The Essence of Fundus Autofluorescence in Hereditary Retinal Disease

Sherry J. Bass, OD, FAAO

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 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. Leber Congenital Amaurosis
      i. Severely reduced vision from birth with nystagmus
      ii. Flat ERG from birth
      iii. Fundus can look like anything
      iv. Fundus autofluorescence demonstrates diffuse hypoautofluorescence including the macula.
   c. Cone and Cone Rod Dystrophy
      i. Hyperautofluorescent abnormalities
         1. Seen at the edges of macular lesions marking metabolically active, stressed cells
      ii. Hypoautofluorescent abnormalities
         1. Seen in the macula
2. 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

d. Stargardt’s Disease

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

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 combined 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 hyperautofluoresce; 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 hypofluorescence.

e. 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. Scattered 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. Future role of fundus autofluorescence imaging in hereditary retinal disease
   i. Management
      1. Identification of predictive markers for determination of disease progression
   ii. Clinical trials
      1. Documentation of the effect of drugs and intravitreal injections as the future of treatment for these diseases evolves
   iii. Phenotype-genotype correlations
      1. Better demonstration of fundus abnormalities than ophthalmoscopy and color fundus photography
      2. Better correlation of the specific mutations with disease characteristics and fundus picture