ffERG – when do we need it?

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Outline

- Retina basics
- ffERG basics
- ffERG indications
- Cases to consider – ffERG – do we need it?
Basics - references

- Webvision (https://webvision.med.utah.edu/)
- American Academy of Ophthalmology Basic and Clinical Science Course (BSCS) 2021
Photoreceptors: facts

Total number of cones in the retina.
- 6,400,000

Total number of rods in the retina.
- 110,000,000 to 125,000,000

Total number of cones in fovea.
- Approximately 200,000. There are 17,500 cones/°. Rod free area is approximately 1° thus there are 17,500 cones in the central rod-free fovea

Age when fovea is fully developed.
- Not before 4 years of age

Rod distribution.
- Rods peak in density 18° or 5mm out from the center of the fovea in a ring around the fovea at 160,000 rods/mm².
- No rods in central 200 µm.
- Average 80-100,000 rods/mm²
Fig. 20. Graph to show rod and cone densities along the horizontal meridian.

Webvision

The retina’s light-gathering rod and cone cells (beige and green, respectively; artificially coloured) die in people with the inherited disorder retinitis pigmentosa. Credit: Steve Gschmeissner/SPL

Nature Medicine 2020
Cones (5% photoreceptors) allow trichromatic vision (Ch. X, 7)
Proper technique critical
Standard ffERG measures function

the aggregate gross electrical response of certain retinal cells to 4 (minimum) protocols of standard light stimuli (ISCEV standard)

isolates rods from cones, inner from outer retina

Standard ffERG does NOT

measure ganglion cell function (or posterior pathways)

indicate foveal function (no info regarding visual acuity)

add information if there are no photoreceptors

substitute for clinical exam (a good ophthalmologist is better than excellent ffERG)
Normal standard ffERG
(proper technique critical)
pigmentary/fibrotic changes if question of global retinal dysfunction

maculopathy

non-traumatic optic nerve pallor, particularly in children

unexplained poor vision or nystagmus (not Va), or poor night vision

panretinal function quantification (after an intervention or over time)

ffERG indications

1)

2)

3)

4)

5)
ffERG indications

1) pigmentary/fibrotic changes if question of global retinal dysfunction
2)
3)
4)
5)
INDICATION #1

50yo asymptomatic woman who had eye exam pre-blepharoplasty (OD similar)

ffERG: shows rod-cone dysfunction
- repeat later to determine if dystrophy (progressive)
INDICATION #1

4yo boy with refractive accommodative esotropia

ERG OD (OS similar)
Enhanced S-cone /Goldmann-Favre syndrome

Both adults & children
- night blindness & pathognomonic ERG; +/- retinoschisis, subretinal fibrosis, vitreous degeneration, hyperopia, biallelic NR2E3 (or NRL) pathogenic variants
- characteristic deep often nummular clumped pigment around the vascular arcades (but can be severe retinal degeneration without pattern)

Children
- often refractive accommodative esotropia; deep retinal mottling or depigmentation around arcades (but can be severe retinal degeneration without pattern)


ffERG indications

1) pigmentary/fibrotic changes if question of global retinal dysfunction

2)

3)

4)

5)
**ffERG indications**

1) pigmentary/fibrotic changes if question of global retinal dysfunction

2) maculopathy

3)

4)

5)
INDICATION #2

20/200 OU

12yo boy with decreasing vision

OS similar
ffERG: shows cone-rod dysfunction
ffERG: macular dystrophy (Stargardt disease), cone-rod dystrophy, rod-cone dystrophy

the most common cause of juvenile macular dystrophy (Stargardt disease)

common signs are early macular changes, flecks, peripapillary sparing

biallelic pathogenic variants in ABCA4

patients should avoid:
 smoking
 trauma (predisposition to fibrosis)
 excessive light (including excessive examinations)
 vitamin A supplements


INDICATION #2

Another 12yo boy with decreasing vision

OS similar
ERG: ROD RESPONSE
Isolated rod response
Mixed rod-cone response
Cone response
Cone 30 Hertz flicker response
Normal individual
Cone-rod dystrophy with supranormal rod response

Childhood sign/symptoms
- congenital or acquired poor vision; nystagmus (often with head shaking) - often improves; photophobia

Retinal appearance
- normal in early childhood; macular changes with time

ffERG
- pathognomonic

Genetics
- specific for biallelic pathogenic variants in KCNV2

ffERG indications

1) pigmentary/fibrotic changes if question of global retinal dysfunction

2) maculopathy

3)

4)

5)
ffERG indications

1) pigmentary/fibrotic changes if question of global retinal dysfunction

2) maculopathy

3) non-traumatic optic nerve pallor, particularly in children

4)

5)
**INDICATION #3**

8yo boy with poor vision since 2yr old (20/400 OU); prior diagnosis optic neuropathy

**OCT:** WNL  
**AF:** WNL

CycloRNS: -6.00-3.00x180 OU

**ERG OD (OS similar)**
Congenital cone-rod synaptic disorder (CABP4-related)

a congenital cone dysfunction (relatively stable)

sometimes characterized as a form of “incomplete” CSNB

characterized by decreased central vision, marked photophobia, and often a grossly normal fundus appearance (+/- optic nerve pallor)

ffERG: cone-rod dysfunction with electronegative waveform

biallelic pathogenic variants in CABP4

often hyperopic - give full refraction


Khan AO. CABP4 mutations do not cause congenital stationary night blindness. Ophthalmology 2014;121(3):e15.

INDICATION #3

9yo girl
decreased vision noted over last year in school
diagnosed with IDDM 1 year ago
20/400 OU

ffERG is normal
OCT shows loss of inner retina

OS similar
Genetic optic nerve atrophy

Classically, a specific phenotype suggested pathogenic variants in a specific gene
  e.g., optic atrophy + diabetes + hearing loss = Wolfram syndrome = biallelic \(WS1\) pathogenic variants

Now, we recognize multiple genes and variable expressivity
  e.g., \(WS1\) pathogenic variants can cause optic nerve atrophy with or without diabetes or hearing loss in an autosomal dominant or recessive manner

Because of this complexity, genetic testing is best done by panels or exome sequencing unless the presentation suggests otherwise (e.g., classic LHON, MELAS, Wolfram)
  detailed review of systems is important (diabetes, hearing, neurological regression, etc.)
  it is often helpful to examine the parents
  unexpected disease is sometimes uncovered
ffERG indications

1) pigmentary/fibrotic changes if question of global retinal dysfunction

2) maculopathy

3) non-traumatic optic nerve pallor, particularly in children

4)

5)
ffERG indications

1) pigmentary/fibrotic changes if question of global retinal dysfunction

2) maculopathy

3) non-traumatic optic nerve pallor, particularly in children

4) unexplained abnormal vision & infantile nystagmus (not Va)

5)
Leber congenital amaurosis - non-recordable ERG within first few years of life

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Rod Specific</th>
<th>Maximum Scotopic Responses</th>
<th>Photopic 30 Hz Flicker</th>
<th>Transient Photopic</th>
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<tbody>
<tr>
<td>Normal</td>
<td></td>
<td>b-wave</td>
<td>b-wave</td>
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<tr>
<td>Rod function</td>
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<td>Mixed rod and cone function</td>
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<tr>
<td>Complete CSNB</td>
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<td>electronegative</td>
<td>b-wave</td>
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<td></td>
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<tr>
<td>Undetectable</td>
<td></td>
<td>Electronegative</td>
<td>Simplified waveform</td>
<td>Borderline normal</td>
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<td>Rod Monochromatism</td>
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<td>Cone Dystrophy</td>
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<td>Normal</td>
<td></td>
<td>Moderate reduction</td>
<td>Undetectable</td>
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<td>Small and slow</td>
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INDICATION #4

6yo girl referred for strabismus esotropia, myopia
mom complains her daughter has poor night vision
was told all is normal by retinal specialist

c c -7.50-1.00x090 either eye 20/40
ETcc’45pd
slight nystagmus (fusion maldevelopment type)
cycloRNS comparable to glasses
retina (myopic) and multimodal imaging WNL
OS similar
ffERG OD
(OS similar)
Congenital stationary night blindness

“complete” (ON-bipolar) vs “incomplete” (photoreceptor synapse)

also Riggs type (photoreceptor)

electronegative ffERG characteristic (with rod dysfunction)

multiple genes implicated

**AR:** GRM6, TRPM1, SLC24A1, GRP179
**AD:** RHO, PDE6B, GNAT1

X-linked (often myopic): NYX, CACNA1F

Often myopic with “normal” fundus

**ffERG indications**

1) pigmentary/fibrotic changes if question of global retinal dysfunction

2) maculopathy

3) non-traumatic optic nerve pallor, particularly in children

4) unexplained abnormal vision & infantile nystagmus (not Va)

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ffERG indications

1) pigmentary/fibrotic changes if question of global retinal dysfunction

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5) quantitating/monitoring pan-retinal function
**ffERG indications**

1) pigmentary/fibrotic changes if question of global retinal dysfunction

2) maculopathy

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4) unexplained abnormal vision & infantile nystagmus (not Va)

5) quantitating/monitoring pan-retinal function
“Difficulty seeing, especially at night”
14yo male

- Difficulty seeing, especially at night
- Longstanding and seems stable
- Retina and multimodal imaging normal by report

- 20/30 cc
- Intermittent exotropia (longstanding)
- Retina (myopic) and multimodal imaging WNL
- CycloRNS: -3.50+3.25x058 20/30; -1.50+1.75x144 20/30
Both eyes similar
Congenital stationary night blindness

“complete” (ON-bipolar) vs “incomplete” (photoreceptor synapse)

also Riggs type (photoreceptor)

electronegative ffERG characteristic (with rod dysfunction)

multiple genes implicated
AR: GRM6, TRPM1, SLC24A1, GRP179
AD: RHO, PDE6B, GNAT1
X-linked (often myopic): NYX, CACNA1F

Often myopic with “normal” fundus

“Infant with shaking eyes; improving”
12m old male

- Eye shaking (improving), chin-down position, photophobia
- Lightly-pigmented compared to siblings
- Previously diagnosed with albinism

- CUSUM OU
- High frequency low amplitude horizontal pendular nystagmus
- Retina appears WNL (tessellated)
- CycloRNS: +2.50-1.00x180 OU
Both eyes similar

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CNAG3
Achromatopsia

Characterized by decreased central vision, marked photophobia, poor color vision, and often a grossly normal fundus appearance

Biallelic pathogenic variants in one of several cone phototransduction genes CNGA3, CNGB3, GNAT2, PDE6C, PDE6H

ffERG: classically lack of photopic responses

Often hyperopic - give full refraction

Glasses that lower transmission and block lower wavelengths useful - e.g., CPF 450

“Worsening vision and a history for breast cancer”
38yo female

- Recent worsening vision; no improvement with manifest refraction (20/40)
- History of treatment for breast cancer
- Retina is normal by report
- Referred to rule out cancer-associated retinopathy

- 20/40 vision
- Small-angle esotropia
- Retina and multimodal imaging WNL
38yo female

- Recent worsening vision; no improvement with manifest refraction (20/40)
- History of treatment for breast cancer
- Retina is normal by report
- Referred to rule out cancer-associated retinopathy

- 20/40 vision
- Small-angle esotropia
- Retina and multimodal imaging WNL
- CycloRNS +4.00

- Given glasses; becomes much more comfortable and eyes straighten
Latent hyperopia

Hyperopia that is 'masked' by chronic accommodation difficult to relax

Can be accompanied by esodeviation

Tends to be symptomatic at near, especially in pre-presbyopia

“Decreased vision noted in school, maculopathy noted”
5yo male

- Decreased vision noted over last year in school
- 20/60, 20/150
- Maculopathy
- CycloRNS: no significant refractive error
Both eyes similar

Isolated rod response

Mixed rod-cone response

Cone response

Cone 30 Hertz flicker response

Normal individual
Neuronal ceroid lipofuscinosis (“Batten disease”)  

A group of storage diseases characterized by progressive neuronal loss in the cerebrum, cerebellum, and retina  

At least 14 subtypes  

CLN3-NCL is the most common & starts with visual loss (juvenile form)  

- A 1.02kb deletion is recurrent in Northern Europeans  
- Visual impairment noted typically 5-6 years old  
  - Rapid deterioration  
  - Bullseye maculopathy sometimes present  
  - ffERG electronegative before non-recordable  

After visual loss noted: progressive dementia, ataxia, extrapyramidal signs, seizures, loss of independent function, & premature death  

- Moody behavior and nightmares are early psychosocial signs  

“Photophobia and worsening vision”
36yo female

- Severe frontal headache x 3 years
- Worsening vision
- Photophobia at times
- Nystagmus since childhood
- M +3.50-1.25 x 180: 20/50 by report
- Eye exam, OCT, MRI: normal by report

- Examination: small angle ET; pendular nystagmus; no AHP
- Posterior segment images...
36yo female

- Small-angle ET, pendular nystagmus; no AHP
- Ring of hypopigmentation around lens edge; no iris transillumination
- CycloRNS: +5.75-1.50x013, +6.75-2.00x153
- Hypopigmented fundus with dysplastic discs
- Slightly hypoplastic fovea
- Is less pigmented than siblings

- Given full hyperopic correction with daily cycloplegic x 5 days; becomes much more comfortable
Latent hyperopia

Hyperopia that is 'masked' by chronic accommodation difficult to relax

Can be accompanied by esodeviation

Tends to be symptomatic at near, especially in pre-presbyopia

Albinism

Phenotypic and genetic heterogeneity
milder cases underdiagnosed

Ocular (Nettleship-Falls) or oculocutaneous

Often dysplastic discs, large angle kappa

Sun protection, refraction, surgery for AHP/strabismus, rule out syndromic disease (Hermansky-Pudlak, Chediak-Higashi)

“Idiopathic macular dystrophy referred for further evaluation”
15yo female

- Referred for “macular dystrophy” 2\textsuperscript{nd} opinion
- Per report: 20/100 OU (-5.00-3.00\times180 OU), macular changes only, normal ERG
- Prior gene panel for macular dystrophy – negative

- Examination confirms vision, refraction, and maculopathy on fundus exam
Both eyes similar

Isolated rod response

Mixed rod-cone response

Cone response

Cone 30 Hertz flicker response

Normal individual
15yo female

- Gene panel did not include *KCNV2*
- Called lab – tested *KCNV2* from sample already taken
- Common homozygous mutation in *KCNV2* confirmed: c.427G>T (p.Glu143*)
Cone-rod dystrophy with supranormal rod response

**Childhood sign/symptoms**
- congenital or acquired poor vision; nystagmus (often with head shaking) - often improves; photophobia

**Retinal appearance**
- normal in early childhood; macular changes with time

**ffERG**
- cone-rod dysfunction with (supra)normal rod response, pathognomonic

**Genetics**
- specific for biallelic pathogenic variants in *KCNV2*

“8yo girl with 2 retinal dystrophies referred for second opinion”
8yo girl with “2 retinal dystrophies” referred for 2\textsuperscript{nd} opinion

- Poor vision and nystagmus since 2yrs old. Father was told would worsen with time. But the father noted improvement with time & thus came for 2\textsuperscript{nd} opinion.
- Parents 1\textsuperscript{st} cousins; no one in family known to have retinal disease
- An NGS gene panel test reported homozygous recessive mutations in 2 different Leber congenital amaurosis genes - \textit{CRB1} and \textit{AIPL1} - both of which were missense & considered pathogenic
- Va 20/200 and RNS -3.00

\begin{itemize}
  \item Rod-specific (scotopic)
  \item Cone-specific (photopic flicker)
  \item Combined (scotopic flash)
\end{itemize}

Both eyes similar
8yo girl with “2 retinal dystrophies” referred for 2nd opinion

- Lab contacted - KCNV2 was not on the NGS panel
- KCNV2 sequencing revealed well-known homozygous nonsense pathogenic variant c.427G>T (p.Glu143*)
- Previously reported homozygous missense variants reported in CRB1 and AIPL1 were not pathogenic variants
- This case shows the importance of careful clinical examination in guiding/interpreting molecular genetic testing
Cone-rod dystrophy with supranormal rod response

**Childhood sign/symptoms**
- congenital or acquired poor vision; nystagmus (often with head shaking) - often improves; photophobia

**Retinal appearance**
- normal in early childhood; macular changes with time

**ffERG**
- cone-rod dysfunction with (supra)normal rod response, pathognomonic

**Genetics**
- specific for bialleic pathogenic variants in *KCNV2*

“ffERG-only request for child with retinal dystrophy”
7yo girl

- Diagnosed with retinal dystrophy soon after birth
- Longstanding nystagmus and low vision
- History of patching left eye
- No night/day difference in vision

- 20/600, 20/70
- Wandering eye movements
- CycloRNS: -3.25-3.75x087, -2.25-1.75x015
Optic nerve hypoplasia

Decreased number of ganglion cell axons

Visual acuity ranges from normal to LP

Can be missed if “double ring sign”

Disc diameter compared to temporal disc to fovea distance can be useful

Isolated or associated with midline defects
“Known retinal dystrophy – wants to follow with new provider”
6yo boy

- Decreased vision
- Diagnosed with retinal dystrophy (photoreceptor degeneration)
  - older brother with genetically-confirmed CRB1-retinopathy
- Diagnosed with traumatic cataract/retinal detachment few years prior

- NLP, 20/60 (+4.25-2.00x18)
- OD: cataract and retinal detachment by ultrasound
splitting of retinal layers and secondary photoreceptor degeneration

almost exclusively males

complete penetrance but variable expressivity

foveal more than peripheral schisis

ffERG: variable dysfunction with electronegative waveform

hemizygous RS1 mutation

ffERG summary

- ffERG is time-consuming to perform, requires skill to perform, and needs careful interpretation.

- ffERG cannot be interpreted without a good clinical exam and specific clinical question (a good ophthalmologist is better than excellent electrophysiology).

- ffERG indications include:
  1) suspicious pigmentary/ changes (for panretinal disease)
  2) maculopathy (for isolated macular or panretinal involvement)
  3) non-traumatic optic nerve pallor, particularly in children
  4) unexplained abnormal vision & infantile nystagmus (not Va)
  5) quantitating/monitoring pan-retinal function
ffERG – when do we need it?

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