Multimodal characterization of macular telangiectasia type 2 and correlation with multifocal electroretinogram

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Research Article

Keywords: Macular telangiectasia, OCT, OCTA, autofluorescence, mfERG

Posted Date: March 15th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-178402/v1

Abstract

1. Purpose: To study the correlation of multimodal imaging in macular telangiectasia (Mac Tel) with foveal function on multifocal electroretinogram (mfERG)

2. Methods: Eyes with non- proliferative Mac Tel diagnosed based on clinical examination, optical coherence tomography (OCT), autofluorescence (AF), fluorescein angiography (FA), OCT angiography (OCTA). Control group with normal eye exam included for multifocal electroretinogram.Staging of OCT, OCTA, AF and FA done in Mac Tel subjects. mfERG done in study subjects and controls. Correlation of imaging modalities and P1 amplitudes at fovea (ring 1) studied in terms of correlation co-efficient.

3. Results: Twenty nine eyes of 16 patients of Mac Tel and 25 eyes of 19 controls were included. BCVA was 0.38 ± 0.266 in study eyes and 0 in control eyes. On OCT it was observed that 41.4% Mac Tel eyes (n = 12) belonged to stage 3, 37.9% (n = 11)) eyes belonged to stage 2 and 20.7% (n = 6) eyes belonged to stage 1. AF- Stage 3 comprised of 75.9% eyes (n = 22); 4 eyes belonged to stage 2 and 3 eyes to stage 1. On FA, 18 eyes belonged to stage 3 (62.1%); stage 2 was seen in 1 (3.4%) eye and stage 1 was seen in 10 (34.5%) eyes. There was decrease in P1 amplitudes from R1($p < 0.001$), R2(0.001), R3 (< 0.001) and R4 (0.001) in Mac Tel eyes compared to control eyes but not in R5 (p 0.785). SD- OCT had positive correlation with FAF (CC 0.747,$p < 0.001$) FFA (CC 0.775, $p < 0.001$) and R1P1 (CC 0.682, $p < 0.001$). With OCTA there was no significant correlation (CC 0.318, p 0.093). There was positive and significant correlation of OCT (0.682,<0.001), OCTA (0.379,p 0.042) AF (0.635, $p < 0.001$) and FA (0.495, $p < 0.006$) with R1P1.

4. Conclusions: Existing multimodal imaging systems can be reliable indicators of foveal function as on mfERG.

Introduction

Macular telangiectasia type 2 (Mac Tel type 2) is a bilateral neurodegenerative disease affecting muller cells in the macula. The age of onset is typically between 40 to 50 years.[1] Symptoms include reduced reading vision, scotoma and metamorphopsia.[2] Loss of best corrected visual acuity (VA) is very gradual and is a late symptom because of relative foveal sparing in the early stages of the disease.[3] Multimodal imaging techniques have identified structural changes in early Mac Tel much before VA is affected. Fluorescein angiography (FA), autofluorescence (AF), confocal blue reflectance (CBR), multicolor (MC) imaging, optical coherence tomography (OCT), OCT angiography (OCTA) have provided data on structural changes in Mac Tel and thus provided insight into its pathogenesis.[4] [5] [6] Although these structural details and their functional implications have been noted in terms of BCVA and microperimetry, correlation of these imaging modalities with multifocal electroretinogram (mFERG) has not been studied.

Methods

The study was carried out in patients attending the retina services of a tertiary referral centre in south India. Macular telangiectasia was diagnosed on basis of slit lamp biomicroscopic examination, AF, spectral domain (SD) OCT, FA and OCTA.

Study design and sample

This was a cross sectional study conducted from May 2017 to May 2019. Twenty nine eyes of 16 macular telangiectasia patients and 25 eyes of 19 normal patients were recruited in the study. Subjects enrolled in the study were explained about the imaging modalities being utilized and informed consent was obtained. Ethical approval was obtained from the Institutional Review Board. The study was conducted in accordance with the ethical standards laid down in the declaration of Helsinki.

All control eyes had BCVA of 6/6 and had spherical equivalent of less than 2 diopter sphere (DS). Both study eyes and control eyes had clear media. Eyes with neovascularization, glaucoma and other optic nerve diseases were excluded.

Clinical staging was done in accordance with Gass et al viz. stage 1- parafoveal graying, stage 2- graying, stage 3- right angled venule, stage 4- pigment plaques, stage 5- choroidal neovascular membrane (CNVM). [7]

SD-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) was done and central macular thickness was noted at the foveal centre as distance from the ILM to the RPE. Spectral-domain OCT was performed with a scan angle of 20 in the infrared photography plus OCT mode with the automatic real-time mode switched on. The distance between 2 B-scans was 30 microns.

Temporal, nasal, and foveal loss of ellipsoid zone was noted. The presence of empty spaces and intraretinal pigment with back shadowing also were noted. The horizontal lengths of ellipsoid zone disruption and external limiting membrane disruption in the line scan passing through the fovea were measured manually using the caliper function in-built in the imaging system.

OCTA scans were carried out (high speed Protocol 15 *15) with a scan angle of 10 degree and a pattern size of 2.9 * 2.9 mm. Distance between B-scans was 11 microns. In case of macular thinning, loss of retinal architecture, or both; manual segmentation was carried out in 5 to 7 scans and semiautomated scans were procured and analysed.

AF and FA were both performed on the Spectralis Heidelberg with both 30- and 55-degree scans as high-resolution scans. FA was performed using 3 cc of 20% fluorescein dye.

AF was classified in accordance with Wong et al. [8] OCT, OCTA and FA were classified in accordance with Toto et al (table 1) [9]

All macular telangiectasia patients and normal subjects underwent multifocal ERG (RETIscan, Roland Consult, Germany). The International society for clinical electrophysiology of Vision (ISCEV) guidelines were followed. Before recording, pupils were dilated using 1% tropicamide and 2.5% phenylepinephrine eye drops. The stimulus matrix consisted of 61 scaled hexagonal elements displayed on a monitor and a central red square was used as a fixation target and good fixation was ensured throughout. The radius of stimulus array subtended at a viewing distance of about 27 cm, and each element was independently alternated between black and white stimuli.

Trace arrays at 61 location points of the first order kernel were analyzed for amplitude of 5 concentric rings (foveal R1,< 2^0 R2 5- 10^0 R3, 10-15^0 R4 and >15^0 R5). The average amplitude P1 waves in all the rings were compared with the age matched normative data. Paracentral responses just temporal and nasal to the central element (element 30 and 32 in a standard 61- element array) were also individually analysed, and the relative difference between the temporal versus nasal amplitudes for each eye was also compared.

Grading of each imaging technique was performed independently by two retina specialists and results were comparable for inter-observer reliability. In case of discrepancy, the staging was arrived at by consensus. The results of grading were used to correlate between multimodal imaging and multifocal ERG. For purpose of correlation, the R1P1 amplitudes were divided into four quartiles. (Table 2)

Data was entered in Microsoft excel data sheet and was analysed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions and analyzed using chi square or Fischer's exact test. Continuous data was represented as mean and standard deviation and paired t test was used for differences in patients and controls. Group wise analysis of individual SD-OCT findings was done to study their influence on mfERG and BCVA. p value of less

than 0.05 was considered statistically significant. Spearman co-efficient was calculated to look for correlation between different imaging systems and mfERG.

Results

Demographic data

A total of 29 eyes of 16 patients and 25 eyes of 19 controls were included in our study. Mean age of patients was 57.14± 11.76 years and controls was 55.14±10.73 years. There were 9 men and 20 women in the study group (controls – 13 females and 6 males). BCVA was 0.38 ± 0.266 in study eyes and 0 in control eyes.

Both eyes of 13 patients were included and one eye of three patients was chosen as the other eye in these patients had proliferative Mac Tel. At the time of study, the other eye in these three patients were treatment- naïve. Nine patients had diabetes and five had hypertension. None of the study eyes had diabetic retinopathy. Twenty four eyes were phakic and 5 were pseudophakic in the study group and all control eyes had crystalline lens.

In study eyes, greying of temporal parafovea was seen in all eyes, right angled venule were seen in 82.3% (n=24).

On OCT it was observed that 41.4% (n=12) belonged to stage 3 where as 37.9%(n=11)) of eyes belonged to stage 2 and 20.7% (n=6) eyes belonged to stage 1 (Table) Subretinal and intraretinal degenerative spaces were noted in 24.1%(n=7) and 55.2% eyes (n=16) respectively. Collapse sign was seen in 69% eyes (n=20). The mean central macular thickness was 147.7 micrometre (µm).

AF- 22 eyes belonged to stage 3 (75.9%); 4 eyes belonged to stage 2 and 3 eyes to stage 1.

FFA- 18 eyes belonged to stage 3 (62.1%); stage 2 was seen in 1 (3.4%) eye and stage 1 was seen in 10 (34.5%) eyes. (Table 3)

Multifocal ERG – There was decrease in P1 amplitudes from R1(p <0.001), R2(0.001), R3 (<0.001) and R4 (0.001) in Mac Tel eyes compared to control eyes but not in R5 (p 0.785).(Table 4) There was also asymmetry in P1 amplitude between temporal and nasal segments which was significant - Temporal(85.83 nanovolt) vs nasal (95.25 nanovolt) segment (p-0.043).

Correlation between imaging modalities and mfERG:

SD- OCT had positive correlation with FAF (CC 0.747,p <0.001)) FFA (CC 0.775, p<0.001)) and R1P1 (CC 0.682, p<0.001). With OCTA there was no significant correlation (CC 0.318, p 0.093).AF staging correlated with all imaging except OCTA. FFA had positive correlation with all imaging modalities. All imaging modalities showed a positive correlation with R1P1 that was significant. (Table 5)

Discussion

Until recently, FFA was the gold- standard for the diagnosis of Mac tel. However, the pathological changes in Mac Tel occur in the deeper capillary plexus as evidenced by OCTA studies. There is a depletion of intraretinal structure causing degenerative spaces and/ or macular thinning. The epicentre of these changes is in the temporal parafovea. [10]

Toto et al found strong correlations between OCTA and SD-OCT, early FFA and late FFA. High correlations were also found between CBR and FFA. Moderate correlations were found between SD-OCT and FFA and also CBR. There was low correlation between FAF and CBR. This study concluded that OCTA had high correlations with established imaging techniques and suggested the use of OCTA as a non- invasive tool for detecting early Mac tel changes.[9] Our study found

positive correlation between OCT, AF and FFA. OCT and AF did not correlate significantly with OCTA. However there was high and significant correlation between imaging modalities and R1PQ. Pauleikhoff et al studied the correlation of vascular change patterns in terms vessel lengths, number of branches, number of vessel segments and fractal dimension with extent of EZ loss on SD- OCT. There was progressive reduction of number of vessel branches, vessel segments and fractal dimension values in both SVP and DVP that correlated with increasing EZ loss. [11]

Structure- function correlation in Mac Tel has been attempted in the past by correlating macular pigment optical density (MPOD) and BCVA. Zeimer et al utilized a dual- wavelength system and classified MPOD into class 1- temporal parafoveal triangular segment of reduced MP, class 2- generalized reduction of foveal MPOD with central sparing, class 3- horizontally oval effacement of MP and rim of MP at 5- 7 degrees eccentrically. They found that higher class of MPOD correlated with higher stages of Mac tel. There was also significant BCVA differences between class 1 and the higher classes. [12]In a later work, Zeimer et al found the MPOD distribution into 3 classes showed strongest correlation with changes in the SVP. [13]

Park et al assessed the correlation of OCTA- based foveal avascular zone (FAZ) area in SVP and DVP with BCVA in Mac Tel and controls. They found significant negative correlation between FAZ of SVP, DVP and BCVA in the study group. [14]

BCVA remains a subjective end-point for macular telangiectasia because the central fovea is affected only in the later stages. BCVA was not used as an end point in the clinical trial (phase 2) of ciliary neurotrophic factor for Mac Tel and EZ loss on OCT was chosen as the primary outcome. Microperimetry as a functional test has been studied in relation to Mac tel. Since microperimetry can test for sensitivity and assess extrafoveal visual loss, it has been used as an end- point in clinical trials of Mac Tel as a secondary outcome. However, challenges are test duration and requirement of good fixation. The test also needs intense concentration and skilled examiners thus limiting it to select patient groups. However after the initial learning curve, high test- retest reliability has been found. Despite this, subtle losses of sensitivity in between testing areas can be missed. Besides, microperimetry is a tool that measures not just retinal physiology but is also influenced by the entire visual pathway.

Kihara et al developed a deep- learning network that could directly estimate retinal function from superpositions of high resolution OCT scans and microperimetry results. The predictions were used to create high- density enface sensitivity maps of the macula. In their study, they found that activation maps generated showed that the important structures identified were in the outer retina especially the ellipsoid zone. [15] MFERG on the other hand is more objective because the first order kernel responses originate solely from the bipolar cells and photoreceptors.

There is limited literature on electrophysiology in Mac Tel. Normal ERG and EOG has been reported in case series ruling out generalized retinal and RPE dysfunction. Ledolter performed full- field ERG and pattern ERG in mac Tel eyes and suggested inner retinal dysfunction in rods and cones attributable to muller cell dysfunction. [16] Goel et al compared the mean P1 amplitudes and implicit time (IT) in R1 to R5 between Mac Tel eyes and controls and found that mean P1 amplitudes were significantly decreased in Mac Tel eyes compared to controls in R1. The P1 amplitudes also decreased gradually from R1 to R5. This trend however was not seen in implicit time. They studied the correlation between BCVA, mfERG amplitudes and CMT. Although they noted a significant and negative correlation between BCVA and P1 amplitude and implicit time, the positive correlation of CMT and P1 was not significant. [17]

Narayanan et al stated there was a significant reduction in amplitudes as well as delay in implicit times of the waveforms in patients with type 2 Mac Tel in all the rings, compared to a matched normal population. The maximum reductions were seen in R1. They hypothesized that the reduction in amplitudes of waveforms, even in the peripheral rings, could be explained by the fact that telangiectatic vessels have been shown on fluorescein angiography even 2500 microns away from the fovea. Our study showed a reduction in P1 in rings 1 to 4 but not in R5. [18]

Mali Okada et al in their study stated that mfERGs showed preservation of the early N1 in R1 but selective reduction of the P1. The temporal paracentral response was also affected in half of the patients, with significant asymmetry between temporal and nasal responses. In their study, peripheral mfERG responses were unaffected and they concluded that Mac Tel is a localized disturbance of macular function, and uniquely provide evidence of an inner retinal site of dysfunction. They further stated that increase in the size of the EZ break area was significantly associated with decreasing central hexagon P1 amplitudes. Our study also showed statistically significant negative correlation between central R1 response with the length of EZ loss on OCT. Increasing length of the EZ break area was significantly associated with decreasing central hexagon P1 amplitudes. Thus the primary pathology in Mac Tel is post- photoreceptoral.[19] Our study found similar results.

Conclusion

To the best of our knowledge there is no other study correlating multimodal imaging with cone function amplitude. We have developed an mfERG staging system for Mac Tel type 2. The clinical application of mfERG is limited by the lack of such equipment in many clinical centers. Positive correlation of R1 P1 amplitudes with existing multimodal imaging systems makes it possible to glean information about macular function from multimodal imaging.

Declarations

Funding: No funding sources

Conflicts of interest: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: The study protocol was approved by the Institutional Review Board (IRB) of

M M Joshi Eye Institute and adhered to the tenets of the Declaration of Helsinki.

Consent to participate: Informed consent was obtained from all patients before study inclusion.

Availability of data and material: The datasets generated during the current study are available from the corresponding author upon request.

Code availability: Not applicable

Authors' contributions

Study design: A.G, G.A

Data acquisition and analysis: A G, L.P

Statistical analysis: A.G

Manuscript drafting: A.G, L.P, S.J ,G.A

Review and approval of the manuscript: A.G, L.P, S.J ,G.A

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Tables

Table 1- Staging of imaging modalities- reproduced from Toto et al.

Staging modality	Stage 1	Stage 2	Stage 3	Stage 4
OCT	A break in the EZ , with inner and outer retinal cysts temporal to the foveal center	EZ break reaching the foveal center with central outer cysts, and inner cysts involving temporal, central and nasal side ; collapse of outer plexiform layer towards choroid. Hyperreflective intraretinal lesion due topigment plaques is visible.	Only minor retinal cysts remain, EZ break involves the nasal side. The “collapse” of the layers is extensive. Hyperreflective Intraretinal pigment plaques seen	Signs of outer retinal neovascularization with activity.
OCTA	Capillary anomalies (deep plexus and/ or superficial plexus) in temporal fovea	Deep and / or superficial vascular plexus anomalies in temporal and nasal parafovea	Diffuse circumferential vascular anomalies in deep and / or Superficial plexus	Neovascularization in outer retina
FAF*	Loss of foveal hypoAF	hyperAF at fovea and slight hyperAF parafoveal	Heterogenous pattern AF	-
FFA	Temporal changes	Temporal and nasal changes	Full involvement	Signs of classic neovascularization

*Staging of AF by Wong et al

Table 2- R1P1 amplitudes divided into four quartiles.

Macular telangiectasia type 2 stages	R1 P1 (n=29) in nV/deg^2
Stage 1	161.0 – 98.0
Stage 2	97.0 - 64.0
Stage 3	63.0 – 43.0
Stage 4	Less than 42.0

Table 3- Distribution of eyes in individual stages of OCT, AF, FFA, OCTA and mfERG

Clinical	Stage 1 (n)	Stage 2 (n)	Stage 3 (n)	Stage 4 (n)
OCT	6	11	12	0
AF	3	4	23	
FFA	10	1	18	0
OCTA	7	6	16	0
mfERG	7	8	14	0

Table 4 Comparison of P1 amplitudes of R1, R2, R3, R4 and R5 between study eyes and control eyes.

P1 amplitudes are in nanovolts (nV/ deg^2)

	R1P1	SD	Mean R2P1	SD	Mean R3P1	SD	Mean R4P1	SD	Mean R5P1	SD
Study eyes	71.7	38.05	79.05	50.89	61.30	30.43	50.68	25.04	44.13	22.4
Control eyes	192.37	69.91	134.34	44.14	104.16	31.88	76.14	22.41	24.88	23.31
P value	<0.001		0.001		<0.001		0.001		0.78	

Table 5- Correlation between imaging modalities and mfERG. Expressed in Spearman's co-efficient.

Correlations								
			SD OCT staging	FAF staging	FFA Grading	OCTA staging	R1P1	R2P1
Spearman's rho	SD OCT staging	Correlation Coefficient		**0.747****	**0.775****	**0.318**	**0.682****	0.223
		P value		**<0.001***	**<0.001***	**0.093**	**<0.001***	.244
		N	29	29	29	29	29	29
	FAF staging	Correlation Coefficient	**0.747****		**0.747****	0.237	**0.635****	0.267
		P value	**<0.001***		**<0.001***	0.216	**<0.001***	0.161
		N	29	29	29	29	29	29
	FFA Grading	Correlation Coefficient	**0.775****	**0.747****		**0.395***	**0.495****	0.153
		P value	**<0.001***	**<0.001***		**0.034***	**0.006***	0.428
		N	29	29	29	29	29	29
	OCTA staging	Correlation Coefficient	0.318	0.237	**0.395***		**0.379***	0.133
		P value	0.093	0.216	**0.034***		**0.042***	0.490
		N	29	29	29	29	29	29
	R1P1	Correlation Coefficient	**0.682****	**0.635****	**0.495****	**0.379***		**0.515****
		P value	**<0.001***	**<0.001***	**0.006***	**0.042***		**0.004***
		N	29	29	29	29	29	29
	R2P1	Correlation Coefficient	0.223	0.267	0.153	0.133	**0.515****	
		P value	0.244	0.161	0.428	0.490	**0.004***	
		N	29	29	29	29	29	29
**. Correlation is significant at the 0.01 level (2-tailed).								
*. Correlation is significant at the 0.05 level (2-tailed).								

Figures

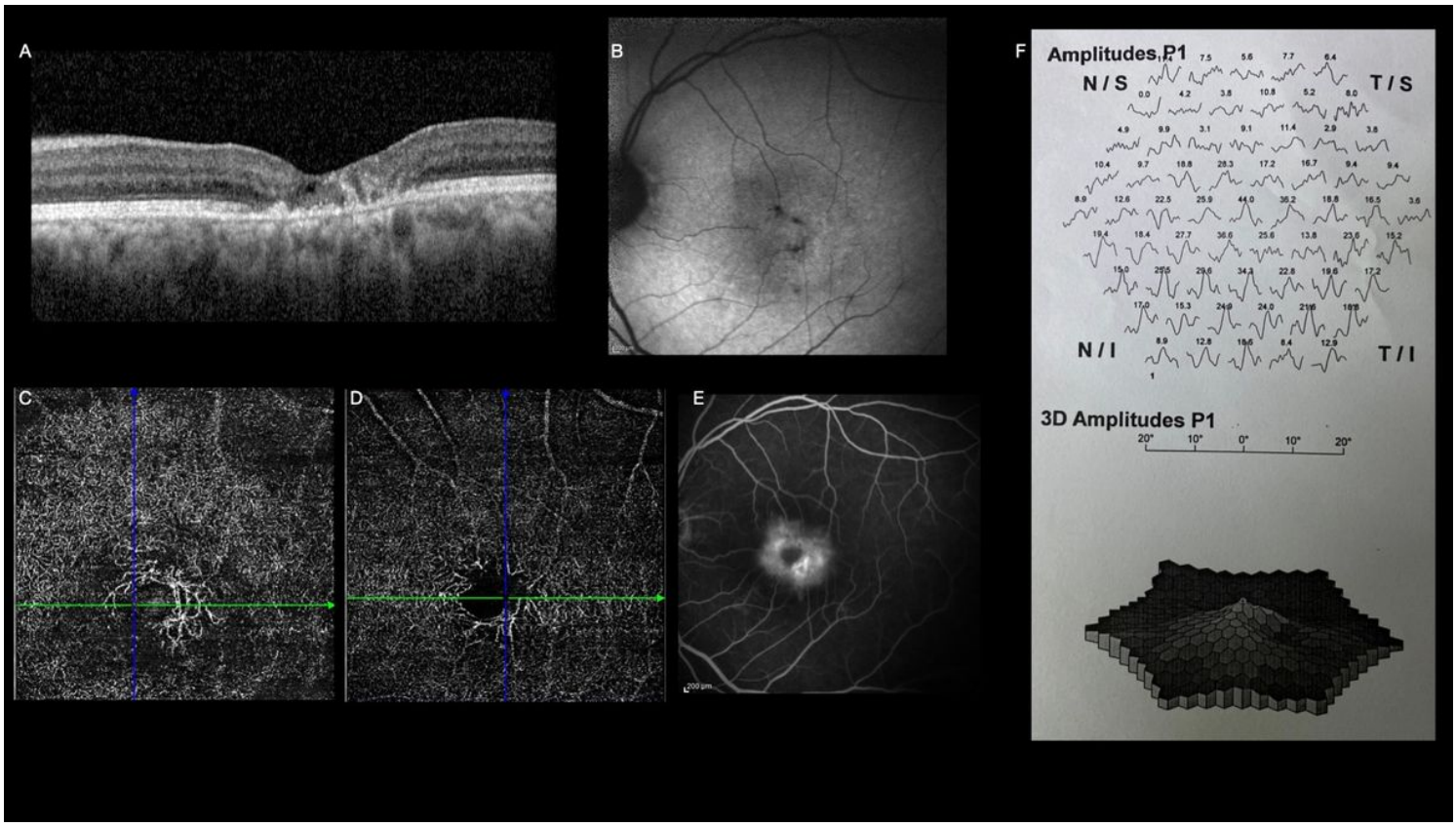

Figure 1

Multimodal imaging and mfERG of a patient with Mac Tel in the left eye. A- EZ break in the temporal, central and nasal fovea with hyperreflective structures signifying pigment plaques. Inner retinal cyst seen in the nasal fovea- Stage 3 OCT. B- Heterogenous pattern of AF signifying stage 3. C- Outer avascular retinal slab showing presence of abnormal capillaries circumferentially- D- deep vascular complex showing circumferential involvement- Stage 3 OCTA. E- FA late phase showing circumferential leakage- stage 3 FA. F- mfERG showing central foveal amplitude (R1P1 = 44nV/deg2) signifying stage 3 mfERG. Since temporal, foveal and nasal involvement is present on OCT, central, temporal and foveal peaks are affected on the mfERG as well.

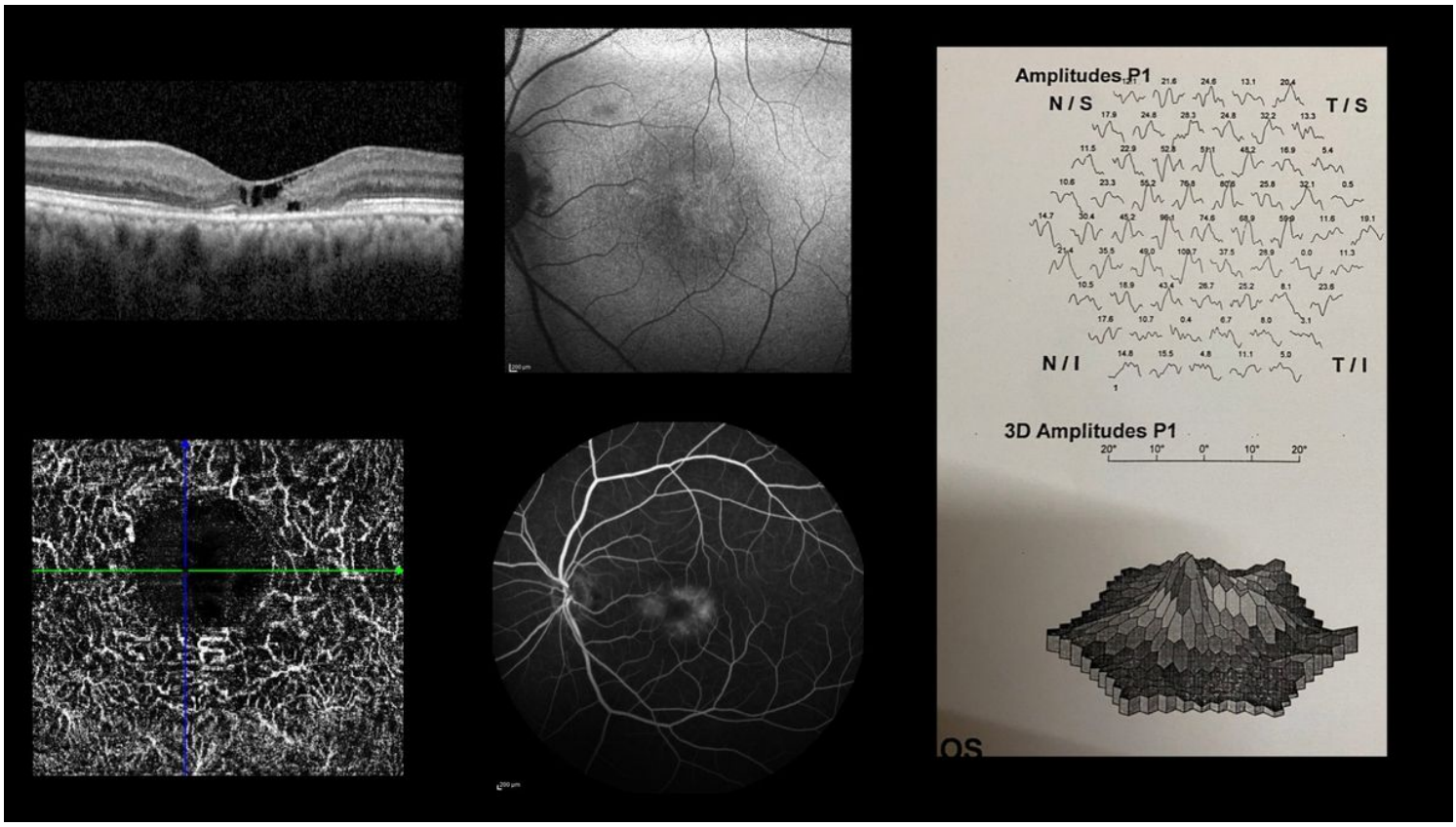

Figure 2

Left eye Mac Tel- A-stage 2 OCT- Inner retinal cysts present in fovea and temporal parafovea, center and nasal parafovea. EZ break extending from temporal parafovea to center but not to the nasal parafovea. B- Stage 2 AF- showing hyperautofluorescence in temporal parafovea and fovea. C- stage 2 OCTA with temporal rarefied capillaries and nasal ectatic capillaries. D- Incomplete ring of hyperfluorescence with predominantly temporal and nasal involvement. Stage 2 mfERG- Foveal amplitude of 74.6nV/deg2 corresponding to stage 2 mfERG.