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RETINAL DISORDERS

Multifocal electroretinography in type 2 idiopathic macular telangiectasia

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Abstract
Background To characterize the electroretinographic response of the macula by multifocal electroretinography (mfERG) in patients with type 2 idiopathic macular telangiectasia (MacTel).
Methods A prospective study of mfERG in patients with type 2 MacTel was conducted from April 2009 to November 2009. mfERGs were recorded using a visual evoked response imaging system (MonElec2, Metrovision, Perenchies, France). The International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines were followed. Patients with type 2 MacTel confirmed by fundus fluorescein angiography without subretinal neovascularisation were included. For recording purposes, 61 stimulus hexagonal elements were used. The first-order kernel mfERG responses were analyzed. Individual mfERG responses for the hexagons were grouped into concentric rings centered on the fovea for analysis (< 2, 5–10, 10–15 and >15°). Student's *t*-test and Mann–Whitney U test and linear regression analysis was performed with STATA ver 11.1 (StataCorp, College Station , TX, USA).
Results Twenty eight eyes of 14 patients and 20 eyes of ten normal controls were included in the study. The mean logMAR visual acuity of the patients was 0.51 (Snellen equivalent 20/63). The mean N1 amplitude (nv/deg^2) of patients were significantly reduced compared to controls and were as follows: 8.91±14.00 vs 43.44±9.55 (p<0.0001) in less than 2°, 9.24±10.47 vs 22.00±3.87 (p<0.0001) in 5–10°, 8.57±10.02 vs 15.24±1.89 (p<0.0001) in 10–15°, and 7.03±6.52 vs 12.47±2.62 in>15° (p<0.001). The mean P1 amplitude (nv/deg^2) was also significantly reduced in patients compared to controls and was as follows: 27.66±37.44 vs 96.20±12.41 (p<0.0001) in less than 2°, 22.61±19.38 vs 53.78±9.79 (p<0.0001) in 5–10°, 18.75±20.21 vs 35.22±4.16 (p<0.001) in 10–15°, and 17.10±12.54 vs 25.71±3.93 (p<0.001). The implicit time of N1 and P1 were also delayed significantly in all the rings. The mean central foveal thickness assessed by optical coherence tomography (OCT) scan was 84.78±45.12 μm. There was poor correlation between mfERG amplitudes or implicit times with either the visual acuity or OCT central thickness.
Conclusion mfERG showed significant reduction in amplitudes and implicit times of the waveforms in patients with type 2 MacTel in all the rings, suggesting a more generalized affection of the macula. The maximum reductions were seen in the <2° rings. Although there was poor correlation between the visual acuity and the amplitudes a of the waveforms, mfERG is a useful investigative modality for functional assessment of macula in type 2 MacTel patients.

Keywords mfERG · PFT · IMT · IJRT

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Authors have full control of all primary data, and we agree to allow Graefe's Archive for Clinical and Experimental Ophthalmology to review their data upon request.

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Introduction

Idiopathic juxtafoveolar retinal telangiectasis (IJRT) was first defined in 1982 by Gass and Oyakawa as a unilateral or bilateral disease associated with incompetent retinal capillaries only in the perifoveal or juxtafoveal area [1]. In 1993, Gass and Blodi presented a revised classification, staging, and hypothesis on the pathogenesis of IJRT which was based largely on clinical examination and fluorescein angiography [2].

Recently, Yannuzzi proposed a new term for this disease, referring to it as idiopathic macular telangiectasia (MacTel) [3].He described a new classification of MacTel comprising of two types. Type 1 or aneurysmal telangiectasia consists of multiple capillary, venular, and arteriolar aneurysms in both superficial and deep retinal circulations. It is associated with minimal ischemia, and does not have secondary neovascularization. Type 2 MacTel manifests in the middle-aged to elderly, and the visual acuity is usually good [4]. The macula shows a perifoveal gray halo due to loss of local retinal transparency, with cystic appearance of the fovea. Type 2 is the more common form of MacTel characterized by bilateral involvement and later onset than group 1, grouped into 2A, acquired, and 2B, congenital. Unlike in type 1 patients, type 2 patients show no haemorrhages, aneurysms, or lipid accumulation. We showed in our previous study that the temporal macula was most commonly involved [5]. We also showed that the distance of the parafoveal telangiectsia from the center of the foveal avascular zone (FAZ) could be up to 2,530 μm. The sight-threatening complications of type 2 MacTel can be a result of either nonproliferative (exudation and foveal atrophy) or proliferative disease [subretinal neovascularization (SRN) or fibrosis].

The pathogenesis of this disease is still not known, though there is speculation that impaired transport and/or storage of lutein and zeaxanthin may play a role. A central depletion of macular pigment in patients with type 2 MacTel has recently been established. This depletion of macular pigments have been studied non-invasively by confocal blue-reflectance, autofluorescence and macular pigment reflectometer [6–9]. Anatomic alterations on optical coherence tomography (OCT) have been also been reported [10, 11]. Botonni et al. described blue-reflectance and autofluorescence changes in correlation to the OCT findings in type 2 MacTel [7]. Functional deficit due to damage have been revealed by microperimetry and fine matrix mapping [12–16].

Currently, the gold standard for diagnosis of this disease is fluorescein angiography [17]. Multifocal ERG (mfERG) is an emerging modality for assessing retinal function in various retinal disorders. However, there is no information regarding macular function in type 2 MacTel patients using noninvasive objective investigative modality like multifocal electroretinography. Topographic information on the retinal response can be derived from the multifocal electroretinogram, which concurrently stimulates a large number of retinal locations [18]. Numerous studies have reported the effects of various retinal diseases on the local responsiveness of the retina, confirming the ability of mfERG to detect and map small dysfunctional regions [9, 19–21]. To the best of our knowledge, there is no literature available on the mfERG responses in MacTel. Analyzing mfERG responses in MacTel could help in understanding the origin and pathophysiology of the disease, which could guide possible management. We hypothesized that since MacTel is a disease localized to the macula, the local electroretinographic response may be reduced, and hence we performed mfERG in these patients to prove our hypothesis.

Methods

A prospective study of mfERG in patients with type 2 MacTel was conducted from April 2009 to November 2009 at LV Prasad Eye Institute, Hyderabad, India. Twenty-eight eyes of 14 patients (study group) and 20 eyes of ten normal controls were included in the study. Patients with a clinical diagnosis of type 2 MacTel and confirmed by fundus fluorescein angiography without subretinal neovascularisation were included. All patients underwent a comprehensive eye examination, which included recording the best-corrected visual acuity (BCVA), intraocular pressure by applanation tonometry (IOP), slit-lamp biomicroscopy and a detailed fundus examination. mfERGs were recorded at each visit using a visual evoked response imaging system (MonElec2, Metrovision, Perenchies, France). The International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines were followed [22]. All patients had clear media before the recordings. Data collection was performed with approval from the Institutional Review Board.

For recording the mfERG, a central red square was used as a fixation target, and good fixation was ensured throughout. Pupils were maximally dilated using 1 % tropicamide eye drops. The stimulus matrix consisted of 61 scaled hexagonal elements displayed on a monochrome monitor driven at a 75 Hz frame rate. The radius of stimulus array subtended was 20°×20° at a viewing distance of about 27 cm, and each element was independently alternated between black (<5 cd/m^2) and white (200 cd/m^2) using a binary m-sequence. The cornea was anesthetized with proparacaine hydrochloride eye drops and the mfERG was recorded using the L.V. Prasad Eye Institute (LVP) electrode [23]. A ground electrode was attached to the ear lobe. Mean stimulus luminance was adjusted to 110 cd/m^2. An individual recording was divided into short segments of 30 s each. The signals were fed into an amplifier with a band pass filtered at 3–100 Hz.

Table 1 Demographic status, visual acuity, lens status, OCT and autofluorescence features

Age	Gender	Visual acuity OD	Visual acuity OS	Lens OD	Lens OS	Foveal thickness OD	Foveal thickness OS	Autofluorescence
55	F	1	0	NS grade 1	NS grade 1	41	64	MacTel AF OU
51	F	0.48	0.48	PCIOL	NS grade 1	157	100	MacTel AF OU
45	F	0.4	0.18	Clear	Clear	75	57	Hyperautofluorescence OU
46	F	0.2	0.6	Clear	Clear	36	38	MacTel AF OU
50	M	0.18	0.5	Clear	Clear	79	54	Hypoautofluorescence pigment OU, MacTel AF OS
47	F	0.1	0.1	Clear	Clear	67	120	Hypoautofluorescence pigment, hyperautofluorescence OD, MacTel AF OU
49	M	0.18	0.18	Clear	Clear	71	88	MacTel AF OU
67	M	1	1	PCIOL	PCIOL	67	90	Hypoautolfluorescence pigment, surrounding hyperautofluorescence OU
58	F	0.6	1.6	NS grade 1	NS grade 1	79	50	MacTel AF OU
56	F	0.3	0.18	NS grade 1	NS grade 1	67	56	MacTel AF OU
58	F	0.8	0.3	NS grade 1	NS grade 1	68	72	MacTel AF OU
48	F	0.6	0.5	Clear	Clear	40	96	Hypoautofluorescence pigment, surrounding hyperautofluorescence OU
47	F	0.18	0	Clear	Clear	141	141	MacTel AF OU, Hypoautofluorescence due to pigment OS
48	F	0.4	0.4	Clear	Clear	112	248	MacTel AF OU

OCT optical coherence tomography, *NS* nuclear sclerosis, *PCIOL* posterior chamber intraocular lens, *AF* autofluorescence
MacTel AF is the typical pattern of autofluorescence seen in MacTel.[4] There is loss of normal central foveal hypoautofluorescence

Trace arrays at 61 location points of the first order kernel were analyzed for noise, recordable implicit time, amplitude and response density of four concentric rings (< 2°, 5–10°, 10–15° and >15°). Individual mfERG responses for the hexagons were grouped into concentric rings centered on the fovea for analysis (< 2°, 5–10°, 10–15° and >15°). The average implicit time and amplitude of N1 and P1 waves in all the rings were compared with age matched normative data.

Fourier domain OCT (FD-OCT) was performed using an RTVue model RT100 (Optovue, Fremont, CA, USA; software version 1.2.6 and 2.0.3.2). This instrument provides a high-speed acquisition time of 26,000 A-scans per second and a high-depth-resolution retinal scanner (5 μm). The protocol used on FD-OCT was the radial slicer that acquires simultaneously (within 0.27 s) 12 6-mm radial line scans through the centre of the fovea at 15 μm intervals using internal fixation, where every radial scan consists of an average of 1,024 A-scans. Correlation of mfERG response with visual acuity and central foveal thickness was analyzed.

Statistical analysis

Student's *t*-test and Mann–Whitney U test and linear regression analysis was performed with STATA ver 11.1

Table 2 Comparison of the mfERG amplitudes of the cases and controls at various ring diameters

Ring	N1 (nv/deg^2)		*P* value	P1 (nv/deg^2)		*P* value
	Patients	Controls		Patients	Controls	
<2°	8.9±14.0	43.4±9.5	<0.0001	27.6±37.4	96.2±12.4	<0.0001
5–10°	9.2±10.4	22.0±3.8	<0.0001	22.6±19.3	53.7±9.7	<0.0001
10–15°	8.5±10.0	15.2±1.8	0.009	18.7±20.2	35.2±4.1	0.003
> 15 °	7.0±6.5	12.4±2.6	0.006	17.1±12.4	25.7±3.9	0.015

Analysis was performed using Mann–Whitney U test
All values are given as mean with standard deviation
nv/deg^2 =nanovolts per degree-squared

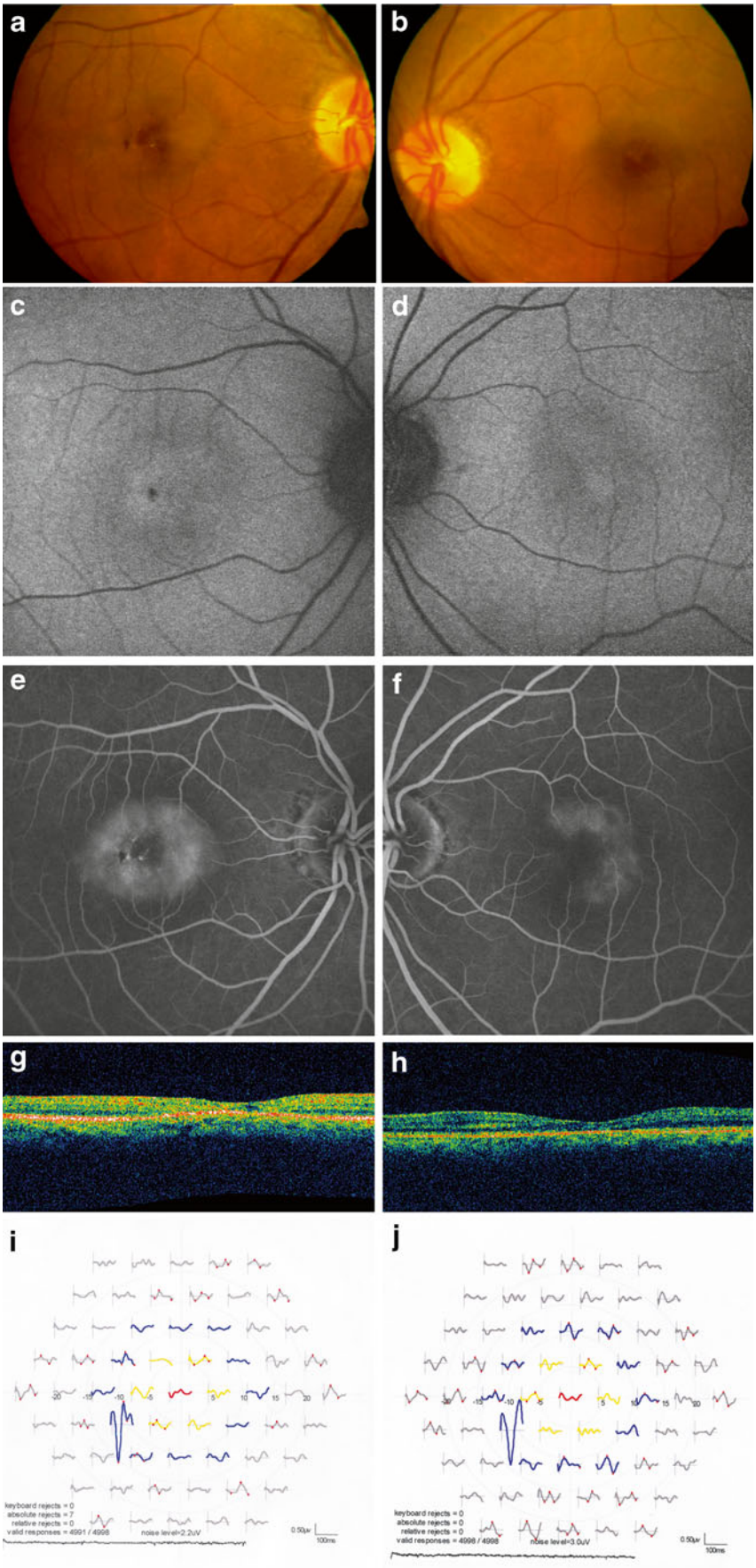

Fig. 1 Color fundus photographs (**1a** and **1b**) of a 55-year female patient with type 2 MacTel showing perifoveal halo in both the eyes, crystalline deposits and pigmentation in the right eye (**1a**). Clinically, MacTel can have different grades of severity between the two eyes, as seen in this case. Fundus autofluorescence (**1c** and **1d**) shows loss of normal central reduced autofluorescence in both eyes, and reduced autofluorescence due to pigment surrounded by increased autofluorescence in the right eye (**1c**). Fluorescein angiography of the right eye shows diffuse leakage in both eyes (**1e** and **1f**) along with focal hyperfluorescent spots in the right eye (**1e**) due to parafoveal telangiectasia. The diffuse hyperfluorescence in MacTel is typically seen temporal to the fovea in the early stage of the disease (**1f**), and later progresses to leak all around the fovea in the later stage of the disease. Optical coherence tomography (OCT) horizontal scan of both eyes (**1 g** and **1 h**) shows foveal atrophy in both eyes along with disruption of the inner segment and outer segment junction. Multifocal electroretinography (mfERG) tracings (**1i** and **1j**) show severe reduction in the N1 and P1 amplitudes and delayed latency in all the rings. The maximum reduction in the amplitude is seen in the $<2^{o}$ ring. The visual acuity was 20/200 in the right eye and 20/20 in the left eye, while the OCT central fovea thickness was 41 and 64 μm in the right and left eye respectively. The single large response in the lower left quadrant of both the eyes is an artifact

(StataCorp, College Station, TX, USA). Measurements from both eyes of the same subject are likely to be correlated, and hence the standard statistical methods for parameter estimation lead to underestimation of standard errors and to confidence intervals that are too narrow. Therefore, the cluster of data for the study subject was considered as a single unit (primary sampling unit) and clustered robust standard errors were estimated during the analysis.

Results

There were 11 females and three males in the study. The mean age of the patients was 51.78±6.21 years. Three eyes were pseudophakic, and the others were phakic (Table 1). The mean central foveal thickness assessed by optical coherence tomography (OCT) scan was 84.78±45.12 μm. The autofluorescence feature of each eye is described in Table 1. The mean logMAR

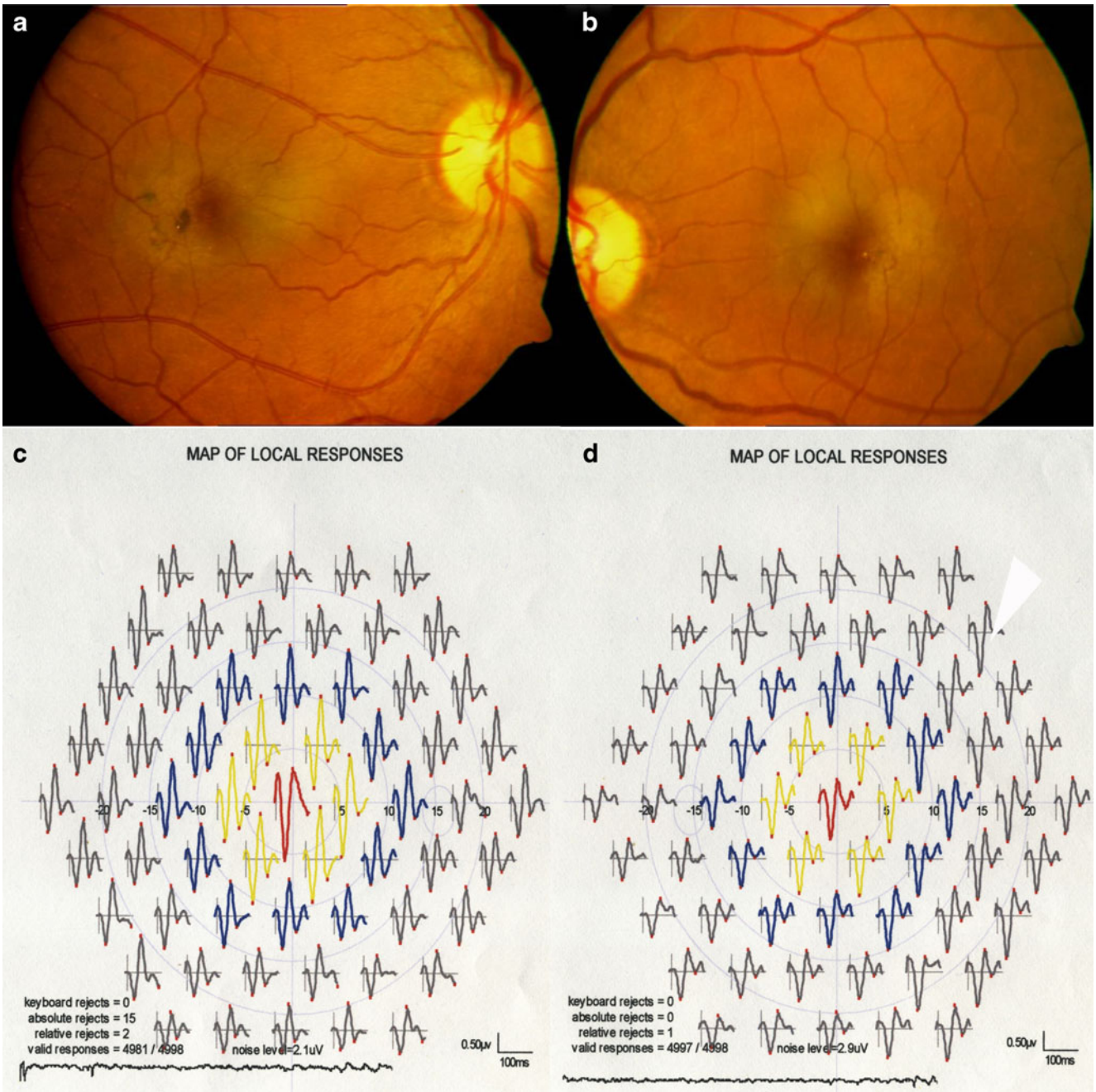

Fig. 2 Color photographs (**2a** and **2b**) showing perifoveal halo in both the eyes and parafoveal pigmentation in the right eye. The mfERG responses (**2c** and **2d**) are depressed, more in the left eye and in the inner rings

Table 3 Comparison of the mfERG implicit times of the cases and controls at various ring diameters

Ring	N1 (ms)		*P* value	P1 (ms)		*P* value
	Patients	Controls		Patients	Controls	
<2°	25.1±21.1[a]	23.8±2.7	<0.0001	67.7±28.4[a]	46.7±2.0	0.001
5–10°	36.2±23.1	23.5±1.7	0.007	47.1±12.1	44.0±2.3	0.158
10–15°	35.2±23.0	24.1±2.1	0.048	45.4±7.8	41.9±2.0	0.012
> 15 °	27.1±3.2	23.5±2.2	0.0001	48.1±3.5	44.9±3.6	0.01

Analysis was performed using Mann–Whitney U test

All values are given as mean with standard deviation

[a] Values are based on the average of responses from 21 eyes, since there was no detectable N1 and P1 response in seven eyes

ms milliseconds

visual acuity was 0.51±0.36 (Snellen equivalent 20/63). The mean N1 and P1 amplitude (nv/deg^2) were significantly reduced compared to controls (Table 2, Figs. 1 and 2). The maximum reduction in amplitudes of N1 and P1 waves compared to normal controls was seen in <2° ring, with progressively less reduction in the outer rings further from the fovea. The reduction in mean amplitudes of N1 waves was as follows: 79.48 % in <2°, 58 % in 5–10°, 43.76 % in 10–15°, and 43.6 % in >15°. The reduction in mean amplitudes of P1 waves was 71.24 % in <2°, 57.95 % in 5–10°, 46.76 % in 10–15°, and 33.48 % in >15°. The implicit times of N1 and P1 were also delayed significantly in all the rings (Table 3). There was no correlation between the visual acuity or central foveal thickness and the amplitude of the waves in any of the rings (Tables 4 and 5).

Discussion

Idiopathic macular telangiectasia is a localized disorder of the macula affecting the fovea and the perifoveal region. The disease had been well-characterized by fundus fluorescein angiography, ocular coherence tomography, autofluorescence imaging and microperimetry [5, 9, 13, 24]. Fundus microperimetry findings reveal reduced retinal sensitivity in nonproliferative (early) and proliferative (late) forms of MacTel. Another interesting observation is that in the early stages of the disease, even though microperimetry shows gross reduction of sensitivity, there is preservation of good visual acuity in these patients. This suggests that microperimetry can pick up functional changes earlier than clinical evidence of visual dysfunction.

The normal reduced autofluorescence at the fovea is believed to be due to masking by luteal pigments. The increase in foveal FAF or the loss of normal reduced autofluorescence is due to loss of masking of the FAF of the RPE. Wong et al. speculated that the change in autofluorescence may not be solely because of loss of pigments, but may occur due to compositional changes in the RPE, including endogenous fluorophores and melanin [13]. Greyish retina in parafoveal area due to loss of retinal transparency can be found in IJRT. This can also be explained by the depletion of macular xanthophyll pigment leading to increased FAF [25]. Powner et al. have shown macular Müller cell loss in post-mortem eyes in MacTel type 2, along with depletion of xanthophylls pigment [26].

mfERG can provide valuable insight into macular pathology by measuring the spatial distribution of the central retinal cone function [27]. The amplitudes in mfERG are believed to originate primarily and substantially from the outer retinal cells (bipolar cells), with small contributions from inner retina cells, the amacrine

Table 4 Correlation of the amplitudes and implicit times with the visual acuity at various ring diameters

Variable	<2°		5–10°		10–15°		>15°	
	R^2	*P*	R^2	*P*	R^2	*P*	R^2	*P*
Mean implicit time (N1)	0.01	0.63	0.20	0.07	0.07	0.001	0.00	0.59
Mean implicit time (P1)	0.02	0.28	0.06	0.34	0.01	0.67	0.03	0.24
Mean amplitude (N1)	0.01	0.45	0.11	0.04	0.19	0.40	0.05	0.14
Mean amplitude (P1)	0.00	0.99	0.07	0.1	0.01	0.57	0.03	0.24

Table 5 Correlation of OCT central foveal thickness and mfERG amplitudes and implicit times

Variable	<2°		5–10°		10–15°		>15°	
	R^2	P	R^2	P	R^2	P	R^2	P
Mean implicit time (N1)	0.14	0.10	0.00	0.59	0.01	0.29	0.06	0.02
Mean implicit time (P1)	0.00	0.93	0.00	0.92	0.05	0.16	0.02	0.13
Mean amplitude (N1)	0.06	0.16	0.00	0.99	0.00	0.84	0.00	0.98
Mean amplitude (P1)	0.00	0.92	0.00	0.89	0.00	0.81	0.00	0.90

OCT optical coherence tomography

and ganglion cells, and the photoreceptors. The N1 component has main contributions from hyperpolarization of the OFF-bipolars and some from the photoreceptor hyperpolarization. The ascending limb and peak of the P1 is contributed mainly by the depolarization of the ON-bipolars, while the descending limb starts as OFF-bipolars depolarization followed by recovery of ON-bipolars, and the last part is shaped by inner retinal influences (amacrine and ganglion cells) [28]. There is evidence that N1 includes contributions from the same cells that contribute to the a-wave of the light-adapted, full-field ERG, and that P1 and N2 include contributions from the cells contributing to the light-adapted b-wave and oscillatory potentials. Although there are homologies between the mfERG waveform and the conventional ERG, the stimulation rates are higher for the mfERG, and the mfERG responses are mathematical extractions. Our study showed a moderate reduction in amplitude and increase in implicit time. This suggests that there may be early damage of bipolar cells in eyes with MacTel. We hypothesize that the xanthophylls pigment depletion as shown by autofluorescence changes may lead to abnormal function of bipolar cells, leading to reduced response on mfERG.

The mfERG results of our study showed significant reduction in amplitudes and delay in implicit times of the waveforms in patients with type 2 MacTel in all the rings, as compared to a matched normal population. The maximum reductions were seen in the < 2° rings. However, since the <2° implicit times were based only on the subset of patients with detectable NI and P1 responses, they may underestimate the true foveal delays in this disease. 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 as far as 2,500 μm away from the fovea [5]. There was poor correlation between the best-corrected visual acuity and the amplitudes of the waveforms, and there was no correlation between the two eyes of the same patient. This could be because of the differences in severity of the two eyes commonly seen in MacTel patients. Even though some of the *p*-values were significant in the statistical analysis, none of the *r*-squared values were clinically relevant.

These findings of significant reduction of amplitudes and delayed implicit times of mfERG in MacTel patients with preservation of good visual acuity suggests that mfERG can serve as a sensitive tool to pick up functional abnormalities in type 2 MacTel. mfERG similar to microperimetry, reveals a more generalized affection of the macular function, which, however, does not necessarily correlate with the subjective function or morphology. OCT scans of most eyes in our study showed severe foveal atrophy with an average central foveal thickness of 84.7 μm, though this did not correlate with the severity of vision loss. Central visual acuity may not be a good tool to assess the foveal function in this disease, as has been described in the MacTel project report no. 2 [4]. OCT foveal thickness also did not correlate well with the amplitudes or implicit times of the waves in mfERG. This suggests that though OCT is a useful tool in aiding the diagnosis of MacTel, it may not correlate well with the severity of the disease or vision loss. Our study suggests that the visual acuity remains good in some patients, in spite of reduction in retinal thickness.

To the best of our knowledge, this is the first study showing the results of mfERG in type 2 MacTel. Being cross-sectional, our study could not assess the changes in mfERG during the course of the disease. Longitudinal studies combining fundus autofluorescence and optical coherence tomography (to assess morphological and structural abnormalities), along with functional assessment modalities such as mfERG in Type 2 MacTel patients may give us a better insight into the pathophysiology of the disease process, as well as clues for early intervention before gross structural and functional damage occur.

To conclude, mfERG is a useful investigative modality for functional assessment of macula in type 2 MacTel patients.

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