6/18 in BE before treatment, after treatment his BCVA was 6/9 in BE.

Patients haematological examination did not reveal any sickle cell anaemia, literature showed other ocular disorders like Retinitis Pigmentosa and chronic retinal detachment also can present with sea fan neovascularisation in the periphery

In Retinitis Pigmentosa the cause for sea fan NV is degeneration of photo receptors which causes increased oxygen tension, high oxygen tension causes toxic effects to the capillaries causing capillary collapse leading to capillary drop out, ischaemia and NV, degeneration of photo receptors will induce intra ocular inflammation causing vascular abnormalities finally leading to ischaemia and NV.[3]

Chronic retinal detachment is one more condition where sea fan NV noted near the retinal holes, due to long standing hypoxia in detached retina.[4]

Finally we could diagnosed as congenital peripheral retinal vascular disorder, may be vascular anomaly which is masquerading sickle cell retinopathy.

FEVR is one condition where the peripheral retina is avascular, four patients in our study presented with macular oedema, three were between 21 to 25 age group, one was a teen ager, 3 young male patients presented with tractional bands in temporal periphery, birth history was normal, macula showed thickening with hard exudates, FFA revealed large non perfusion area in periphery with straitening of the vessels. PRPC done in all patients, one patient with macular edema and without tractional band treated with anti VEGF injections. One patient developed combined retinal detachment after one year in one eye, tractional plus exudative retinal detachment with massive sub macular exudation and also cholesterol crystals which were masquerading like adult onset coats disease, surgery planned, Pars plana vitrectomy with membrane peeling, endo drainage, endo laser and silicone oil tamponade done.

Angiography is important investigative modality for diagnosis in cases where no peripheral retinal changes are not clinically seen and management of patients with FEVR.[5] In our study also all cases presented with exudation in macular area, with some changes in peripheral retina, diagnosis was not easy to manage the disease, though history was not giving any evidence of Retinopathy of prematurity (ROP), clinically the peripheral retinal changes were masquerading the ROP. FFA showed peripheral retinal non perfusion, straitening of vessels in temporal periphery, telangiectatic vessels and also vascular leak in the periphery which helped to confirm the diagnosis. FEVR is a lifelong disease which requires frequent examinations and regular FFA to study the capillary drop out areas, so that laser therapy to the ischaemic retina helps in maintaining the stability of the retina.

In our study all cases presented to the department did not show any extra ocular manifestations like hearing loss and developmental delay, we did not do any genetic analysis in our cases. Norrie disease is an inherited condition which is usually noted in infants presenting with severe FEVR phenotype associated with progressive hearing loss and development delay. Severity of disease and extra ocular manifestations are associated with FZD4 variants; hence

genetic analysis is very important to study the case in detail. Two cases in our study were progressed very badly, may be due to FZD4 variant.[6] FFA was not helpful to diagnose and treat. Treatment in these cases did not show any response. Role of FFA is very limited particularly in hereditary vitreo retinopathies.

FEVR can mimic Persistent foetal vasculature (PFV) if retinal folds from Disc to peripheral retina are oriented radially and anteriorly to the ciliary process. Confusion arises when one eye is involved with severe findings and other eye is normal without any clinical findings. FEVR shows falciform fold, where as in PFV the fold is not typical retinal fold, it is unregressed hyaloid stalk of persistent vascular tissue which extends from optic nerve head to the posterior lens capsule.[7] Proper clinical examination and FFA helps in differentiating, diagnosis and management.

One male patient of middle age showed macular thickening and hard exudates, peripheral examination of the fundus revealed small orange red solitary mass like lesion in periphery in infero temporal quadrant. Common site of choroidal haemangioma is posterior pole first and supero temporal quadrant next common site, but in our case choroidal haemangioma was located in the infero temporal quadrant. FFA shows hyperfluoresence in early phase with increase in intensity like staining, ICG has definitive role in diagnosis which shows early hyper fluorescence and late hypo fluorescence termed "washout phenomenon," characteristic finding of choroidal haemangioma.[8] FFA and B Scan done in our case and treated with anti vegf injection. Small Choroidal tumours of size less than 3mm and thickness less than 1.5 mm are treated with laser therapy. Usually peripheral tumours are missed, proper indirect ophthalmoscopy is done rather than FFA in these cases.

55 years old female presented with mass like lesion with diffuse elevated exudative retinal detachment nasally extending from periphery to the disc and causing serous macular detachment in Right eye, her BCVA in right eye was 6/36, temporal retina was normal, B Scan done to see the internal reflectivity, tumour size and shape, FFA done. B Scan and MRI orbit showed mass like lesion with variable reflectivity, referred to Ocular Oncologist for further management. Enucleation done by the Ocular Oncologist after explaining the risk of metastases. In our case FFA was not much informative, our diagnosis was confirmed based on clinical findings. FFA has characteristic findings like irregular and patchy fluorescence during the arteriovenous phase and increased staining in the later phases. The patchy hypo pigmented areas correspond to orange pigmentation (lipofuscin). The hyper fluorescence increases through all the phases of the angiogram.[9]

Vaso proliferative tumours are small benign tumours which can cause various vitreo retinal complications, if not properly managed it can lead to blindness. One 46 years' male presented with eccentric macular hole, some vascular changes in the retina like retinal vascular sheathing, FFA done in this patient, angiography revealed vascular staining, capillary non perfusion areas in the inferior and temporal quadrant, isolated stained round lesion in the inferior quadrant may be VPT, OCT showed pseudo macular hole, probably due to chronic macular oedema. Pan retinal photo coagulation done and intra vitreal avastin given. Patient BCVA was improved from CF $\frac{1}{2}$ Mt to 6/60.

Vaso proliferative tumours usually noted in chronic retinal vascular disorders. VPT has an impact on vision because of macular involvement, needs to be evaluated when a patient present with macular exudates. Prompt diagnosis and appropriate treatment helps in preventing from blindness.[10] Clinically VPT shows small red macro aneurysms which will be noted in retina.FFA in these cases will not show any leak or hyper fluorescence. Here macular edema is due to vascular disorder.

The vaso proliferative tumours considered as reactive process, secondary to the breakdown of the blood-retinal barrier, which lead to an uncontrolled proliferation of fibrous tissue and angiogenesis in the retina.[11]

X Linked retinoschisis can present as only macular schisis or peripheral involvement of retina or both. When peripheral retinischisis is present patient will present very late, because splitting is in the periphery, patient is usually asymptomatic, when they develop outer and inner retina breaks, retinal detachment will occur. In our study we saw two young adults, male patients between 20 to 25 years presented with foveoschisis. Role of FFA is not there in these retinal disorders.

Prophylactic laser therapy to barricade along the margins of the schitic retina to prevent the progression of splitting in one patient and followed frequently, after one year there was progression of splitting extended posterior to the equator, foveoschisis noted without foveal detachment which resulted in drop of vision, other patient presented with foveal detachment, explained about the prognosis after surgery, patient refused for the management. Retinoschisis is continuous inherited degeneration process, any treatment cannot stop the degeneration in the inner retinal layers, there is deficiency of the retinoschicin protein which is important in binding the retinal layers together. Muller cells have very important role in maintaining the structural integrity of the macula. RS1 protein is transmitted to the inner retina by the Muller cells. Mutation of the RS1 gene give rise to a dysfunctional adhesive protein, results in defective cellular retinal adhesion which finally leads to schisis formation.[12]

Retinoschisis patients are usually asymptomatic. Treatment for these patients should be regular follow-up and observation.[13]

Peripheral haemorrhagic exudative chorio retinopathy (PHECR) noted in three patients, two females and one male patient, all three were mean age of 52 years, BCVA in the

involvement eye was CF 3mts, initially all the three patients were diagnosed as Wet ARMD (Figure 1) in one eye, because hard drusen were noted in other eye and given two injections of anti VEGF, response was good, BCVA after anti VEGF injections was 6/18. After one year again they presented with haemorrhage extending to the anterior and posterior to the equator (Figure 2), FFA was repeated, FFA showed irregular hyper fluorescence and hypo fluorescence in the macula corresponding to the RPE changes, temporal to macula hypo fluorescence corresponding to the sub retinal bleed and hyper fluorescence in the sub retinal bleed corresponding to CNVM (Figure 3), inferior to the mass, fresh and organised haemorrhage showed hypo fluorescence, hyper fluorescence in the mid portion of fresh bleed indicates CNVM with hyper fluorescence near the edge of the haemorrhage corresponding to exudates (Figure 4).

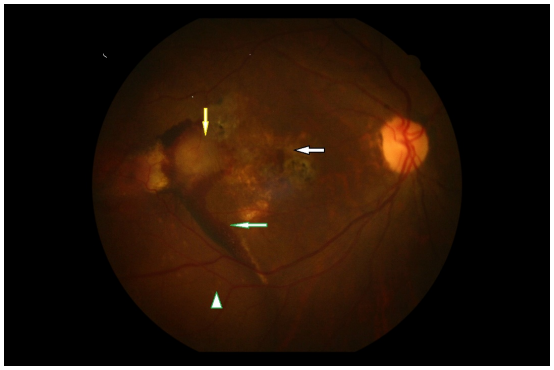


Fig. 1: Fundus image of RE white arrow with black outline indicates irregular RPE changes in macular area, white arrow with yellow outline indicates CNVM, white arrow with green outline indicates sub retinal bleed, white triangle with green outline indicates peripheral exudative mass lesion

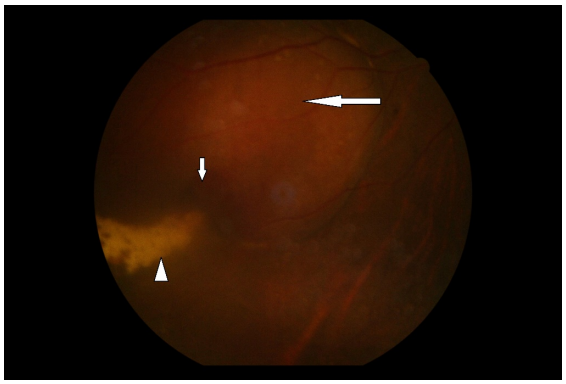


Fig. 2: Fundus image of RE big white arrow depicts peripheral exudative mass, small white arrow depicts bleed and white triangle indicates exudates

One female patient after diagnosing PHECR, anti VEGF injections were advised, one day before injection she

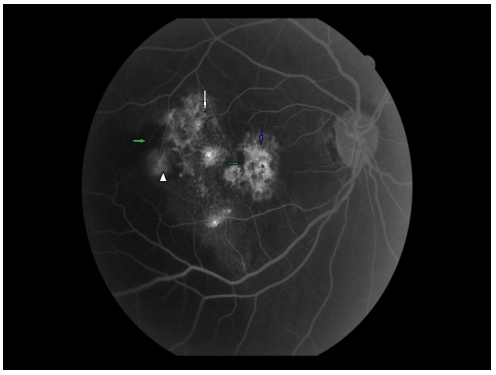


Fig. 3: FFA image of RE white and blue arrows depicts irregular hyper fluorescence suggestive of RPE changes, green arrows indicate hypo fluorescence due to sub retinal bleed and small triangle depicts CNVM which shows small hyper fluorescence area in the sub retinal bleed

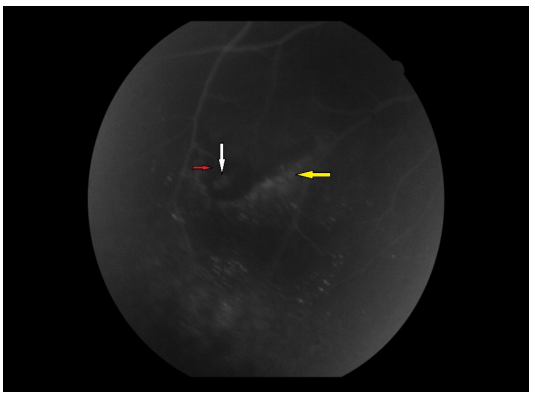


Fig. 4: FA image of RE red arrow depicts hypo fluorescence corresponding to the sub retinal bleed, white arrow in the bleed depicts CNVM which is hyper fluorescence area in the sub retinal bleed and the yellow arrow indicates the exudates which shows hyper fluorescence at the edge of the peripheral mass lesion

developed break through vitreous haemorrhage and media became hazy due to vitreous haemorrhage, PPV done and intra vitreal anti VEGF injection given, Laser therapy also given to the leaking areas after surgery, patient developed sob retinal scar in the macula with part of the scar involving the fovea, one month after surgery vision improvement was not significant. Six months after the surgery patient presented with extra macular haemorrhage extending to the macular area, sub retinal bleed involving nasal to the disc, inferior to disc which is extending to the macula causing vision drop in the other eye, intra vitreal anti VEGF injections were given.

All three cases were using anti-hypertensive drugs, one female had hypothyroidism. Shields et al. reported 173 cases of PEHCR. They showed that PEHCR is mainly a disease of elderly women, and manifests as bilateral lesions located in the temporal area between the equator

and the ora serrate.[14] Pathogenesis in this disease is Choroidal neo vascular membrane. Recurrent haemorrhage due to PHECR will cause enlargement of the lesion which can extend to the macular area and finally vision loss. PHECR is considered as variant of age related macular degeneration that commonly reported in Asians. Idiopathic Polypoidal Choroidal Vasculopathy (IPCV) and PHECR are neo vascular phenotypes which are seen in fifth decade or after fifth decade, both the conditions involve the inner choroid and considered as sub type of ARMD. Initially response to anti VEGF injections is good, but recurrent episodes will cause RPE changes and damages the photo receptors and eventually leads to vision loss.

Central serous chorioretinopathy (CSR) is serous macular detachment, usually leaking points are seen in macular area, in our study we want to describe two cases where the leaking points are away from the macular area. First case is above 40 years old patient, agriculture occupation person presented with vision impairment in both eyes, Right eye had more vision impairment, patient was more worried when there is blurring of vision in Left eye. On examination Right eye showed wide area of RPE defects in macula and part of the macula showed serous detachment extending almost to the inferior quadrant in mid periphery with RPE degenerative changes which is described as tear drop sign and Left eye showed shallow serous macular detachment with sub retinal precipitates in the inferior foveal region. FFA showed multiple leaking points in the macular and para macular area suggestive of atypical CSR, continuous sub retinal fluid leakage is collected inferiorly due to gravity, chronic retinal detachment in the mid periphery will induce the RPE degenerative changes in the macula and surrounding retina.[15]

One more young adult presented with vision impairment in both which is gradually progressing, on fundus examination there was serous macular detachment with surrounding RPE changes, FFA showed few leaking points, one-disc diameter above the disc and also gravitational patterns of RPE atrophy suggested chronic CSR. OCT showed multiple cystic spaces in the sub foveal area. Focal laser tried in both eyes, patient was asymptomatic for one year and again after one year presented with same symptoms. FFA revealed leak half disc diameter away from the macular area. Anti VEGF injection tried, patient was happy for 2 years without any symptoms.

CSR is very difficult to diagnose when there is atypical presentation especially in chronic cases, FFA helps in confirmation by noticing the mid peripheral gravity related RPE degenerative changes that is atrophic pattern which forms the gravitational tract described as Tear Drop tract.[16]

Peripheral retinal vascular occlusion (PRVO) is reported in two elderly individuals, they were in fifth decade, presented with vision impairment in both eyes, both were hypertensive patients, clinically only macular changes were seen, FFA showed staining of peripheral vessels and also few leaking points near the periphery in inferior and temporal quadrants, with macular oedema, basic investigations were done, the reports were not significant, then we thought is it atherosclerosis or chronic hypertensive changes causing ischaemia in periphery which is leading to new vessel formation.

Ageing, clinical factors such as hypertension, heart failure, diabetes, smoking and alcohol will cause loss of arterial elasticity and increase the risk of cardio vascular diseases. Peripheral arterial volume distensibility is reduced in hypertensive aged patients compared to normal subjects.[17]

Intermediate and posterior uveitis cases after resolving can have residual macular edema, these cases need to evaluated in detail to know the cause of macular edema. One middle age male patient presented with cystoid macular edema in both eyes. Detailed ocular and systemic evaluation revealed ocular tuberculosis, In India most common infective aetiology is Tuberculosis.

Detailed examination in uveitis cases showed old healed changes in retina, sometimes these changes are not noticed and diagnosis will become challenging, FFA is always better standard and sensitive diagnostic tool to detect macular edema in cases where clinically undetected by Ophthalmoscopy.[18,19]

FFA is very useful to examine retinal perfusion and to detect vascular hyper permeability. It will present as progressive leakage of dye in the macular region which is seen as increasing hyper fluorescence.[20]

The Patho mechanism of Retinitis Pigmentosa (RP) associated with macular edema is failure of the pumping mechanism in the retinal pigment epithelial, Müller cell dysfunction and anti-retinal antibodies.[21] Main cause for macular edema in RP cases is due to chronic low grade inflammation.

In our study inherited retinal diseases causing macular edema were treated with topical Dorzolamide, intra vitreal steroids, anti VEGF, oral Carbonic anhydrase inhibitors and topical non-steroidal anti-inflammatory drops. FFA in these cases can detect the leak in macular area but not the degenerative changes in the periphery particularly in atypical Retinitis Pigmentosa cases where clinically retinal changes are not visible. In atypical retinitis pigmentosa, there will be no apparent clinical signs visible, here FFA role is also limited, electro physiological test has major role in diagnosis.

The Retinal arterial macro aneurysm (RMAs) were seen most commonly (94.7%) in the temporal half of the retina, with an almost equal distribution between the superior temporal (50%) and inferior temporal arcades (44.7%).[22] In cases of RAMs haemorrhage in macula will mask the details of cause. FFA helps in detecting the cause of haemorrhage, though some studies showed that FFA has limited utility

in RAMs, still in our study FFA helped in detecting the macro aneurysm which shows hyper fluorescence dot in the area of hypo fluorescence corresponding to the hour glass haemorrhage which is present at all the levels of retina. In OCT it is not possible to see the lesion, we can only quantify the macular edema.

5. Conclusion

Peripheral examination of fundus is very important to diagnose these conditions, FFA has major role in studying the peripheral retina particularly in conditions where the clinical presentation is not apparent. FFA is a useful tool for detecting peripheral retinal ischaemia, which helps in the diagnosis, follow-up and treatment such as targeted peripheral photocoagulation.[23] It is important investigative modality in the diagnosis of macular edema due to inflammatory diseases, macular dystrophy, and also helps in differentiating macular edema from macular ischaemia. All peripheral retinal diseases will cause macular edema but role of FFA in some disorders is limited.

6. Abbreviation

FFA: Fundus fluorescein angiography, FEVR: Familial exudative vitreo retinopathy, PHECR: Peripheral haemorrhagic exudative vitreo retinopathy, IU & PU: Intermediate and posterior uveitis, RP: Retinitis Pigmentosa, IPRT: Idiopathic peripheral retinal telangiectasia's, PRVO: Peripheral retinal vasculitis occlusion.

7. Ethical Approval

The study received ethical clearance from the Osmania Medical College ethics committee /Sarojini Devi Eye Hospital, Hyderabad, Telangana State.

8. Source of Funding

None

9. Conflict of Interest

The authors declare that they have no conflict of interest.

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