The Essence of Fundus Autofluorescence in Hereditary and Acquired Retinal Disease

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I. Principles of Fundus Autofluorescence

a. Definitions
   i. An imaging technique that uses a bandpass filter from 535 to 580 nm for excitation and a bandpass filter of 615 nm to 715 nm as a barrier filter to image lipofuscin distribution in the RPE

b. Normal fundus autofluorescence
   i. Uniformity of autofluorescence (isoautofluorescence) throughout the entire fundus except for the optic nerve head, retinal blood vessels and macula.
   ii. Optic nerve head is dark (hypoautofluorescent) due to absence of the RPE and lipofuscin
   iii. Blood vessels are dark (hypoautofluorescent) due to absorption from blood
   iv. Foveal signal is reduced due to absorption by the luteal pigment (lutein and zeazanthin)
   v. Parafoveal signal is greater than the fovea but still slightly less than the rest of the retina likely due to the presence of increased melanin deposition and lower density of lipofuscin

c. Abnormal Patterns in Hereditary Retinal Disease
   i. Hyperautofluorescence
      1. Marks lipofuscin accumulation
      2. Sign of stressed, metabolically active photoreceptor and RPE cells
   ii. Hypoautofluorescence
      1. Sign of photoreceptor and RPE degeneration/death

II. Current Clinical Applications of Fundus Autofluorescence in Hereditary Retinal Disease

a. Identification of disease
   i. “normal” ophthalmoscopy

b. Monitoring of disease progression
   i. Changes in autofluorescent patterns over time

c. Identification of specific patterns of autofluorescence in specific diseases
   i. Macular involvement
   ii. Posterior pole abnormalities
iii. Mid and Far Peripheral Abnormalities

III. Fundus Autofluorescence (AF) Findings in Hereditary Retinal Diseases

a. Retinitis Pigmentosa

   i. A heterogeneous group of complex retinal degenerations that affect the rods initially and then the cones
   ii. Mutations have been identified on a number of genes, mostly RHO (Rhodopsin) in dominant RP, over 60 genes in recessive RP and primarily RPGR in sex-linked RP.
   iii. Some forms are severely progressive and others are mildly progressive
   iv. Attenuated arterioles in the affected retina is the most consistent finding
   v. Types of retinitis pigmentosa

   1. Diffuse retinitis pigmentosa
      a. Bull’s Eye Ring abnormalities around the macula
         i. A large ring signifies early disease
         ii. A small ring signifies more advanced disease
      b. Hyperfluorescent abnormalities
         i. Signify borders of stressed photoreceptors and RPE cells that have increased metabolic activity.
      c. Hypofluorescent abnormalities
         i. Signify areas of degenerated outer retina
      d. Comparison of fundus photography and fundus autofluorescent images
         i. Dissociation of color fundus photos and fundus autofluorescence
         ii. More abnormalities are evident in fundus autofluorescent images

   2. Peripapillary/Pericentral retinitis pigmentosa
      a. A pericentral ring along the arcades and peripapillary region are affected

      b. Hyperautofluorescent abnormalities
         i. At the edge of the affected areas
         ii. Bull’s eye macular hyperautofluorescent ring
      c. Hypoautofluorescent abnormalities
i. In affected areas, representing photoreceptor and RPE degeneration
d. Comparison of fundus photography and fundus autofluorescent images

3. Sector retinitis pigmentosa
   a. Specific sectors of the retina are affected
      i. Typically inferior
      ii. The remainder of the retina appears normal
   b. Autofluorescent Abnormalities
      i. Hyperautofluorescent abnormalities
         1. Hyperfluorescence at the edge of the affected area with hypofluorescence
      ii. Hypofluorescent abnormalities
         1. Hypoautofluorescence in degenerated areas but the rest of the retina remains intact
   c. Comparison of fundus photography and fundus autofluorescent images
      i. Autofluorescent abnormalities are greater than abnormalities seen on ophthalmoscopy and fundus photography, especially in areas mildly affected by disease

4. Retinitis Punctata Albescens
   a. RP with scattered diffuse white spots
      i. Autofluorescent abnormalities
         1. Hyperautofluorescent ring in the macula
         2. Diffuse uniform areas of hypoautofluorescence in the periphery
   b. Cone and Cone Rod Dystrophy
      a. Hyperautofluorescent central and peripheral abnormalities
      b. Seen at the edges of macular lesions marking metabolically active, stressed cells
      c. ‘Bull’s eye hyperautofluorescence signifying rod component of disease
      d. Central hyperautofluorescence signifying loss of foveal cones
      ii. Hypoautofluorescent abnormalities
1. May be scattered areas in the periphery as the cone dystrophy progresses to a cone-rod dystrophy

iii. Comparison of fundus photography and fundus autofluorescent images

c. Stargardt’s Disease

i. A recessive form of macular degeneration that typically has its onset in the early teens but as early as age 4

ii. May be associated with fundus flavimaculatus flecks
   1. Pisciform or fish-tailed shape
   2. Can progress outward from the macula over time

iii. The disease is caused by mutations on the ABCA4 gene on chromosome 1.
   1. Three types have been identified that mirror autofluorescent abnormalities
      a. Type I: Normal ERG
         i. Minimal central areas of hypoautofluorescence confined to the macula
      b. Type II: Abnormal photopic ERG
         i. More extensive areas of central hypoautofluorescence
      c. Type III: Abnormal photopic and scotopic ERG
         i. More peripheral hypoautofluorescence in addition to the central areas of hypoautofluorescence

iv. Hyperfluorescent abnormalities
   1. Fundus flavimaculatus flecks are composed of lipofuscin and hyperautofluorescence; may hypoautofluoresce around the edges as outer retinal cells degenerate

v. Hypofluorescent abnormalities
   1. Typically seen in the macula, representing outer cell degeneration which explains the reduced visual acuity

vi. Comparison of fundus photography and fundus autofluorescent images
   1. Areas that appear normal on ophthalmoscopy and mildly affected by disease may show hyperautofluorescence or hypoautofluorescence.
d. Best’s Vitelliform Disease

i. An autosomal dominant disease that affects the retinal pigment epithelium
ii. Is caused by mutations in the bestrophin gene responsible for lipofuscin metabolism
iii. Is characterized by different stages
   1. Vitelliform lesion (Egg-yolk) stage
      a. Composed of lipofuscin
      b. Normal visual acuity
   2. Scrambled egg stage
      a. Breakup of lipofuscin leads to breaks in Bruch’s membrane
         i. Risk of development of CNV
            1. Hemorrhage
            2. Exudation
            3. Serous detachment
iv. Autofluorescent abnormalities
   1. Hyperautofluorescent abnormalities
      a. Vitelliform lesion will uniformly hyperautofluoresce
      b. Sacttered lipofuscin will hyperautofluoresce as the vitelliform lesion breaks up
   2. Hypoautofluorescent abnormalities
      a. Degeneration of photoreceptors and RPE as lesion deteriorates
      b. Retinal hemorrhage and disciform scar from CNV lesions will block underlying autofluorescence
v. Comparison of fundus photography and fundus autofluorescent images

IV. AF findings in Acquired Retinal Disease and Congenital (but not hereditary) Retinal Disorders

i. Ophthalmic artery occlusions
   1. Pattern of hypo and hyperautofluorescence and how it differs from the patterns seen in hereditary disease
   2. Note that CRA occlusions do not affect AF but ophthalmic artery occlusions typically do (because the CRA does not supply the RPE)
   3. Case presentation
ii. Central serous retinopathy-wide spectrum of AF findings from completely normal to profound AF abnormalities

1. Acute Disease
   a. Pattern of hypo and hyperautofluorescence and how it differs from the patterns seen in hereditary disease
   b. Case presentation

2. Chronic Disease
   a. Pattern of hypo and hyperautofluorescence and how it differs from the patterns seen in hereditary disease
   b. Large descending tracks of both hyper AF and hypo AF are common
   c. Case presentation

iii. Age-related macular degeneration

1. Pattern of hypo and hyperautofluorescence and how it differs from the patterns seen in hereditary disease
   a. Drusen
   b. Geographic AMD
   c. Exudative- Wet- AMD
   d. Comparison with OCT
   e. RPE rips in wet AMD reveal hyper AF at “rolled” RPE edge

2. Case presentations

iv. Toxoplasmosis

1. Clinical characteristics
2. Patterns of hypo and hyperautofluorescence and how it differs from the patterns seen in hereditary disease
3. Old lesions surrounded by hyper AF rings suggest new activity and need to followed carefully or treated
4. Comparison with SD OCT quite useful
5. 3 mirror lens exams may reveal vitritis and supports activity
6. Case presentation

v. Histoplasmosis

1. Clinical characteristics
2. Patterns of hypo and hyperautofluorescence and how it differs from the patterns seen in hereditary disease
3. Peripapillary AF is usually hypo but hyper AF may indicate recent activity
4. Case presentation

vi. AZOOR and MEWDS

1. Clinical characteristics
2. Patterns of hypo and hyperautofluorescence and how it differs from the patterns seen in hereditary disease
3. In most disorders, hyper AF is encountered first and may become hypo AF when the RPE dies
4. In AZOOR, large changes in AF may occur in 4-8 wks and hence questionable cases of activity should be followed carefully
5. Treatment in AZOOR with Imuran should be considered if the macula is threatened
6. Comparison with SD OCT quite helpful
7. MEWDS is nearly always self-limited- lesions may increase in number for the first month and then typically fade-
8. As in nearly all conditions, hyper AF precedes hypo AF
9. Case presentations

vii. Harada’s Disease

1. Clinical characteristics
2. Patterns of hypo and hyperautofluorescence and how it differs from the patterns seen in hereditary disease
3. Hypo AF alone suggests dead RPE and no activity
4. In contrast, hyper AF indicates metabolically sick RPE and treatment with steroids PO may be indicated
5. Case presentation

viii. White fundus lesions

1. Solitary Idiopathic Choroiditis- typically hyper AF
2. Osseous Choristoma
3. Scleral choroidal calcification
4. Patterns and how they differ from hereditary degens

ix. Dark fundus lesions

1. CHRPE – virtually always hypo AF
2. Choroidal nevus- essentially always disappears with AF- iso
3. Malignant melanoma –
4. Above lesions essentially never show symmetry between eyes as do hereditary retinal degenerations
x. Angioid streaks and other cracks in Brooks membrane
   1. Streaks radiate from disc and also surround disc
   2. older cracks typically are hypo AF
   3. newer streaks are generally hyper A
   4. some symmetry between eyes but not mirror images
   5. some streaks are completely invisible to ophthalmoscopy

V. Summary and Conclusions

   a. Hereditary Retinal Degenerations are often quite symmetrical OD/OS
   b. Lesions due to any etiology are sometimes invisible to ophthalmoscopy
   c. Comparing and contrasting SD OCT findings and AF images very helpful
   d. Remember that some AF abnormalities are invisible to BIO as well
   e. Although AF is not the standard of care at the present time, it may be soon.