Aetna Better Health®
2000 Market Street, Suite 850
Philadelphia, PA 19103

AETNA BETTER HEALTH®

Clinical Policy Bulletin:
Electroretinography

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Policy

Aetna considers electroretinogram or electroretinography (ERG) an acceptable alternative adjunctive modality useful in establishing loss of retinal function and distinguishing retinal from optic nerve lesions. Aetna considers ERG experimental and investigational for all other indications.

Aetna considers multi-focal ERG (mfERG) medically necessary for detecting chloroquine (Aralen) and hydroxychloroquine (Plaquenil) toxicity. Aetna considers mfERG experimental and investigational for all other indications.

Background

The retina is composed of rod and cone cells in the photoreceptive layer of tissue at the back of the inner eye. It acts like the film in a camera -- images come through the eye's lens and are focused on the retina. The retina then converts these images to electric signals and sends them via the optic nerve to the brain. The macula, composed mainly of cones, is used primarily for central and color vision (photopic vision) while the remaining retina, composed mainly of rod photoreceptors, is utilized primarily for peripheral and night (scotopic) vision.

The electroretinogram or electroretinography (ERG) records the electrical response evoked from the entire retina by a brief flash of light and consists of an "A" wave, a photoreceptor response, and a "B" wave that emanates from the Muller and bipolar cells. The ERG provides information about the performance of the rods and cones. The ERG helps to distinguish retinal degeneration and dystrophies. Multi-focal electroretinography (mfERG) measures the photoreceptors' activity. It is an advanced form of ERG in that it produces images with higher resolution than ERG. It involves stimulating areas of the retina using an electrical signal and mapping the response. Multi-focal ERG also allows the stimulation of multiple spots simultaneously, producing a changing pattern that is
An assessment conducted by the Australian Medical Services Advisory Committee (MSAC, 2001; Johnston et al, 2003) concluded that multifocal electroretinography is experimental. The report reached the following conclusions regarding mfERG: “All the studies of multifocal ERG were classified as level IV evidence. They did not present diagnostic characteristics or sufficient data to compute them. Although the studies showed that the multifocal ERG was able to discriminate between some visual parameters of patients with disease and controls with normal vision, they had little consistency and comparability. It is apparent from the available studies that much of the attention is focused on the mechanics of the technique and issues concerned with averaging signals and presentation of results. Thus, the clinical benefits of this technique are not yet apparent”.

Feigl et al (2005) investigated the cone- and rod-mediated mfERG in early age-related maculopathy (early ARM). A total of 17 eyes of 17 subjects with early ARM and 16 eyes of 16 age-matched control subjects with normal fundi were examined. These researchers concluded that their findings show a functional impairment of the rods in early ARM subjects. As there is histopathological evidence showing earlier rod than cone impairment in early ARM, following the rod function with the mfERG might be helpful in diagnosis or for monitoring the progression of early ARM.

In a prospective cohort study, Lai and colleagues (2005) assessed the longitudinal changes in mfERG in patients receiving hydroxychloroquine and examined the effects of cumulative hydroxychloroquine dose on mfERG. Twenty-four eyes in 12 patients receiving hydroxychloroquine underwent mfERG recordings at baseline and 1 to 2 years later. The first negative (N1) and first positive (P1) response amplitudes and peak latencies were compared with normal controls. Serial changes in the pattern of mfERG abnormalities and in response amplitudes and peak latencies were also compared between eyes in which hydroxychloroquine therapy was continued or stopped. Correlation analyses were performed to assess the effects of a cumulative dose of hydroxychloroquine on mfERG. These investigators concluded that patients receiving hydroxychloroquine showed a longitudinal decline in retinal function; patients who stopped hydroxychloroquine therapy showed improvement. Although these data are insufficient to demonstrate the sensitivity of mfERG for evaluating early hydroxychloroquine toxicity, the results suggest that serial mfERG assessment may help detect early retinal changes associated with hydroxychloroquine therapy. Further studies with long-term results will be useful in clarifying the value of mfERG in evaluating early retinal toxicity due to hydroxychloroquine.

Lai et al (2007) stated that mfERG is an investigation that can simultaneously measure multiple electroretinographic responses at different retinal locations by cross-correlation techniques. Thus, mfERG allows topographic mapping of retinal function in the central 40 to 50 degrees of the retina. The strength of mfERG lies in its ability to provide objective assessment of the central retinal function at different retinal areas within a short duration of time. Since the introduction of mfERG in 1992, mfERG has been applied in a large variety of clinical settings. mfERG has been found to be useful in the assessment of localized retinal dysfunction caused by various acquired or hereditary retinal disorders. The use of mfERG also enabled clinicians to objectively monitor the treatment outcomes as the changes in visual functions might not be reflected by subjective methods of assessment. By changing the stimulus, recording, and analysis parameters, investigation of specific retinal electrophysiological components can be performed topographically. Further developments and consolidations of these parameters will likely broaden the use of mfERG in the clinical setting.
Moon et al (2012) conducted a study to investigate the association between automated perimetry, mERG, and optical coherence tomography (OCT) measurements in patients with advanced retinitis pigmentosa (RP). In 25 patients with advanced RP central visual field sensitivity (VFS) was evaluated using an average of visual sensitivity value at central four test points during central 30-2 static automated perimetry. When OCT imaging was conducted the inner and outer segment (IS/OS) line was classified into three groups: Group 1, absence; Group 2, partially intact; and Group 3, intact. Central retinal thickness (CRT), defined as the retinal thickness of central 3.0 mm, was also evaluated. Average amplitude and implicit time of N1 and P1 in ring 1 and 2 were measured on mERG and comparisons of VFS, mERG and OCT among the three subgroups were performed following IS/OS integrity. The relationship between VFS, mERG and CRT was evaluated by regression analysis. The authors reported that group 3 patients with an intact IS/OS line showed a better VFS, and amplitude of mERG response than those of Group 1 and 2. VFS and amplitudes of mERG were correlated significantly with CRT in linear regression analysis. The authors concluded that disrupted IS/OS integrity was associated with visual dysfunction which was shown by decreased amplitude of mERG response and reduced central VFS. CRT was significantly correlated with amplitude of mERG response and central VFS and an eye with the more reduced CRT was associated with the worse amplitude of mERG response and central VFS.

Narayanan et al (2013) conducted a prospective study of mERG in patients with type 2 MacTel to characterize the electroretinography response of the macula by mERG. The study was conducted from April 2009 to November 2009 and mERGs 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 and the study included patients with type 2 MacTel confirmed by fundus fluorescein angiography without subretinal neovascularisation. Individual mERG responses for the hexagons were grouped into concentric rings centered on the fovea for analysis (1<2, 5-10, 10-15 and >15°). Twenty eight eyes of 14 patients and 20 eyes of 10 normal controls were included in the study. The authors reported that the mean logMAR visual acuity of the patients was 0.51 (Snellen equivalent 20/63) and the mean N1 amplitude (nv/deg(2)) of patients were significantly reduced compared to controls as follows: 8.91 ± 14.00 versus 43.44 ± 9.55 (p < 0.0001) in less than 2°, 9.24 ± 10.47 versus 22.00 ± 3.87 (p < 0.0001) in 5-10°, 8.57 ± 10.02 versus 15.24 ± 1.89 (p < 0.0001) in 10-15°, and 7.03 ± 6.52 versus 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. The results specified 27.66 ± 37.44 versus 96.20 ± 12.41 (p < 0.0001) in less than 2°, 22.61 ± 19.38 versus 53.78 ± 9.79 (p < 0.0001) in 5-10°, 18.75 ± 20.21 versus 35.22 ± 4.16 (p < 0.001) in 10-15°, and 17.10 ± 12.54 versus 25.71 ± 3.93 (p < 0.001). The implicit time of N1 and P were also delayed significantly in all the rings. The mean central foveal thickness assessed by OCT scan was 84.78 ± 45.12 μm. There was poor correlation between mERG amplitudes or implicit times with either the visual acuity or OCT central thickness. The authors concluded that mERG 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(o) rings. Although there was poor correlation between the visual acuity and the amplitudes a of the waveforms, mERG is a useful investigative modality for functional assessment of macula in type 2 MacTel patients. However, this study by Narayanan et al. was limited by the sample size of 28 eyes in 14 patients.

In a review on “Hydroxychloroquine-induced retinal toxicity”, Hansen and
Schuman (2011) stated that at the initiation of treatment with hydroxychloroquine, the prescribing physician should refer the patient to an ophthalmologist. During the initial examination, it is recommended that the patient receive:

A thorough ocular examination documenting any pre-existing conditions; and
A Humphrey visual field central 10-2 white-on-white pattern; and At least 1 of the following objective tests, if available: Fundus autofluorescence (FAF) test; or mfERG; or Spectral domain OCT (SD-OCT).

Moreover, these investigators noted that mfERG, a test that is typically available in large clinical centers, objectively evaluates function and can be used in place of visual fields. They also stated that it is also worth considering the use of color fundus photographs to assist in documenting changes over time, especially if there is pre-existing retinal pathology. However, the dilated fundus examination should not be considered a screening tool, as it only picks up relatively late toxic changes. http://www.aao.org/publications/eyenet/201106/pearls.cfm.

Costedoat-Chalumeau et al (2012) stated that new recommendations for screening of hydroxychloroquine retinopathy, updating those of 2002, have been recently published by the American Academy of Ophthalmology (AAO). These recommendations have been necessary because of new knowledge about the prevalence of toxicity and because of improved screening tools. Amsler grid testing, color vision testing, fluorescein angiography, full-field ERG, and electro-oculogram are no longer recommended. It is now recommended to perform fundus examinations with 10-2 automated fields, and whenever possible, at least 1 objective test including mfERG, FAF or SD-OCT. A baseline examination is advised as a reference and then, annual screening should be initiated no later than 5 years after starting hydroxychloroquine therapy.

An eMedicine review on “Chloroquine and Hydroxychloroquine Toxicity” (Roque, 2013) listed full-field ERG or electro-oculogram as one of the ancillary tests, although not recommended for toxicity screening because of sensitivity, specificity and reliability issues, may also be used in diagnosing toxicity. Moreover, the author also indicated that the ophthalmic examination should also include a Humphrey visual field central 10-2 white-on-white pattern, and at least one of the following objective tests, if available: http://emedicine.medscape.com/article/1229016-workup.

SD-OCT
FAF test
mfERG

Browning and Lee (2014) determined the relative sensitivity and specificity of 10-2 visual fields (10-2 VFs), mfERG, and SD-OCT in detecting hydroxychloroquine retinopathy. A total of 121 patients taking hydroxychloroquine (n = 119) or chloroquine (n = 2) with 10-2 VF, mfERG, and SD-OCT tests were retrospectively reviewed. Rates of test abnormality were determined. Retinopathy was present in 14 and absent in 107; 11 of 14 (78.6 %) patients with retinopathy were overdosed; 12 (85.7 %) had cumulative dosing greater than 1,000 g. The sensitivities of 10-2 VF, mfERG, and SD-OCT in detecting retinopathy were 85.7 %, 92.9 %, and 78.6 %, respectively. The specificities of 10-2 VF, mfERG, and SD-OCT in detecting retinopathy were 92.5 %, 86.9 %, and 98.1 %, respectively. Positive-predictive values (PPVs) of 10-2 VF, mfERG, and SD-OCT in detecting retinopathy were less than 30 % for all estimates of hydroxychloroquine retinopathy prevalence; negative-predictive values (NPVs) were greater than 99 % for all tests. The authors concluded that based on published estimates of hydroxychloroquine retinopathy prevalence, all 3 tests are most reliable when negative, allowing confident exclusion of retinopathy in patients taking less than or equal to 6.5 mg/kg/day. Each test is less useful in allowing a confident diagnosis.
of retinopathy when positive, especially in patients taking less than or equal to 6.5 mg/kg/day.

An UpToDate review on “Antimalarial drugs in the treatment of rheumatic disease” (Wallace, 2014) states that “The earliest retinal abnormalities are asymptomatic and can only be detected by ophthalmologic examination. These “premaculopathy” changes consist of macular edema, increased pigmentation, increased granularity, and loss of the foveal reflex. Subtle functional loss in the paracentral retina can occur before biomicroscopic changes in the retinal pigment epithelium. Detection of changes at this stage, using techniques such as multifocal electroretinography, is desirable since they may be completely reversible upon discontinuation of the medication”.

Guidelines from the American Academy of Ophthalmology (Marmor, et al., 2011) on screening for chloroquine and hydroxychloroquine toxicity state that newer objective tests, such as multifocal electroretinogram (mERG), spectral domain optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF), can be more sensitive than visual fields. The guidelines recommended that along with 10-2 automated fields, at least one of these procedures be used for routine screening where available. The guidelines state that, because multifocal electroretinography testing is an objective test that evaluates function, it may be used in place of visual fields.

CPT Codes / HCPCS Codes / ICD-9 Codes

**CPT codes covered if selection criteria are met:**

92275

**CPT codes covered if selection criteria are met:**

Multifocal electroretinography no specific code

**ICD-9 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>228.03</td>
<td>Hemangioma of retina</td>
</tr>
<tr>
<td>361.00 - 361.9</td>
<td>Retinal detachments and defects</td>
</tr>
<tr>
<td>362.01 - 362.89</td>
<td>Other retinal disorders</td>
</tr>
<tr>
<td>363.00 - 363.72</td>
<td>Chorioretinal inflammations, scars, and other disorders of choroid</td>
</tr>
<tr>
<td>377.00 - 377.49</td>
<td>Disorders of optic nerve</td>
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</tbody>
</table>
The above policy is based on the following references:


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