Imaging Modalities in Inherited Retinal Disorders

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ABSTRACT

Purpose/Relevance: With the advent and refinement of retinal imaging modalities, information has accumulated on specific features of many retinal dystrophies. Some findings are nearly pathognomonic and helpful in the diagnosis, management and guidance of molecular genetic testing while others are useful in establishing a baseline of information about the patient for future comparison. As new therapies are developed in the treatment of retinal dystrophies, precise molecular diagnosis and detailed clinical documentation of findings are critical in patient management.

Target Audience: Pediatric ophthalmologists, general ophthalmologists, researchers.

Current Outcomes: Pediatric ophthalmologists in private practice and those in small groups currently refer patients with retinal dystrophies to specialized clinics. They need to be familiar with the imaging features of such patients and be ready to participate in their follow-up as treatments emerge. Proper diagnosis leads to improved care and counseling of patients.

Results: At the conclusion of this presentation, attendees will be able to: (1) recognize specific imaging features of several retinal dystrophies of childhood such as some types of LCA, retinoschisis and Goldmann-Favre disease, and Stargardt disease; (2) incorporate OCT, fundus autofluorescence, and other imaging modalities into their practice, interpret the results of these tests and use them in the diagnosis and management of patients with retinal dystrophies.

Summary: We will cover the general principles of OCT and fundus autofluorescence and provide several examples of childhood retinal dystrophies. We will present cases with retinal cysts and give their differential diagnosis and possible treatment. We will give guidelines for the use of imaging studies in guiding molecular testing.
Optical Computed Tomography in Retinal Dystrophies
Daniel Chung
Pediatric Retinal Dystrophies and their Characteristic Findings in Spectral-Domain Optical Coherence Tomography (SD-OCT)

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• No disclosures to report

Optical Coherence Tomography

• Non-contact imaging system similar to ultrasound and MRI.
• Reflected light is used to produce detailed cross-sectional and 3D images of the eye.
• An early version, time-domain OCT (TD-OCT), uses a moving reference mirror for measuring the time it takes for light to be reflected.
• Mechanical process limits both the amount of data that can be captured as well as image quality.
• Approximately 400 axial scans, or A-scans, per second.
Optical Coherence Tomography

• The newer Spectral (or Fourier)-domain OCT (SD-OCT) uses a significantly faster, non-mechanical technology.
• Simultaneously measures multiple wavelengths of reflected light across a spectrum
• SD-OCT 100 times faster than TD-OCT and acquires 40,000 A-scans per second.
• Higher resolution and a better chance of observing disease.

Giani et al., 2009
Pediatric Inherited Retinal Degenerative Disease

• About 200,000 individuals with inherited retinal degenerative disease in the US (Daiger, 2002)
• Significant forms of early childhood retinal degenerative disease
  – Stargardt Disease
  – Retinitis pigmentosa
  – Leber Congenital Amaurosis
  – Choroideremia

Stargardt Disease

• 25,000 affected in US
• 1 in 10,000-20,000 children affected
• Most common inherited childhood maculopathy
• Autosomal recessive
• ABCA4 gene
• Central visual defect with progressive vision loss (plateau 20/200-20/400)
• No Treatment

Stargardt Disease

Unaffected

Affected
Stargardt Disease

- 14 y.o. female, Va 20/125
- White arrows: Loss of ONL
- Loss of FAF in macula

Stargardt Disease

- 12 y.o. male
- Va 20/80

Retinitis Pigmentosa

- Refers to a heterogeneous group of inherited diseases causing retinal degeneration.
- Prevalence 1 in 4000-5000 in the US
- Autosomal Dominant, Recessive and X-linked, most common is simplex cases
- X-linked earlier onset and more progressive
- Onset commonly before 20 y.o. of age, maintains central vision late in disease
- No current treatments
Retinitis Pigmentosa

- Non-Syndromic
  - Over 60 different genes and hundreds of mutations
- Syndromic:
  - Usher (RP and neurosensory deafness)
  - BBS (multiple other organ involvement, developmental delay)
  - Joubert Disease (RP with kidney, neurological pathology)

Retinitis Pigmentosa

- Rod photoreceptor apoptosis initially
- Nyctalopia, night blindness
- Peripheral field loss
- Fundus:
  - Attenuated retinal vessels
  - Optic nerve pallor
  - Bone spicules
  - Retinal cysts

Retinitis Pigmentosa

- 14 y.o. Male ADRP
- 12 y.o. male XLRP
- 12 y.o. female ADRP with cysts
Choroideremia

- Deletion of Rab escort protein (REP-1)
- Prevalence 1:50,000
- X-linked inheritance
- Nyctalopia first sign in childhood
- Effects choriocapillaris, RPE, photoreceptors
- Classic fundus findings of patchy areas of chorioretinal degeneration beginning in the mid-periphery.

Choroideremia

Choroideremia

19 y. o. Male
Choroideremia

- Carrier
- Affected

Leber Congenital Amaurosis

- 1 in 40,000 - 80,000
- Autosomal recessive
- Early-onset childhood Severe retinal dystrophy
- Hypermetropia/myopia
- Sluggish pupillary response
- Non-recordable ERG
- Nystagmus
- At least 14 known genes

Leber Congenital Amaurosis (LCA)

- Rare autosomal recessive disease (3000 in USA)
- Early onset retinal degeneration
  - blindness, abnormal eye movements in infancy & early childhood, diminished ERGs
- No treatment (currently in gene therapy clinical trials)
- Many cases of LCA are caused by mutations in RPE65

[Patient #8 in the CHOP-Penn Study]

Non-recordable ERG
Retinal Pigment Epithelium Protein 65 (RPE65)
LCA (LCA2)

- Good to fair vision until 2nd decade
- Normal looking fundus
- Night blindness

Stone, AJO, 2007

Leber Congenital Amaurosis

26 y.o. male RPE65

27 y.o. female RPE65

Areas of Autofluorescence correspond to areas of visual field, and retained retinal structure as seen on SD-OCT
Summary

• SD-OCT imaging provides for highly detailed structural analysis of the retina
• SD-OCT provide for a expeditious and non-contact method for disease progression analysis of inherited retinal degenerative disease
Macular Cysts in Retinal Dystrophies
Alex V. Levin
Macular cysts in retinal dystrophy
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Introduction
Cystoid macular edema (CME) has been reported to occur in 3–25% of patients with retinitis pigmentosa [1–5]. CME in retinitis pigmentosa is believed to occur because of leakage of fluid through the retinal pigment epithelium (RPE) consequent to failure of the RPE pump, or secondary to changes at the vitreo-retinal interface, such as vitreous traction and preretinal membranes [1,6]. The edema may also develop consequent to a nonimmune response to toxic products liberated by the degenerating retina [7]. The clinical diagnosis of CME is made based on the characteristic findings on ophthalmoscopy and a typical pattern of late hyperfluorescence on intravenous fluorescein angiography (IVFA). Optical coherence tomography (OCT) is helpful in identifying the changes of CME [2]. Some patients with retinal dystrophies who have cystic lesions on OCT demonstrate absent or minimal dye accumulation on IVFA [2,3,8,9]. Studies have also shown lack of correlation between intensity of fluorescence on IVFA and foveal thickness as measured by OCT in these eyes [2,8,10,11]. These cysts may be termed as non-CME macular cysts.

Cystoid macular edema
A blood–retinal barrier normally keeps extracellular fluid out of the retina, and is composed of tight junctions between retinal vascular endothelial cells (inner blood–retinal barrier) and the RPE cells (outer blood–retinal barrier). The cells of the RPE not only maintain an anatomical barrier between the chorioid and the retina, but also keep the extracellular fluid out of the retina through an energy-dependent RPE pump [12]. The fluid from the choriocapillaries travels across the RPE and collects in the outer plexiform (Henle’s) layer of the macula which is comprised of synapses between the pedicles of the photoreceptor cells and the surface of the horizontal cells in the inner nuclear layer. This accumulation is facilitated by the presence of loose intercellular

Purpose of review
To describe the entity of macular cysts in retinal dystrophy, differentiate it from cystoid macular edema (CME), and review the role of carbonic anhydrase inhibitors in management.

Recent findings
Macular cysts in retinal dystrophy are seen in retinopathies caused by mutations in the \textit{NR2E3} gene, juvenile X-linked retinoschisis (XLRS), and some other retinal dystrophies. These must be distinguished from CME. Optical coherence tomography can clearly demonstrate intraretinal cysts which may not be clinically detectable. Intravenous fluorescein angiography (IVFA) does not show macular hyperfluorescence (i.e. leakage). Molecular genetic testing aids in the diagnosis and elucidation of pathophysiology. Carbonic anhydrase inhibitors may promote resolution of the cysts resulting in visual improvement.

Summary
Non-CME macular cysts in retinal dystrophies can be differentiated from CME by a combination of clinical examination, IVFA, and molecular genetic testing to identify causative phenotype. Carbonic anhydrase inhibitors may be effective in promoting resolution.

Keywords
carbonic anhydrase inhibitors, fluorescein angiography, macular cyst, \textit{NR2E3} retinopathy, retinal dystrophy, \textit{X-linked retinoschisis}

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connections and the absence of Muller cells in the macula, and is in contrast to CME in which fluid leaking from retinal capillaries accumulates predominantly in the inner nuclear layers [13]. The anatomical configuration of the Henle’s layer gives rise to the characteristic radially orientated, ovoid spaces on ophthalmoscopy. Additional features of CME on ophthalmoscopy include altered macular reflex and diminished foveal light reflex [14].

**Optical coherence tomography**

OCT is a noninvasive imaging modality that provides a cross-sectional image of the retina [15,16]. The cystoid spaces because of CME appear as hyporeflective (black) spaces, interspersed with high-signal septae which represent bridging retinal elements [15]. In retinitis pigmentosa, these cystic spaces are located mostly in the outer plexiform layer. There is loss of the normal foveal depression or concavity, and with increasing severity, the foveal contour becomes convex and dome-shaped (Fig. 1). OCT is a very sensitive tool for detecting CME and has been shown to demonstrate cystoid lesions in 25% eyes with retinitis pigmentosa which appear to have a normal morphology by ophthalmoscopy and contact lens biomicroscopic examination [2].

**Intravenous fluorescein angiography**

Leakage of fluorescein in eyes with CME results in characteristic patterns of hyperfluorescence in the macula. Diffuse, petalloid, or honeycomb patterns have been described in CME consequent to pooling of dye in the cystoid spaces (Fig. 2) [17]. The amount of fluorescein leakage depends on the extent of dysfunction in the blood–retinal barrier, and the degree of CME can be graded by the intensity of dye leakage on IVFA [18].

**Key points**

- Macular cysts in retinal dystrophy are not always due to cystoid macular edema.
- They may be seen in retinopathies caused by mutations in the NR2E3 gene, juvenile X-linked retinoschisis (XLRS) and some other retinal dystrophies.
- These non-CME macular cysts do not leak on intravenous fluorescein angiography.
- Carbonic anhydrase inhibitors may be effective in promoting resolution.

**Macular cysts (non-cystoid macular edema cysts)**

Macular cysts in retinal dystrophies may also develop because of tissue loss secondary to disruption of retinal architecture in the macular region. The normal appearance of the macula on angiography in patients with these lesions suggests that vascular leakage plays a minor role, if any, in their development. The macular region has a predilection to develop these changes because of its unique structural features that includes the absence of multiple supportive retinal layers [19].

**Discordance between findings on optical coherence tomography and intravenous fluorescein angiography**

Several authors have reported a discordance between findings on OCT and IVFA in some eyes with retinitis pigmentosa and macular cysts. OCT shows the presence of...
of cystoid lesions in the macula, but there is little or no dye accumulation on IVFA [2,3,8,9]. This has led the authors to propose that OCT is a better tool than IVFA for diagnosing and monitoring cystoid maculopathy in patients with retinal dystrophy [10]. Upon studying the characteristics of such cysts on OCT, Hirakawa et al. [2] reported that the intraretinal cystoid lesions in these eyes were as prominent as those with intense dye accumulation in the angiogram, but noted that these lesions had symmetric patterns both horizontally and vertically (unlike eyes with CME which often showed asymmetry of the cystoid lesions in the horizontal and vertical sections) and were located centrally in the OCT images.

A discrepancy has also been noted between findings on OCT and visual acuity in some patients with retinal dystrophy and macular cysts [2]. Best-corrected visual acuity could not be predicted from neurosensory retinal thickness at the fovea in these patients. This was in contrast to eyes with macular edema because of vascular causes like diabetic retinopathy which showed a good correlation between thickness of the neurosensory retina at the center of the fovea and best-corrected visual acuity [20].

**Juvenile X-linked retinoschisis**

XLRS is a leading cause of juvenile macular degeneration in men. Affected patients present between 5 and 10 years of age with decreased visual acuity [21]. XLRS develops because of the loss of function mutations in the RS1 gene on Xp22. RS1 encodes the protein retinoschisin, which has a highly conserved discoidin domain and is involved in cell–cell interaction [22]. Impaired cellular adhesion consequent to RS1 mutations leads to splitting of the retinal layers and bilateral macular cysts and peripheral schisis. Complications include vitreous hemorrhage, retinal detachment, and neovascular glaucoma [23]. XLRS exhibits considerable phenotypic variability even among those with the same mutation, and no correlation has been identified between the mutation type and disease severity or progression [24].

The macular cysts of XLRS have a characteristic cart–wheel pattern on ophthalmoscopy (Fig. 3a), and are associated with peripheral retinal lesions, alterations of the vitreous gel and a negative electroretinogram. The macular appearance is often best appreciated clinically with red-free lighting. Histopathological findings include splitting of inner retinal layers, and deposition of amorphous material within the cystic areas, along with photoreceptor and outer nuclear layer degeneration, and thinning of the ganglion cell layers [25].

High-speed, high-resolution, Fourier domain OCT in patients with retinoschisis revealed schisis cavities involving the outer and inner plexiform layers of the retina, disrupting the photoreceptor inner and outer segment layers, and occupying the entire foveo-macular region. Vertical hyperreflective columns often traverse across and bridge the cavities (Fig. 3b). Progressive changes in retinal morphology have been noted with OCT in older patients with XLRS, including coalescence of cystic changes, flattening of schisis cavities, and disappearance of tissue pillars [26–28]. Morphological changes within the foveal photoreceptors that correlate with age but not with visual acuity or genotypic variation have been documented [27,29] In XLRS, IVFA does not show dye leakage.

**NR2E3 retinopathy**

A group of autosomal recessive retinal dystrophies including the enhanced S-cone syndrome (ESCS), Goldmann–Favre syndrome (GFS), and clumped pigmented retinal...
dystrophy (CPRD) are attributed to mutations in the \(NR2E3\) gene on chromosome 15q23 [30]. Macular schisis with decreased visual acuity is a common feature in all these disorders (Fig. 4a) [31]. Additional features include degenerative vitreous changes; a liquefied vitreous cavity; preretinal band-shaped structures (veils); peripheral retinoschisis and round, irregular pigment clumps in the mid-peripheral fundus in patients with GFS [32]; nummular, pigment clumps deep to the neurosensory retina in the mid-peripheral fundus in CPRD [33]; electroretinographic abnormalities characterized by undetectable rod-specific ERG, a large but delayed photopic response, and relative hypersensitivity of the S (short wavelength or blue) cones on spectral electroretinography in ESCS [34,35]. A marked phenotypic heterogeneity has been reported and fundus examination in patients with mutations in the \(NR2E3\) gene may at times be normal [34]. Histopathological studies have shown groups of abnormal RPE cells laden with melanin granules and extensive photoreceptor degeneration in eyes with CPRD [33], and greater number of S-cone photoreceptors in eyes with ESCS [36].

The \(NR2E3\) gene, also called photoreceptor-specific nuclear receptor (PNR), encodes a ligand-dependent transcription factor involved in the signaling pathway regulating photoreceptor cell differentiation and/or maintenance [37,38]. Mutations in the \(NR2E3\) gene are believed to result in abnormally differentiated rods that have features of cones (hybrid cells) with a disproportionate increase in the number of S-cones [36,39]. It has been postulated that the hybrid rod–cone cells seen in patients with \(NR2E3\) mutations may be unable to form efficient tight junctions, compromising retinal structural integrity and leading to development of macular schisis [38]. Disorganization of the retinal lamination with densely packed cones intermixed with inner retinal neurons has been reported in these patients [36,40–42].

OCT demonstrates schisis cavities of varying sizes involving primarily the outer retinal layers of the neurosensory retina (Fig. 4b) [43]. Employing spectral domain OCT and microperimetry, Sohn et al. [38] proposed a three-stage disease evolution in patients with ESCS, with early onset of peripheral retinal degeneration, followed by a second phase heralded by development of macular cysts and reduction of central visual acuity in young adulthood, with a final phase marked by resolution of the cysts. The absence of schisis in some patients with \(NR2E3\)

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**Figure 4 Goldmann–Favre syndrome**

(a) Fundus photographs showing loss of macular and foveal reflex. (b) Optical coherence tomography showing macular schisis with the separation of inner and outer layers and vertical bridging columns.
retinopathy may therefore represent an evolutionary stage [44]. Rarely, cysts may have a late onset in ESCS with preservation of good visual acuity until the fourth decade [45].

Despite cystic changes in the macula documented by OCT, IVFA does not show detectable pooling or leakage of dye (Fig. 5) [42]. Fundus autofluorescence shows the absence of autofluorescence outside the vascular arcades because of loss of photoreceptors, and a ring of relatively increased autofluorescence in the transitional area between the region of absent autofluorescence and the central zone of relatively normal autofluorescence [34].

A few patients with fundus abnormalities seen in CPRD have had no detectable mutations in NR2E3. No differences in visual acuity, visual field area, and ERG amplitude were observed between these patients and those with NR2E3 mutations [30]. The likelihood of other genes responsible for the phenotype has been considered. Some patients with mutations in the CRB1 gene have clumped pigmentation, in addition to preserved paravenous RPE (PPRPE).

We have observed bilateral macular cysts in a patient with retinal dystrophy and compound heterozygous CRB1 mutations. In addition to bilateral optic nerve head drusen, PPRPE, and a diminished macular reflex, fundus examination was unremarkable. OCT showed macular cysts in both eyes. IVFA did not show any macular leakage. Evaluation of the NR2E3 gene showed no disease causing variation.

**Differential diagnoses**

Macular cysts may also be seen in other conditions. Patients usually present with visual loss, and IVFA does now show CME. The accompanying history, examination findings, and lack of supportive evidence for retinal dystrophy help in differentiating these disorders from XLRS and NR2E3 retinopathies.

**Autosomal dominant cystoid macular edema**

This entity usually has an onset in the third decade and slowly progresses. Patients present with visual loss and extensive perifoveal capillary leakage [46]. A histopathological study reported large retinal cysts in the macula, atrophy and marked disorganization of the inner nuclear layer, advanced degeneration of Müller cells with nodular aggregates of basement membrane-like material, and preretinal membrane formation. The pathologic features are different from those of macular edema caused by other disease processes [47].

**Fenestrated sheen dystrophy**

This is an extremely rare, autosomal dominant macular dystrophy characterized by the presence in the central macular zone of a golden sheen with tiny red fenestrations [48]. Perifoveal RPE defects can be visualized with fundus autofluorescence photography and OCT [49]. This condition is associated with a good prognosis for visual acuity.

**Optic nerve pits**

Two-third of patients with optic nerve pits develop macular neurosensory detachments. These macular

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**Figure 5 Goldmann–Favre syndrome**

Intravenous fluorescein angiography in the same patient as Fig. 4 showing no macular leakage.
changes may be preceded by retinal cystic degeneration. On OCT, they mimic a retinoschisis cavity with bridging retinal elements. It is believed that macular detachments in optic nerve pits develop from the preexisting schisis cavities created by fluid entering the retinal stroma from the optic pit [50].

**Pathologic myopia**

Macular cystic lesions may be seen in 8–34% eyes with high myopia. These lesions represent intraretinal cleavage, usually in a posterior staphyloma, and are most often detected in patients over 40 years old. They are believed to develop because of tractions exerted by epiretinal membranes or the posterior vitreous cortex on the retina [51]. Subretinal cavities may also be seen.

**Degenerative macular schisis**

Macular schisis in older patients might be the result of degenerative changes. In most cases, these involve the inferonasal retina in the periphery and the outer plexiform layer [52]. Inner retinal layer and foveal involvement may, however, rarely occur [53].

**Drug-induced**

About 0.67% of patients taking high doses of niacin for hyperlipidemia develop cystoid maculopathy and visual impairment. This condition is reversible and the macular cyst resolves on cessation of drug intake [54].

**Vitreomacular traction**

Macular traction because of vitreous detachment or a central epiretinal membrane may result in a macular schisis [55,56].

**Isolated foveomacular schisis**

This condition presents with a central schisis without any peripheral involvement. Electoretinography reveals normal retinal peripheral function. Most reported cases have been female patients. Isolated foveal retinoschisis has been postulated to be a form of macular dystrophy [57].

**Management**

Immunohistochemical studies have shown the presence of the enzyme carbonic anhydrase in the apical and basolateral walls of the RPE, as well as choriocapillaries [58,59]. Carbonic anhydrase is important in the regulation of fluid movement across the RPE. Inhibition of carbonic anhydrase activity by acetazolamide has been shown to increase fluid movement from the retina across the RPE to the choroid and strengthen retinal adhesiveness [58,60].

Several studies have shown that oral (acetazolamide) [6,61] as well as topical (dorzolamide hydrochloride) [62,63] carbonic anhydrase inhibitors are effective in more than 80% of patients in promoting resolution of CME in retinal dystrophy. Their use is associated with a reduction in foveal thickness on OCT with or without decreased macular leakage on angiography. One-third of patients experience subjective as well as objective improvement in visual acuity [63]; but, changes in visual acuity show poor correlation with OCT changes [63]. Recurrence of CME while patients are still on therapy and after discontinuation of therapy with acetazolamide has been noted and patients need to be monitored carefully [64]. A study comparing the effectiveness of topical and oral carbonic anhydrase inhibitor in patients with retinitis pigmentosa concluded that oral acetazolamide was more effective than dorzolamide in improving visual acuity [65].

Studies have shown that oral [66], as well as topical [67,68,69], carbonic anhydrase inhibitors are effective in patients with XLRS. Although the cystic spaces in XLRS do not contain fluid that has leaked across the blood–retinal barrier, the cavities probably contain some endogenous intraretinal fluid, and carbonic anhydrase inhibitors presumably promote resorption of this fluid. The response to dorzolamide in patients with XLRS was observed to be independent of the mechanism of retinoschisin protein dysfunction [69]. Changes in visual acuity often do not correlate with the cystic changes on OCT and appreciable improvement in the cystic changes on OCT may result in only a modest improvement in vision [67]. Recurrence after discontinuation of therapy has been noted in patients with XLRS. Acetazolamide was administered for 9 months in an 8-year-old boy with XLRS and resulted in normalization of macular anatomy and visual acuity. On cessation of therapy, however, the cysts recurred, but once again resolved after medication was restarted [66].

The efficacy of carbonic anhydrase inhibitors (CAI) in patients with NR2E3 retinopathy has not been specifically investigated, but isolated reports suggest that they might be of benefit in this subset of patients [45]. The ideal duration of therapy is currently unknown. As in CME, recurrence after discontinuation of therapy has been noted and patients need to be on therapy for a prolonged period, and weaned off therapy slowly with careful monitoring. Acute onset visual loss because of macular cyst in an adult with ESCS was successfully treated with oral carbonic anhydrase inhibitor acetazolamide. In an attempt to prevent relapse, the patient was subsequently maintained on topical dorzolamide therapy. Our experience with use of carbonic anhydrase inhibitors is that they are effective in aiding the resolution of macular cysts, with or without improvement in visual function. Oral acetazolamide appears to be more effective than dorzolamide (unpublished data). Rinaldi et al. [44] reported lack of success with use of dorzolamide in patients with GFS.
Spontaneous resolution of macular cysts has been reported, but this occurs gradually and is associated with visual decline [38,44]. Early treatment of the macular schisis with restoration of normal retinal architecture might be associated with better visual outcome because of recovery of photoreceptor function.

Conclusion

Non-CME macular cysts in retinal dystrophies are a unique entity with a genetic basis for development. Disruption of retinal architecture because of impaired cell–cell adhesion and tight junctions underlie their origin. They are difficult to differentiate from CME by clinical examination or OCT alone. IVFA is essential for accurate delineation. The efficacy of carbonic anhydrase inhibitors in treatment warrants future study.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 442).


26 Menke MN, Feke GT, Hiore T. Effect of aging on macular features of X-linked retinoschisis assessed with optical coherence tomography. Retina 2011; March 3 (Epub ahead of print).


This study describes two important characteristics of the enhanced S-cone syndrome (ESCS), namely central (macular) retinoschisis and peripheral photoreceptor loss. ESCS occurred in three clinical phases. Peripheral retinal degeneration in early childhood, followed by a second phase heralded by the development of macular schisis in young adulthood, and a final phase is marked by resolution of the schisis and return of macular thickness to normal. Retinal sensitivity (measured by microperimetry) was significantly attenuated in patients with schisis and did not recover when schisis had resolved and retinal thickness was comparable to that of controls.


This study describes spontaneous flattening of macular schisis in a patient affected by Goldmann–Favre syndrome. Like the study by Sohn et al. [38], this study highlights the evolitional stages of macular alterations in patients with NR2E3 mutations.


This study describes the acute loss of visual acuity from acute, adult-onset, asymmetric macular retinoschisis in a patient with enhanced S-cone syndrome (ESCS). It is the first study to describe the efficacy of oral carbonic anhydrase inhibitor in promoting resolution of macular schisis and improving visual acuity in ESCS. The authors report the stabilization of results with maintenance therapy with low-dose acetazolamide and topical carbonic anhydrase inhibitor.


**Fundus Autofluorescence in Pediatric Ophthalmology**
Elias I. Traboulsi

**Introduction**
Fundus autofluorescence (FAF) imaging utilizes the fluorescent properties of lipofuscin to study the health and viability of the retinal pigment epithelium/photoreceptor complex. Lipofuscin is a heterogeneous fluorescent waste material that accumulates with age in some active postmitotic cells such as cardiac myocytes, select neurons, and the RPE. RPE lipofuscin can be visualized in vivo using FAF imaging and its patterns of distribution, accumulation, or absence can be characteristic of a variety of inherited or age-related retinal disorders. This presentation will review examples of FAF in selected inherited childhood retinal disorders and its usefulness in the diagnosis and follow-up of patients.

**Physiology**
Lipofuscin is derived from phagocytosed photoreceptor outer segments and normally accumulates in the RPE. RPE lipofuscin differs from that of other cells in that it is mainly derived from chemically-modified residues of incompletely digested photoreceptor outer segments. It is composed of a mixture of lipids, proteins, and different fluorescent compounds, the main fluorophore of which is a derivative of vitamin A (retinoids). Formation of RPE lipofuscin fluorophores is almost completely dependent on a normal visual cycle, and absence of retinal (both all-trans and 11-cis) for example in RPE65-knockout mice drastically reduces its formation. Hence normal FAF reflects the anatomic integrity of RPE and photoreceptors, normal outer segment turnover, and normal vitamin A metabolism (Scholl et al., 2004).

**FAF Imaging Technology**
Fundus autofluorescence (FAF) is recorded with a confocal scanning laser ophthalmoscope. The distribution of lipofuscin in fundus RPE using FAF was described by von Ruckmann et al. In the normal fundus in subjects over the age of 15 years, they found diffuse autofluorescence with the retinal blood vessels and optic disc appearing as negative shadows. In patients with long-standing retinal atrophy, they observed absent autofluorescence that corresponded spatially to the atrophy but present fluorescence in adjacent regions of surviving retina. FAF can be visualized with other cameras such as the Topcon TRC 50IX fundus camera.

The highest degrees of fundus AF are detected in normal individuals at 7 degrees from the fovea and the lowest degrees are at the fovea (Delori et al.). Physiologically reduced FAF is observed in the absence of RPE cells (e.g., at the optic disc) or may be due to absorption of the incident short wavelength light by melanin, macular pigment, and the retinal vessels. Reduced FAF in retinal diseases may be due to a number of factors, including photoreceptor and/or RPE cell loss, disrupted phagocytosis or disruption of the retinoid cycle (Scholl et al., 2004).

**FAF in Children**
Because lipofuscin accumulates with aging, levels of autofluorescence may be low in very young children.

**Sargardt Disease (ABCA4)**
In Stargardt disease there are high levels of lipofuscin in the RPE. This results in high levels of autofluorescence on FAF imaging. As the disease progresses, patchy areas of loss of FAF are visualized and correspond to loss of retinal sensitivity reflecting photoreceptor cell death (Sunness, 2008).

**Bestrophinopathies**
In the bestrophinopathies, including Best disease, there is increased autofluorescence in the fovea and in extrafoveal lesions as a result of the accumulation of larger-than-normal levels of lipofuscin in the RPE (Lois et al. 2010). A diffuse increase in FAF is detected due to the generalized accumulation of lipofuscin in RPE cells.
Leber Congenital Amaurosis
FAF may be preserved in the presence of severe photoreceptor dysfunction, as shown by undetectable full-field ERGs (Scholl et al., 2004) and indicates structurally intact photoreceptors and preservation of the photoreceptor/RPE complex. In patient with CEP290 (NPHP5) and NPHP6 mutations, there is diffuse loss of FAF except in the foveal region in which there a preserved disc of FAF that corresponds to overlying remaining functioning cones; all rods and underlying RPE have degenerated (Cideciyan, 2011). Patients with RPE65 mutations have reduced or severely reduced levels of FAF as a result of the severely reduced levels of retinoids.

Retinitis Pigmentosa
More than half of RP patients have an abnormally high-density parafoveal FAF ring (AF ring) (Popovic et al, 2005). This AF ring represents the border between functional and dysfunctional retina (Robson et al., 2006). Aizawa et al. (2010) showed that that the size of AF ring decreased with the progression of RP. This was accompanied by a shortening of the length of the IS/OS line, a decrease in retinal sensitivity and a worsening of best-corrected visual acuity.

Fundus Albinopunctatus (RDH5, RLBP1)
In fundus albinopunctatus there are areas of increased AF of the RPE that correspond to the ophthalmoscopically visible lesions and RPE lesions on OCT images; in retinitis punctata albescens, in addition to the white lesions there is an enhanced AF ring in a parafoveal location (Genead et al. 2010). Mutations in RDH5 lead to a defect in oxidation of 11-cis-retinol into 11-cis-retinal. In the absence of this conversion, there is presumed storage of a retinoid, likely in an esterified form, within RPE cells. RLBP1 encodes the protein CRALBP, located within RPE and Müller cells, which binds to the vitamin A derivatives 11-cis-retinol and 11-cis-retinal. Impaired function of this protein could lead to the accumulation of a retinoid compound(s) within RPE cells, hence increased FAF.

Conclusions
Because of its ability to detect lipofuscin mainly at the RPE level, FAF is a useful method to assist in the diagnosis and progression of a wide variety of inherited and acquired retinal diseases even at stages in which fundus changes are not clearly evident on routine ophthalmoscopy. Normal or near-normal FAF may reflect the presence of structurally intact photoreceptors and preserved photoreceptor/RPE complex. Hence FAF imaging findings may have implications for gene and other therapies of inherited retinal disorders.

References
Fundus Autofluorescence in Pediatric Ophthalmology

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Financial Interests

• Oxford Biomedica, UK – C
• Sanofi – C,L

• No financial interests that pertain to this presentation

Definition

• FAF refers to the naturally detectable fluorescence that emanates from the RPE
• Imaging of this autofluorescence is possible using the scanning laser ophthalmoscope

Utility of FAF

• Patterns and properties of FAF are used to study the health and viability of the RPE/photoreceptor complex
• Detect abnormalities and characterize distribution of lipofuscin in inherited and acquired retinal diseases even when fundus changes are not clearly apparent on ophthalmoscopy and fluorescein angiography
• Could be used to follow the progression of disease course and response to therapies

Physiology

• Lipofuscin is derived from the phagocytosed photoreceptor outer segments and normally accumulates in the RPE
• Excessive accumulation and/or additional metabolic factors lead to toxicity and RPE death

FAF Imaging Technology

• When lipofuscin is exposed to blue light it glows or fluoresces spontaneously
• Fundus autofluorescence (FAF) is recorded with a confocal scanning blue laser ophthalmoscope in a non-invasive fashion
• Areas with normal fluorescence indicate normal accumulation of lipofuscin
• Brighter areas indicate increased accumulation and risk for future RPE death and atrophy
• Dark areas indicate absence of lipofuscin, hence of RPE cells
Uses in Pediatric Ophthalmology

- FAF is now obtained more frequently as it has become available
- Utility is being determined
- Photography does require some cooperation so FAF cannot be done in very young or non-cooperative children
- Because lipofuscin accumulates with age, levels of autofluorescence may be low in very young children

Jonathan Greenberg, MB, Laboratory of Ted Smith

Stargardt Disease

Autosomal Recessive Mutations in ABCA4

Stargardt Disease

More Advanced Stargardt Disease
Stargardt Disease

Bestrophinopathies
- Mutations in Bestphin
  - Dominant in Best disease
  - Recessive in bestrophinopathies
- Increased accumulation of lipofuscin in RPE
  - Increased FAF in vitelliform lesions
  - Horizontal level in pseudohypopyon lesions

Leber Congenital Amaurosis
- Group of autosomal recessive disorders
- More than 15 genes identified to date
- CEP 290
  - Most common in Northern Europeans
  - Preservation of central cones

Retinitis Pigmentosa

RP1
(Oxygen-regulated Photoreceptor Protein 1)

RP and CME
**Juvenile Retinoschisis**

- X-linked
- Mutations in Retinoschisin
- Petaloid pattern of FAF

**Summary**

- FAF is useful in assessing the health and viability of the RPE/photoreceptor complex
- There are characteristic patterns in inherited and acquired retinal diseases
- Could be used to follow the progression of disease course and response to therapies
- Utility in pediatric ophthalmology is being elucidated

**Thank You**