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EVALUATION OF AGE-RELATED MACULAR DEGENERATION BY ff-ERG AND mf-ERG BEFORE AND AFTER TREATMENT USING DIFFERENT MODALITIES

Ophthalmology

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ABSTRACT

Age-related macular degeneration (ARMD) is a common cause of blindness in the world. It has two types: dry ARMD and exudative ARMD. mfERG and ffERG are important electrophysiological tools to assess retinal function and carry prognostic significance with respect to success of the applied therapeutic modalities. Anti-VEGF intravitreal injections are the mainstay treatment, however, combination approaches consisting of medical and surgical interventions have also been tried. The following review article sheds some light on the above aspects of ARMD.

KEYWORDS

ARMD, blindness, mfERG, ffERG, anti-VEGF

INTRODUCTION

Age-related macular degeneration (ARMD) is the most common cause of vision loss and blindness in the world, with serious social and economic repercussions. The condition affects 9–25 percent of people aged 65–75, and it causes blindness in more than 80 percent of those who are affected after the age of 70.[1]

ARMD is divided into two types: dry ARMD, which accounts for about 90% of cases, and wet or exudative ARMD, which commonly affects those over 85 years old .[2] Exudative ARMD accounts for 10–20 percent of all instances of ARMD with 90 percent of cases resulting in significant visual loss.[3]

A further distinction is made based on the severity of the disease: (i) early type, i.e. mild, which includes retinal changes such as retinal pigment epithelium (RPE) abnormalities and/or large soft drusen (≥63 mm), and (ii) late type, i.e. severe, which includes geographic atrophy or exudative ARMD, which includes choroidal neovascularization (CNV), pigment epithelium detachment and at end stage, disciform scar.[4]

Drusen with or without retinal pigment epithelium (RPE) alterations characterise age-related maculopathy (ARM), which frequently precedes ARMD. Both ARM and ARMD are referred to as age-related macular disease (ARMD).[5] The RPE phagocytizes the photoreceptors' outer segment discs and serves as a metabolite and waste exchange point, both of which are important for retinal function. Variation in the pigmentation of the RPE, with or without the development of drusen, is one of the first symptoms of ARMD.

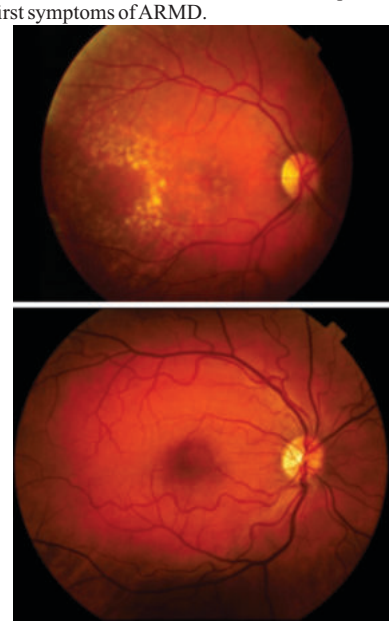

Fig 1: ARMD fundus versus Normal fundus

Current treatments to preserve vision in patients with non-exudative AMD include antioxidant vitamins and mineral supplementations. Exudative AMD is currently most often treated monthly with anti-VEGF intravitreal injections. However, investigators are beginning to experiment with combination therapy and surgical approaches in an attempt to limit the number of treatment and reduce the financial burden on the health care system.

Ophthalmic electrophysiology has been found to be a good way of objectively assessing retinal function because it can measure the function of the choroid, RPE, and photoreceptor layer.[6]

Multifocal electroretinography (mfERG) allows for the measurement of localised retinal cell function abnormalities in ARM over time due to its objectivity and topographical mapping. mf ERG may also be used to monitor the success of surgical and therapeutic interventions, according to evidence.

Whereas, ffERG produces a large number of electrical retinal responses to light stimulation, but does not provide spatial retinal information. Therefore, ffERG may miss small retinopathy, such as those seen in ARM, so there are conflicting reports about the appropriateness of using ffERG to assess the condition.

ffERG Of Untreated Patients

Holopigian et al. studied the effects of normal aging, ARM and ARMD on ffERG. They proved that with age, the amplitude of normal subjects and subjects with ARM and ARMD under both photopic and scotopic conditions will decrease over time, while the latencies of the waves in ffERG will increase over time.[7] The similarities between elderly normal subjects and ARM patients highlight the importance of using same-age normal values for comparison when observing elderly ARMD subjects. These results are related to the results of other studies, showing that when paired flash ERG technique is used to measure the recovery of a wave, the rod-shaped and cone-shaped ERG amplitudes decrease with age.[8] Marcus et al.[9] studied ERG b wave in 24 eyes of 12 ARMD subjects and found that b wave amplitude in the diseased eye was low-to-normal and was not related to clinical morphology.

In addition to the delayed and reduced photopic cone dominated a-wave responses, ffERG was also used to examine the scotopic rods that dominate the a-wave and b-wave responses in retina. Scotopic responses are also reduced and delayed, indicating that ARMD affects rod-shaped and cone-shaped photoreceptors.[10] Since ffERG is a collective response, the sensitivity of this test is limited when evaluating small lesions seen in ARMD.

mfERG of untreated patients

Compared to normal controls of the same age range, ARM eyes have been found to have a reduced amplitude of foveal mfERG P1 and increased N1 latency. Interestingly, the asymptomatic homologous eye of the ARM eye in this study by Li et. al also showed the same findings, indicating that mfERG may be a sensitive means of detecting early changes in ARM [11]. Feigl et al. [12] contrastingly, found no such correlation, which may be due to inconsistent use of grading and

grading systems and different age ranges of participants used in different studies. A study by Huang et al.[13] comparing mfERG between exudative ARMD, non-exudative ARM and normal controls has shown that the P1 and N1 amplitudes of eyes with CNV and ARM are reduced compared to the controls. A study by Nabeshima et al.[14] reported the influence of aging on mfERG and held it partly responsible for the reduction in amplitude. Seiple et al.[15] demonstrated a significant 10.5% reduction in amplitude from N1 to P1 per decade, highlighting the significance of using age-matched controls. The mfERG guidelines described by the International Society for Clinical Visual Electrophysiology (ISCEV)measure cone function. [16] The rod-mediated mfERG is recorded after dark adaptation and as compared with cone mfERGs, the signal-to-noise ratio is worse, and is time-consuming. On comparing rod and cone-mediated mfERG in ARM, the amplitude of N1 and P1 was found to be reduced as compared to the control in rod and cone-mediated mfERG.[17]

On comparison with age-matched normal controls, the rod-mediated delayed P1 implicit time in the eyes of ARM has been reported [18,19] which means that both rod and cone functions are affected in ARM. However, further work using a larger sample size will provide clearer rod-mfERG information, as conflicting results have been shown so far. Global-flash mfERG has also been used to try to overcome some of the conflicting findings observed with traditional mfERG and to better reflect the adaptability defects in ARM.[19] Research results show that global-flash mfERG detects reduced adaptive responses earlier than traditional mfERG. Therefore, it can be considered that global-flash mfERG may be more advantageous to recognize ARM before standard mfERG. More research is needed in this direction to prove this hypothesis.

Some interesting work has been done on the use of mfERG to study the role of ischemia in ARM.

Hypoxia has been experimentally induced in healthy young and elderly eyes, leading to a decrease in central and peripheral nerve and retina function, which is manifested as a decrease in mfERG response density.[20]

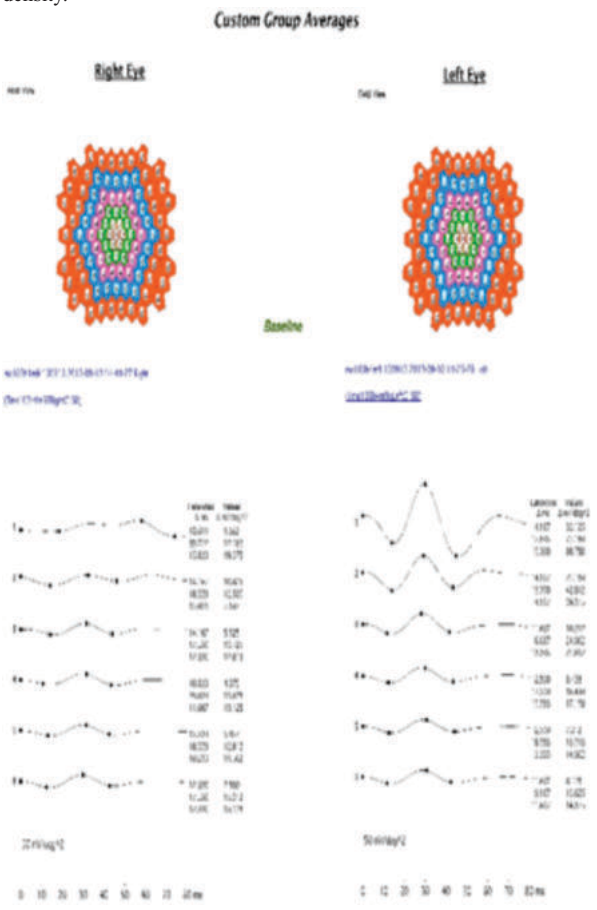

Fig 2: Reduced central peak amplitude in right eye (ARMD) as compared to normal left eye

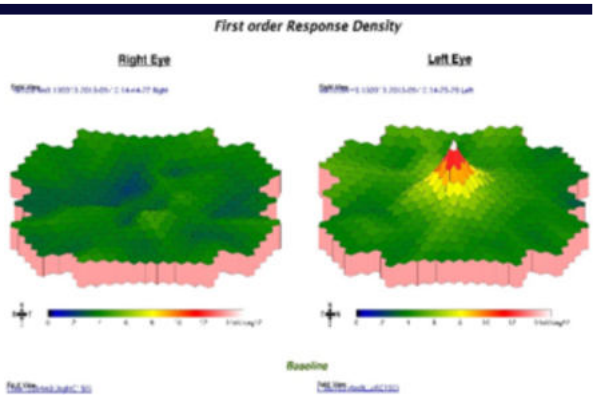

Fig 3: Representative mfERG responses of an ARMD right eye with reduced central peak response amplitude and normal left eye

Treatment Of ARMD And Side-effects

The antioxidant supplement indications include the presence of a wide range of drusen (63-124 mm) or at least a large drusen (>125 mm) having paracentral geographic atrophy or progressive lesion in at least one eye.[21] The CARMIS (Carotenoids in Age-Related Maculopathy Italian Study) suggested the use of vitamin C (180 mg), vitamin E (30 mg), zinc (22.5 mg), copper (1 mg), along with the daily intake of lutein (10 mg), zeaxanthin (1 mg) and astaxanthin (4 mg) can improve the stabilization of visual acuity, contrast sensitivity and visual function for at least 12 months.[22] Patients with ARMD should further adjust their lifestyle, smoking habits, alcohol, high consumption of meat and elimination of obesity. The intra-vitreal injection of anti-VEGF is a standard therapy in ARMD exudation. The four basic anti-VEGF agents are: (1) ranibizumab; (2) bevacizumab; (3) pegaptanib sodium; (4) Aflibercept. The incidence of atherothrombotic events tripled with those treated with Bevacizumab (4.6%) compared to healthy individuals.[23] A MARINA study emphasized the therapeutic benefit of Ranibizumab in CNV such as improvement of the vision, improvement of the mesopic and photopic contrast sensitivity, the central macular thickness reduction, decrease in intraretinal fluid and the pigment epithelium detachment.[24] The most common complications of Ranibizumab are intraocular inflammation, increased intraocular pressure, cataract and sub-conjunctival haemorrhages. More serious but rare complications include endophthalmitis, intravitreal bleeding, cracks of retina, retinal detachment and lens damage. Non-ocular bleeding and thromboembolic events are the main systemic side-effects of Ranibizumab.

The role of combination of Photodynamic therapy (PDT) and anti-VEGF agents or triamcinolone injection which eliminates the inflammatory agents released after PDT, remains doubtful. Photodynamic therapy (PDT) with verteporfin has become the standard treatment mainly for classic CNV.[25] PDT elicits a photochemical reaction that is toxic to vascular endothelial cells, but not to the photoreceptor layer.

Laser photocoagulation is applied on CNV, based on findings of FA. However, given that this treatment is related to thermal damage, irreversible vision loss, recurrence or relapse of vascular lesions, the percentage of patients who experience therapeutic benefits in the macular area are low (10 to 20%).

Classic surgical approaches deal with ARMD complications. Sub macular surgery has shown results in a wide range of bleeding complication, fibrous membranes and in people who do not respond to PDTs. Second surgical option would be a macular translocation with normal capillary.

ERG Response After Treatment

Due to the small sample size, uneven disease characteristics, and / or short follow-up time, the studies investigating retinal reactions before and after PDT are often of little value.

PDT-treated patients who were primarily classic CNV patients showed improvement in mfERG scalar products at 13-15 months of long-term follow-up.

Moschos et al.[26] describe mfERG data from 20 patients who received

PDT for classic sub foveal CNV. The average response density in ring 1 and ring 2 (representing the fovea and parafovea) decreased after treatment and improved six months after treatment, but the level was lower than baseline.

Neveu et al.[27] conducted a two-year follow-up of 13 patients with mainly classic CNV and found progressive retinal dysfunction from the central to the paracentral area.

It was found that the detectable PERG response before treatment is the best indicator of vision improvement after treatment. Patients with the greatest PERG or mfERG amplitude asymmetry between the eyes before treatment have the worst prognosis.

After a brief follow-up of one month, Oner et al. tested a sample size greater than 30 patients with classic CNV through PERG. They found that the amplitudes of P50 and N95 decreased briefly one week after PDT, and then the response returned to the pre-treatment value 1 month after treatment.[28]

The results of a small case series of 9 patients who received intravitreal bevacizumab injection after failure of previous treatment with laser photocoagulation, intravitreal triamcinolone injection, PDT or combination therapy also pointed to the insignificance of using PDT or other non- surgical management. The results showed no changes in response of ffERG and mild changes in the amplitude of the averaged mfERG response.[29] Other studies also found that patients receiving treatment for minimal or large occult classic CNV, no detectable changes in mfERG were observed even three months after the intra vitreal injection.

Macular translocation is a surgical method that moves the macula to an area outside of the affected RPE and the choroidal capillaries that are mainly affected.

In a study by Luke et al.[30] which tested the changes in the longitudinal response of the retina after macular shift, it was found that the ffERG response of 32 patients four months after the operation, was significantly reduced. Compared with the data before the macular translocation procedure, the a- and b- waves of photopic vision worsened by 27% and 43% respectively.

Tresaki et al. obtained similar results for the ffERG response, but it was shown that the mfERG response of 17 patients improved after macular shift surgery.[31]

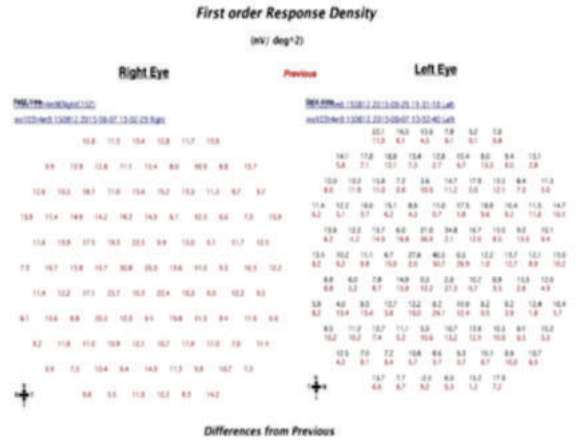

Fig 4: Comparison of response amplitude before and six weeks after treatment. Pre-treatment response amplitude indicated in red and post-treatment response amplitude indicated in black.

CONCLUSION

Multifocal electroretinography (mfERG) allows for the measuement of localised retinal cell function abnormalites in ARM over time due to its objectivity and topographical mapping. mfERG may also be used to monitor the success of surgical and therapeutic interventions, according to evidence.

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