Multifocal Electroretinography in Assessment Of Diseases Of Posterior Pole Of Retina

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Abstract: Background: Multifocal electroretinography (mfERG) based on the m-sequence stimulation technique which allows quick simultaneous recording of many local electroretinograms from the posterior pole. The multifocal ERG is a powerful tool in patients with an affected cone system, especially when defects are localized and therefore not detectable with full field electroretinography. Aim: The purpose of the present study was to investigate and describe differences in regional dysfunction between groups of patients with impaired vision due to diseases affecting predominantly the posterior pole. Method: This is a retrospective study of patient who were clinically diagnosed and sent to us by M&J Regional Institute of Ophthalmology,Ahmedabad, India. 31 patients were divided into 4 groups including Stargardt's macular dystrophy (SMD), age-related macular degeneration (AMD), cone dystrophy (CD), central retinal vein occlusion (CRVO) and 11 normal subjects were taken as control. mfERG was done in all subjects and the responses were analysed using t test. Result:In patients with SMD or with AMD functional defects were mainly at the foveal region and extended to eccentricity only in advanced cases. A reduction of response amplitude even in the most peripheral ring was found in cone dystrophies and moderately in patients with central retinal vein occlusion. Prolonged implicit times were found in all but in the patients of SMD and they were maximal in patients with CRVO. Conclusion: The multifocal electroretinography provides detailed information of local activity of the cone dominated retina. In most of the patients with maculopathies, the photopic Ganzfeld ERG was normal, so that multifocal ERG can be valuable in diagnosing these diseases.

Key Words: Multifocal ERG, Maculopathy; Cone dystrophy; Central vein occlusion

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Introduction: The mfERG is a relatively newer technique for assessing the local ERG from different regions of the posterior retina[1]. It was initially developed by Eric Sutter and Tran, which attempts to measure the spatial distribution of the central retinal cone function[2].

The electroretinogram (ERG) is a mass potential, the result of the summed electrical activity of the cells of the retina. Typically, the clinical ERG is elicited by full-field (Ganzfeld) flashes of light. With an appropriate selection of test and background lights, rod and cone function can be assessed separately[3]. As the ganglion cells contribute relatively little to the full-field flash ERG, the ERG has helped neuro-ophthalmologists to distinguish between diseases of the outer retina (affecting photoreceptors and/or bipolar cells) and diseases of the inner retina (ganglion cells) and optic nerve. However, because the ERG is the sum of all retinal activity, relatively large retinal defects may not be detected by standard full-field ERG testing. Although the pattern ERG and focal ERG can both provide information about visual loss from lesions in the foveal region[4,5] these techniques do not provide topographical information or assessment of nonfoveal lesions.

Multifocal electroretinography (mfERG) based on the m-sequence stimulation technique[2] allows quick simultaneous recording of many local electroretinograms from the posterior pole. The multifocal ERG is a powerful tool in patients with an affected cone system, especially when defects are localized and therefore not detectable with full field electroretinography. With the multifocal technique, 100 or more focal ERG responses can be recorded from the cone-driven retina in 8 minutes. The purpose of the present study was to investigate and describe differences in regional dysfunction between groups of patients with impaired vision due to diseases affecting predominantly the posterior pole.

Material and Method: This is a retrospective study of patients who were clinically diagnosed and sent

to us by M&J Regional Institute of Ophthalmology, Ahmedabad. The patients were divided in 4 groups on the clinical established diagnosis and compared with the 11 normal subjects (15 eyes) with age 11 to 64 years who were examined with the multifocal ERG under the same conditions, to serve as a control group. Normal subjects were those sent to us for testing malingering or the normal eye in uniocular disease .They had full visual acuity and no history of eye disease or other relevant disorders in the eye taken as control.

Group diagnoses included Stargardt's macular dystrophy (SMD), age -related macular degeneration (AMD), cone dystrophy (CD), and central retinal vein occlusion (CRVO).

In group 1 were 11patients (22 eyes) with age (13±3.2) years in whom Stargardt's macular dystrophy (SMD) was diagnosed on the basis of history, symmetric bilateral involvement, the typical alterations of the pigment epithelium layer (assessed by Fundus autoflorescence or optical coherence tomography), by visual field, and by Ganzfeld-electroretinography according to the ISCEV standard were taken. Group 2 consisted of 8 patients(13 eyes) of age (56 ±7.1) years with age related macular degeneration (ARMD) whose diagnosis was made on the basis of medical /ocular history, visual acuity, Amsler grid test and fundus photograph.

In group 3, 7 patients (14 eyes) with age (58 ± 9.5) years CRVO was diagnosed by the clinical picture of typical haemorrhages in all four quadrants of the retina associated with dilatation and tortuosity of the venules. 5 patients (10eyes) with age (35.5 ±16.4) years in group 4 were diagnosed cone dystrophy on basis of history, vision loss, sensitivity to bright lights, poor color vision and assessment of fluorescein angiography and visual field testing.
The study was conducted according to the tenets of the Declaration of Helsinki, and after a detailed explanation of the procedure; all patients gave informed consent before the study.

The stimulus, consisting of 103 hexagons covering a visual field of 50°, was presented on a 9 inch CRT (Cathode ray tube) with a frame rate of 75 Hz at a distance of about 40 cm from the subject's eye. Every 13.3 ms the frame of the monitor changes and each sector has a 50/50 chance of appearing "white" (briefly flashed) or "black" (no flash). The white hexagons were 200 cd/m^2 and the black hexagons the darkest the screen allowed, less than 5 cd/m^2. The area surrounding the array of hexagons was set to 100 cd/m^2 and a central cross was used for fixation. All recordings were performed with the room lights on to help assure a constant state of light adaptation. Because of the light levels employed and the rapid rate of stimulation, the mfERG is a response of the cone system. The duration of the recording session was about 4 minutes, which included 8 recording segments of approx. 30 sec between samples, during which the subjects were not allowed to blink or move.

Both the eyes were dilated with tropicamide (1%)and 2.5% phenylephrine hydrochloride and anesthetized with 0.5% proparacaine. The ERG responses were recorded by means of a bipolar Burian-Allen contact electrode which makes use of a large speculum to hold the eyelids apart. A smaller clear corneal contact lens is held against the cornea with a spring assembly. The skin electrode (gold cup electrodes) fixed to the forehead with a conducting paste served as a ground electrode. The electroretinograms were amplified (x 50,000 -100,000) and band pass filtered (10–300 Hz). The VERIS software 6.1.1 (EDI, San Mateo) developed by Sutter, using a fast m transform algorithm[2] was employed for the calculation and analysis of the 103 local ERG responses from the measured signal. All the data was statistically analysed using student t test and were found to be statistically significant ($p \leq 0.05$).

Result: For data analysis, the 103 local responses were grouped six concentric rings (R1- R6) centred on the fovea (Fig 1a). A typical waveform begins with a negative deflection (N1), followed by a positive deflection (P1), and a second negative Deflection (N2) (Fig 1b). Response densities and implicit times of the major components N1, P1, N2 in each ring was calculated and analysed.
In normal subjects: As expected from retinal anatomy, there was a continuous decrease in response density from the maximum at the fovea towards the periphery. The responses were

obtained from foveal ERG (ring 1) to ERG at eccentricity (ring 6) and were density scaled. The response density can be obtained by dividing local ERGs by the area they were elicited from. Besides the decrease in response density with eccentricity, localized areas of low amplitude such as the blind spot are also visible. All component densities decreased with eccentricity, although there was no further decrease from ring 5 to ring 6(fig 2a) .The implicit times were highest in the fovea (ring 1) and lowest in ring 3 for all three components.(fig 2b).

Fig1a: Concentric rings centering in fovea

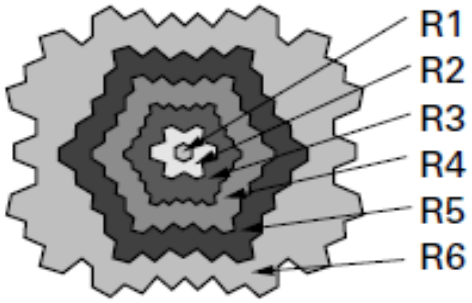


Fig 1b: Typical Waveform in ERG

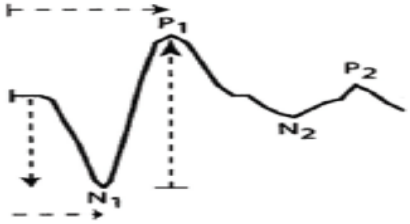


Fig 2a: Response density in normal subjects

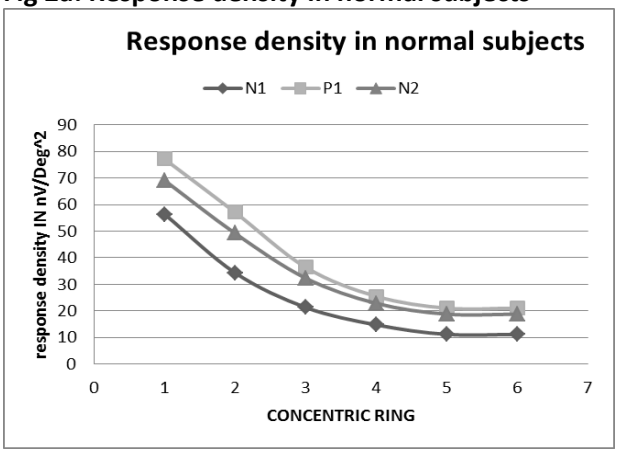
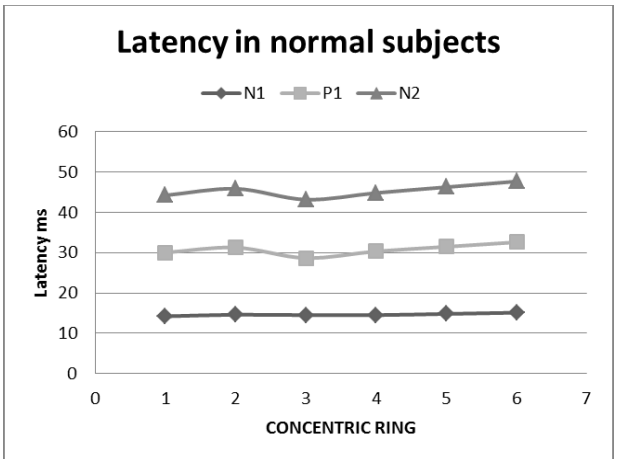


Fig 2b: Latency in normal subjects



For the comparison of latency and response density among various disease and that to the normal all P1 amplitudes and N1 latencies of the mfERG responses in the 6 concentric rings were calculated and compared.

Stargardt's Macular Dystrophy: -Patients with juvenile (SMD) and age-related (AMD) maculopathies exhibited patterns of extinguished or markedly diminished responses in the centre, which approached normal values towards the periphery (fig 3a). In the SMD group, a deep functional defect was restricted to the macula. The three-dimensional plot of the response density had a crater-like appearance due to that central defect. No change of implicit times could be detected.**ARMD: -** The functional lesions in ARMD were restricted to the macular area, with good responses in the periphery. Response density decreased and latencies increased in the rings from fovea to eccentricity (Fig 3a). Implicit times were prolonged. (Fig 3b)

Cone Dystrophy: -All patients with cone dystrophy had strongly reduced or non-detectable responses in the entire test field. The patient had no focal response distinguishable from noise in any of the 103 focal ERG traces. In all patients with cone dystrophy, no foveal response was discernible, and the response densities were diminished up to ring 6. (Fig 3a) The implicit times were prolonged

CRVO: -In the patients with CRVO, the functional defect was similar to that found in maculopathies. No foveal responses were found that exceeded the noise level, but, unlike SMD and AMD, the

peripheral responses were also significantly diminished (Fig 3a). The smaller wavelets following N2 were absent. The implicit times were markedly prolonged in the entire test field. (Fig 3b)

Fig 3a: Comparison of P1 response density

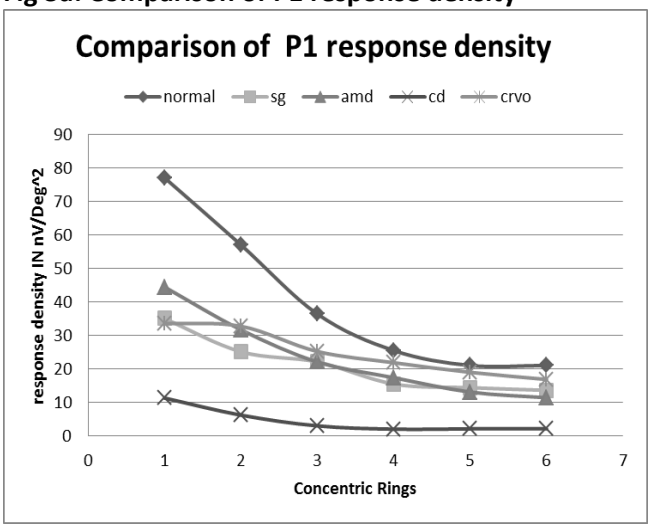
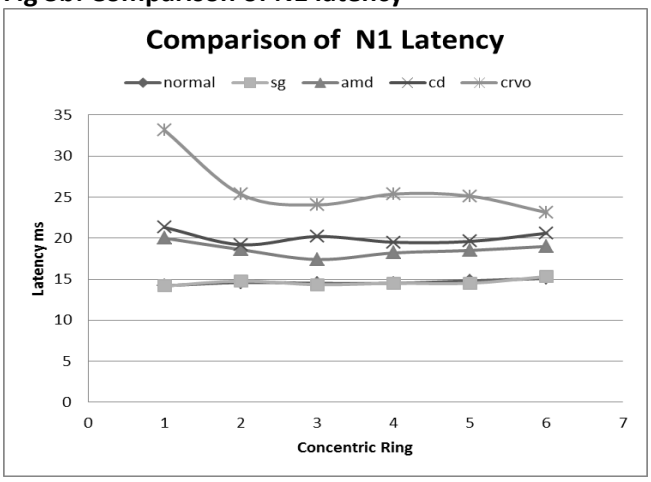


Fig 3b: Comparison of N1 latency



Discussion: The multifocal ERG based on the m-sequence stimulation approach[6, 7]is capable of mapping the central visual field functionally by means of local electroretinographic responses. As shown by Sutter and Tran[8] using recordings with higher spatial resolution and longer recording time, the response density decreases markedly from the foveal area towards the periphery. This response distribution resembles the anatomical distribution of cones as well as the electroretinographic findings obtained with focal flicker stimulation by Maxwellian view

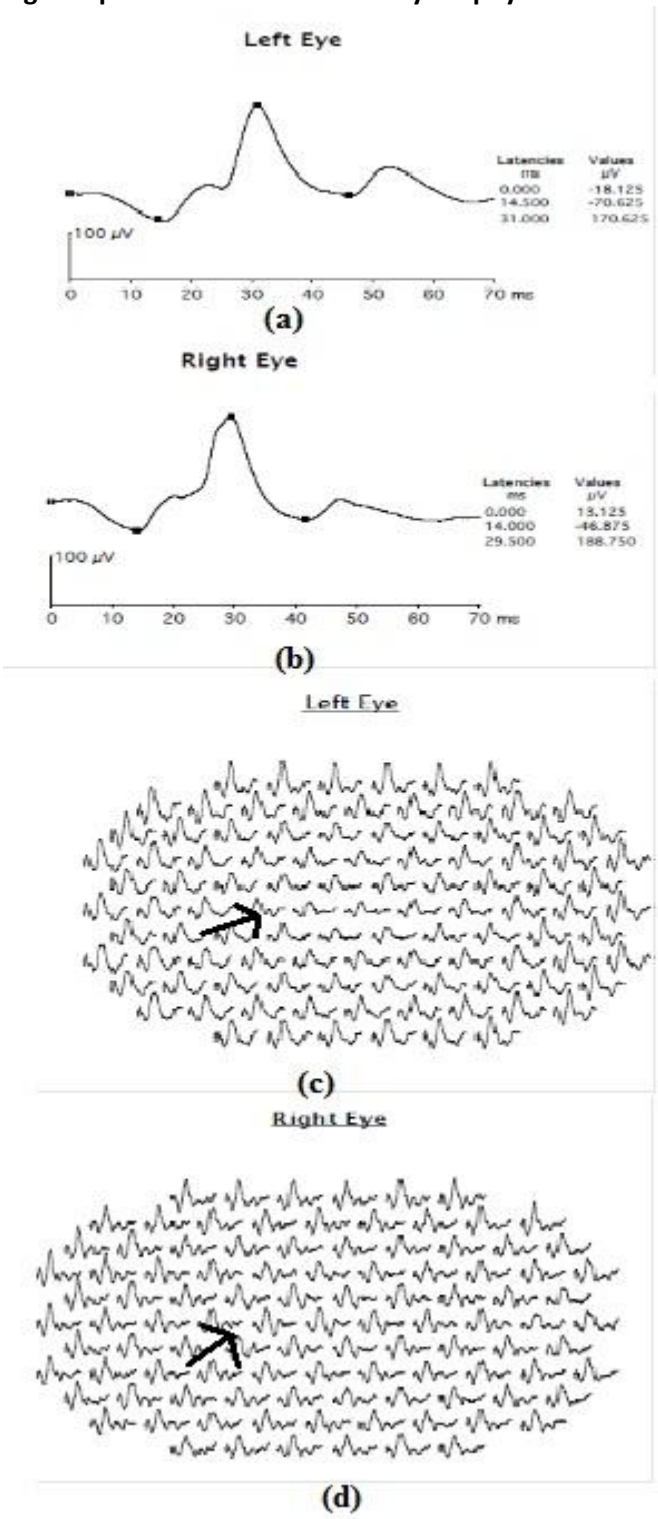
Given that the multifocal ERG is in principle a photopic ERG under special conditions of light adaptation, the most impressive alterations in the multifocal ERG can be expected in patients with general receptor dystrophies leading to reduced and delayed Ganzfeld responses. Consequently, the most prominent and widespread changes of amplitudes were found in the cone dystrophy group. Since there were barely any clear responses in the macular region it was difficult to reliably measure implicit times.

Juvenile (Stargardt's) and age-related maculopathies were considered diseases in which a primary defect in the retinal pigment epithelium leads to a secondary, localized degeneration of photoreceptors. Recently, a defect in the ABCR-gene which is expressed in rods was found in patients with Stargardt's macular dystrophy[9]. Therefore, changes in the pigment epithelium and cones might be secondary to a primary defect in the rod photoreceptors at least in some of the patients. Similar mechanisms were proposed for AMD[10]. The following thoughts may illustrate why Ganzfeld-ERG cannot detect the photoreceptor loss in these diseases. The area stimulated by the multifocal ERG setup used here covers roughly 35% of the entire cone population. The contribution of the macular area (ring 1 and 2) to the overall sum of multifocal ERG responses is only about 12%. Under the simplifying assumption that all cones are reached by the photopic Ganzfeld-ERG and each cone contributes equally, the estimated loss caused by an isolated defect of the macula would be about 4%, which is certainly within the range of inter-individual variability in normal.

The data presented show that the multifocal ERG detected the central functional defect in every patient with a maculopathy, regardless of the stage of the disease. Even in the stargardt's macular dystrophy patient with nearly full visual acuity, the foveal responses were diminished.

In many cases, multifocal ERG can be used to verify unclear visual field defects of retinal origin, although it is not possible to predict visual field defects from a reduced or extinguished mfERG.

Fig 4: A patient of macular cone dystrophy



The overall outcome of the multifocal ERG in patients with CRVO was a decrease in amplitude and an increase in implicit times as in flicker Ganzfeld- ERG. The effect on the fovea was more pronounced than the effect on the extramacular area. One reason for this may be the greater susceptibility of the macula to develop oedema [11] Compared to the findings in maculopathies; the defect had a patchy appearance.

The shape of the waveform with its major components N1, P1, and N2 was not affected by the different diseases beyond amplitude reduction and implicit time increase.

In the above figure of macular cone dystrophy showed (a) and (b) normal Photopic waves in both eyes in full field ERG (c) Decreased response density in foveal region of affected eye(left) and (d) Normal response density in other eye (right) in mfERG.

Conclusion: The multifocal electroretinography provides detailed information of local activity of the cone system. It was possible to detect macular cone dysfunction in patients with early and advanced SMD, AMD, cone dystrophies, and retinal vein occlusions (Fig 4). In most of the patients with maculopathies, the photopic Ganzfeld ERG was normal, so that multifocal ERG can be valuable in diagnosing these diseases.

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