Full-field electroretinography – when do we need it?

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Abstract:

Multimodal imaging and genetic testing allow sophisticated assessment of suspected inherited retinal disease. Given the availability of such technology, some question whether the full-field electrogram (ffERG) is needed anymore. In fact, a ffERG remains essential for certain clinical scenarios. The goal of this case-based review is to provide a clear understanding of what clinical situations warrant a ffERG. All practicing ophthalmologists should be familiar with this information.

Keywords:

Electroretinogram, ERG, retinal dystrophy, maculopathy, nystagmus, unexplained visual loss

Introduction

On more than one occasion, I have been asked if a full-field electroretinogram (ffERG) is still needed for the assessment of inherited retinal disease. With advances in retinal multimodal imaging (wide-field imaging, short-wave autofluorescence [AF], near-infrared imaging, optical coherence tomography [OCT], OCT angiography, adaptive optics) and in genetic testing techniques (multi-gene panels, whole exome sequencing, whole genome sequencing), is there reason anymore to perform a ffERG for a patient with inherited retinal disease? The answer is yes. The ffERG remains the only clinically available objective method to assess pan-retinal function when clinically indicated. Multimodal imaging provides information regarding retinal structure. Genetic testing provides information regarding DNA sequencing. On the other hand, the ffERG provides information regarding global retinal function. The ffERG objectively measures pan-retinal function, clinically dissects the inner from the outer retina, functionally separates rods (scotopic function) from cones (photopic function), and can have a pathognomonic signature for certain rare genetic diagnoses.[1-3]

The ffERG measures pan-retinal electrical activity under standardized conditions of light stimulation and retinal adaptation.[1,2] The central macula, being a small percentage of the total retinal function, is not specifically assessed. Therefore, the ffERG does not provide information regarding foveal function or visual acuity. A patient with a normal ffERG could have hand-motion vision (e.g., a macular hole or scar) and a patient with a nonrecordable standard ffERG could have 20/20 vision (e.g., typical adult-onset retinitis pigmentosa). In addition to not being an assessment of foveal function, the ffERG is not an assessment of optic nerve pathology. Retinal ganglion cell function is not measured by the ffERG. A patient with no light perception from optic neuropathy can have a normal ffERG.

The ffERG must be performed by a healthcare provider who is highly skilled in the technique. This is critical to meaningful results. The International Society for Clinical Electrophysiology of Vision provides guidelines for standard protocols and techniques.[2]

During ffERG testing, standard light stimuli need to pass through the anterior segment and vitreous to reach the retina. Anything that disrupts the ability of this standard amount of light getting to the retina such as significant media opacity or eye misalignment can decrease ffERG amplitudes.[4] The ffERG cannot be properly interpreted unless it is performed in the context of a good clinical eye examination. Moreover, the ffERG should only be performed to answer a specific question that

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arose after the clinical examination (see INDICATIONS section below).

The ffERG is only one of different electrophysiological tests that objectively assess the visual system.[5] It is not the goal of this article to review different electrophysiology tests, to describe how to perform a ffERG, or even to instruct on how to interpret ffERG results. There are many excellent articles that address these topics.[1-5] Rather, the goal of this case-based review is to provide a clear understanding of what clinical situations warrant a ffERG. All practicing ophthalmologists should be familiar with this information.

Indications

Pigmentary or fibrotic changes that raise suspicion for underlying pan-retinal dysfunction

Retinal pigmentary or fibrotic changes can be signs of diffuse retinal disease. When this is suspected, ffERG is indicated to understand if the changes are only localized changes or are a sign of underlying pan-retinal dysfunction. When there is pan-retinal dysfunction, the ffERG results can help guide diagnosis and interpretation of genetic testing results.

a. A 51-year-old female without visual complaints had an eye examination as a preoperative evaluation for blepharoplasty. Visual acuity was 20/30 in either eye. Pigmentary retinopathy along the vascular arcades was noted during the examination. Both eyes were similar; the right eye is shown in Figure 1. She denied night blindness. OCT and AF showed outer retinal loss and reduced signal, respectively, in the areas of pigmentary change. The ffERG showed significantly depressed scotopic function and also, to less of an extent, delayed and depressed photopic function. This suggested the diagnosis of retinitis pigmentosa.[6] Repeat ffERG 2 years later confirmed progression.

b. A 4-year-old male was evaluated for new-onset esotropia and was found to have refractive accommodative esotropia related to high hyperopia (+6.25 in either eye). His eyes straightened with his hyperopic refraction and vision was 20/30 in either eye with correction. However, a nodule of subretinal fibrosis was noted in the posterior pole of both eyes. Both eyes were similar; the left eye is shown in Figure 2. When specifically asked about his night vision, the mother stated he had difficulty navigating in dim light. The ffERG showed no recordable scotopic function, a dull, rounded combined response to flash that was similar to the photopic flash response, and a delayed and depressed photopic flicker with an amplitude less than that of the a-wave of the photopic flash response. This pattern is that of the enhanced S-cone syndrome, one of the few genetic retinal diseases with a pathognomonic ffERG.[3] Genetic testing confirmed homozygosity for a pathogenic variant in *NR2E3*, the gene primarily associated with the enhanced S-cone syndrome.[7,8]

Maculopathy

When a patient presents with maculopathy, it can represent isolated macular disease (macular dystrophy, congenital macular lesion, or acquired macular lesion) or can be the sign of underlying pan-retinal disease (typically cone-rod dystrophy or congenital dysfunction). The ffERG is indicated to understand if the maculopathy is isolated or is part of pan-retinal disease. The ffERG results can help to make proper diagnosis, can guide interpretation of genetic testing results, and can inform prognosis.

a. A 5-year-old male was examined because of having difficulty seeing the board in school for the past year. The parents had expected that he would have myopia like his father. The vision was 20/60, 20/150 but there was no significant refractive error by cycloplegic

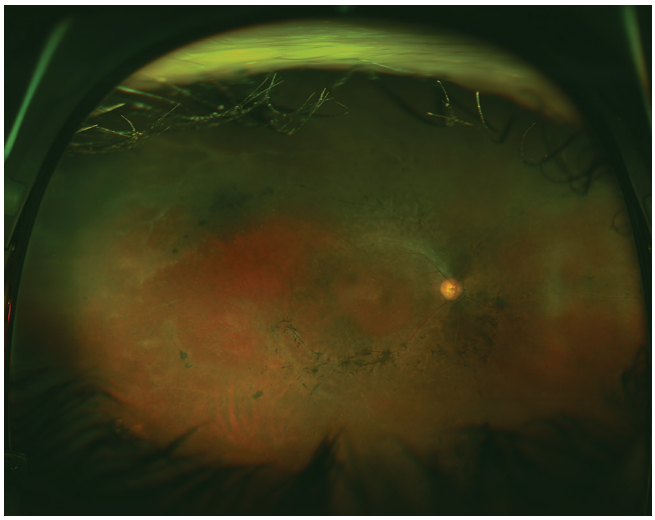

Figure 1: A 51-year-old asymptomatic female was found to have pigmentary retinopathy. A wide-field retinal image of the right eye shows pigmentary retinopathy along the vascular arcades. The left eye was similar (not shown)

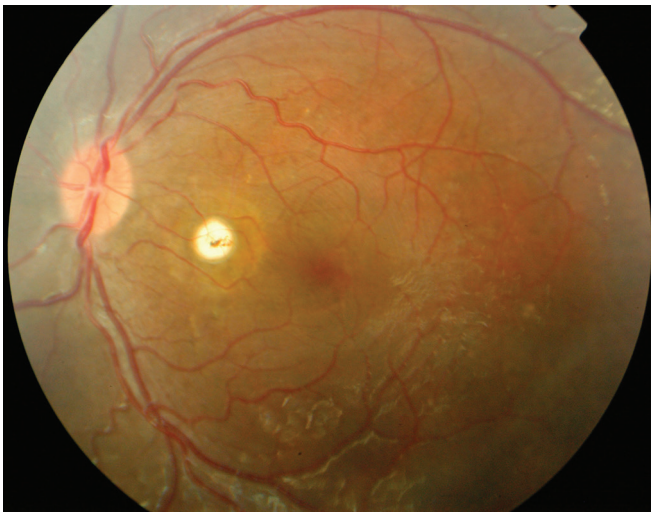

Figure 2: A 4-year-old male with accommodative esotropia was found to have focal subretinal fibrosis. Fundus photography of the left eye shows a solitary subretinal nodule between the optic nerve head and the fovea. The right eye was similar (not shown)

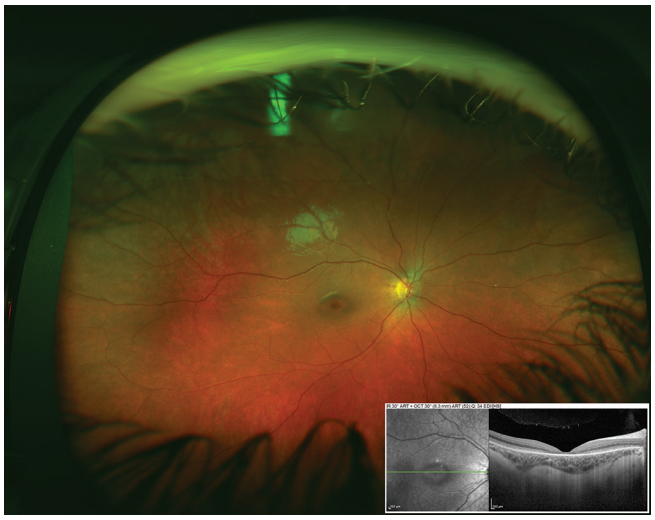

Figure 3: A 5-year-old male with reduced visual acuity over the last year was found to have maculopathy. A wide-field retinal image of the right eye shows central maculopathy, confirmed by optical coherence tomography (inset). The left eye was similar (not shown)

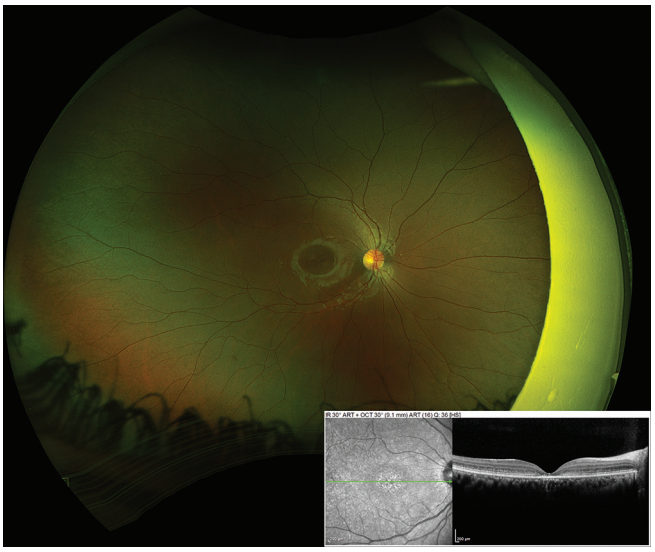

Figure 4: An 18-year-old female with a reduced vision since childhood that recently reduced further was found to have maculopathy. A wide-field retinal image of the right eye shows central maculopathy, confirmed by optical coherence tomography (inset). The left eye was similar (not shown)

refraction. Ophthalmic examination was significant for maculopathy. Both eyes were similar; the right eye is shown in Figure 3. OCT and AF showed central macular outer retinal loss and reduced signal, respectively. When the mother was asked about his night vision, she stated he was very afraid of the dark. The ffERG showed almost no recordable scotopic function, a delayed and decreased combined response to flash with an electronegative waveform, and delayed and depressed photopic responses. This pattern in this context suggested the neurodegenerative disease juvenile neuronal ceroid lipofuscinosis.[9] The mother confirmed the child was recently exhibiting aggressive behavior and suffered from nightmares. Genetic testing confirmed biallelic pathogenic variants in *CLN3*, the major gene associated with juvenile neuronal ceroid lipofuscinosis.[10] Because the diagnosis was made early, he was eligible for an intrathecal gene therapy trial with a goal of warding off neurodegeneration.

b. An 18-year-old female had difficulty with vision since childhood but particularly for the past year. She was also light sensitive. When questioned specifically, she did not report difficulties with night vision. Best-corrected visual acuity (−1.00, −1.75) was 20/125, 20/60. Cycloplegic refraction was comparable to her current glasses. Ophthalmic examination was significant for maculopathy. Both eyes were similar; the right eye is shown in Figure 4. OCT and AF showed central macular outer retinal loss and reduced signal, respectively. The ffERG was within the normal limits. In this context, the patient had macular dystrophy as opposed to pan-retinal dysfunction. Genetic testing confirmed biallelic pathogenic variants in *ABCA4*, the gene most commonly associated with macular dystrophy in children and young adults.[11,12] In addition to allowing the diagnosis of macular dystrophy in general, ffERG results inform patient prognosis for *ABCA4*-related retinopathy specifically.[13] Her normal ffERG in this setting predicted a better long-term pan-retinal survival than had it been abnormal.

Optic nerve head pallor

Optic nerve head pallor is often a sign of optic neuropathy, but it can be a sign of retinal dysfunction. A ffERG may be indicated to rule out retinal dysfunction, particularly if OCT does not show ganglion cell loss or if there are retinal pigmentary abnormalities.

a. An 8-year-old male who had stable reduced vision noted since he was 2 years old had been diagnosed with idiopathic optic neuropathy. Brain magnetic resonance imaging had been normal. Best-corrected visual acuity (−6.00 −3.00 × 180 in both eyes) was 20/400 in both eyes. He was photophobic and denied night vision problems. Cycloplegic refraction was comparable to current glasses. Ophthalmic examination was significant for optic nerve pallor. Both eyes were similar; the right eye is shown in Figure 5. OCT and AF were within normal limits. The ffERG showed almost no recordable scotopic function, a delayed and decreased combined response to flash with an electronegative waveform, and delayed and depressed photopic responses. This pattern in this context suggested *CAB4*-related retinopathy, also known as a congenital cone-rod synaptic disorder.[14,15] Genetic testing confirmed homozygosity for a pathogenic variant in *CABP4*.[16]

b. A 46-year-old male noted a gradual loss of vision in both eyes for the previous 20 years. Past medical history was significant for gradual acquired eyelid ptosis, strabismus, and inability to move the eyes that also started 20 years prior; this constellation was consistent with mitochondrial

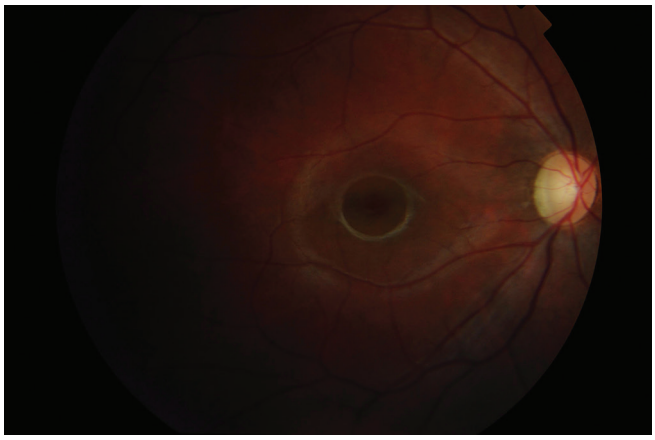

Figure 5: An 8-year-old male with a stable reduced vision since he was 2 years old had been previously diagnosed as having optic neuropathy Fundus photography of the right eye shows temporal optic nerve head pallor and a healthy inner retinal reflex. The left eye was similar (not shown)

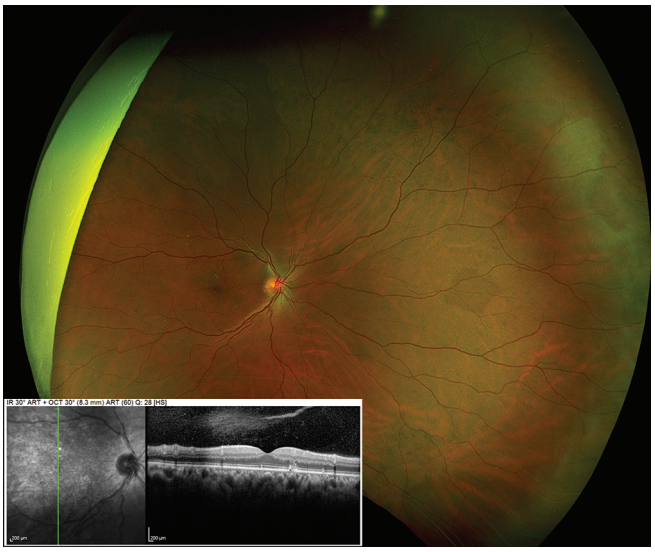

Figure 6: A 46-year-old male with acquired ptosis and ophthalmoplegia over the last 20 years that was consistent with mitochondrial disease also noted progressive loss of vision over the same period The etiology of the visual loss was unclear. A wide-field retinal image of the right eye shows macular scattered punctate yellow deposits confirmed to be at the level of the retinal pigment epithelium by optical coherence tomography (inset). The left eye was similar (not shown)

disease.[17] Visual acuity was hand-motion, 20/40. Orthoptic examination showed a right esotropia of 20 prism diopters at near and limited ductions of both eyes in all positions of gaze. There was no afferent pupillary defect or significant refractive error. There was mild temporal optic nerve head pallor. There were scattered punctate yellow deposits throughout the macula that was confirmed to be at the level of the retinal pigment epithelium by OCT. Both eyes were similar; the right eye is shown in Figure 6. OCT optic nerve head ganglion cell parameters were within normal limits. The ffERG was normal, excluding pan-retinal disease but not excluding macular or optic nerve disease.[2] Additional electrophysiologic testing was needed to understand the cause for visual loss in this patient.[5] Pattern ERG and pattern visual evoked potential testing revealed optic nerve dysfunction with no evidence for maculopathy.[5]

Unexplained reduced vision or nystagmus

Unexplained reduced vision – nyctalopia, light sensitivity (photophobia), or reduced visual acuity – is an indication for ffERG. For unexplained nyctalopia or photophobia, the ffERG can directly measure scotopic and photopic retinal function. For unexplained reduced vision or nystagmus, an abnormal ffERG confirms pan-retinal disease. However, a normal ffERG in this setting does not rule out maculopathy or optic nerve dysfunction and thus would need to be supplemented by additional forms of electrophysiology testing for these possibilities.

a. A 6-year-old female with high myopia was referred for strabismus surgery. The child had been previously evaluated by a retinal specialist for slightly subnormal vision and nystagmus, and the family was told there was no retinal abnormality based on normal multimodal imaging. Best-corrected visual acuity (−7.50 -1.00 × 090 in either eye) was 20/40 in either eye. There was an esotropia at near of 45 prism diopters (with correction) with full ductions. There was slight nystagmus (fusion maldevelopment type). Cycloplegic refraction was comparable to current glasses. The retina had an appearance consistent with high myopia. Both eyes were similar; the right eye is shown in Figure 7. OCT and AF were consistent with high myopia and otherwise unremarkable. When directly questioned, the mother admitted that her daughter had difficulty with night vision. ERG showed no recordable scotopic response, a combined response to flash with an electronegative waveform and normal a-wave, and normal photopic responses. This pattern in this context suggested congenital stationary night blindness.[18] Genetic testing confirmed homozygosity for a pathogenic variant in *TRPM1*.[19-21]

b. A 14-year-old female with long-standing reduced vision and nystagmus was referred for visual evaluation. Past medical history was significant for neonatal encephalitis complicated by stroke. Since this event, she was noted to have intellectual disability, a left hemiplegia, reduced vision, and nystagmus, all of which were attributed to her neonatal neurological event. Best-corrected visual acuity (−2.75 -3.50 × 013, −1.75 -3.75 × 169) was 20/300 in either eye. The child was photophobic. When the mother was specifically questioned, she noted that the child was afraid of the dark. There was horizontal pendular nystagmus that dampened in right gaze. Cycloplegic refraction was comparable to her current glasses. Retinal examination revealed a blunt foveal reflex in either eye. Both eyes were similar; the right eye is shown in Figure 8. Multimodal imaging was limited by the patient's nystagmus and lack of cooperation. The ffERG showed no recordable scotopic response, a delayed combined

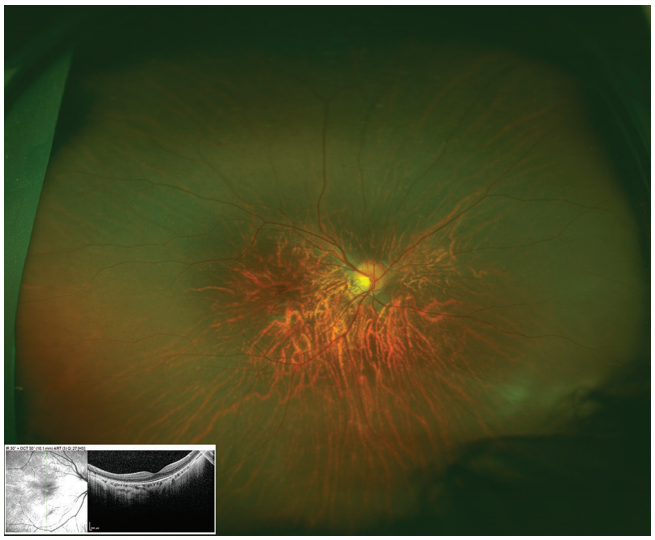

Figure 7: A 6-year-old female with high myopia was referred for strabismus surgery Based on previous multimodal imaging for subnormal vision and nystagmus, the family had been told the retina was normal. A wide-field retinal image of the right eye shows an appearance consistent with high myopia, as did optical coherence tomography (inset). The left eye was similar (not shown)

response to flash but with a supranormal b-wave, and depressed and delayed photopic responses. This pattern is that of cone-rod dystrophy with supranormal rod response, also known as *KCNV2*-related retinopathy, which is one of the few genetic retinal diseases with a pathognomonic ffERG.[3] Genetic testing confirmed homozygosity for a pathogenic variant in *KCNV2*.[22]

A need to assess or monitor pan-retinal function

Reasons to monitor pan-retinal function include following disease progression, checking for the potential toxic effect of a drug or retinal foreign body, or assessing the effect of a retinal vascular event or a treatment. However, as the ffERG measures global retinal function, relatively large changes need to occur before they are detected. There are other electrophysiological and psychophysical tests that may be more appropriate for these scenarios.

Conclusion

The ffERG continues to be an important tool in ophthalmic practice, for which there is no substitute when clinically indicated. Clinical scenarios that warrant a ffERG include: (1) Pigmentary or fibrotic changes that raise suspicion for underlying pan-retinal dysfunction; (2) Maculopathy; (3) Optic nerve pallor; (4) Unexplained reduced vision or nystagmus; (5) A need for assessing or monitoring pan-retinal function.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

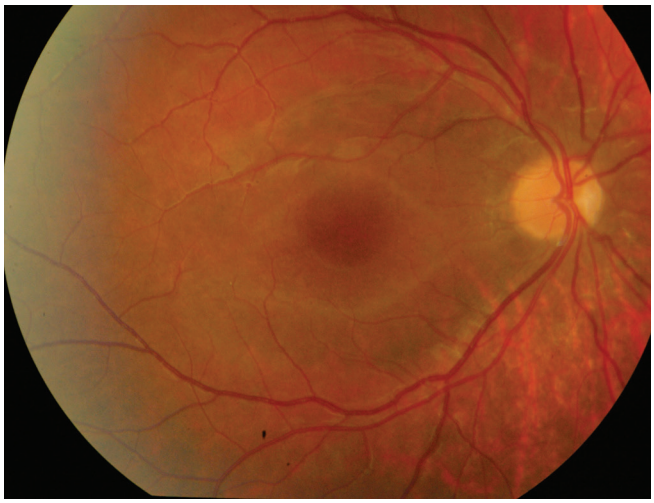

Figure 8: A 14-year-old female had long-standing reduced vision and nystagmus that had been attributed to neonatal encephalitis complicated by stroke. She also had an intellectual disability and a left hemiplegia noted following that event. Fundus photography of the right eye shows a blunted central macular appearance. The left eye was similar (not shown)

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Nil.

Conflicts of interest

There are no conflicts of interest.

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