Drusen always Autofluoresce
Do they, always?
And why do they fluoresce?
How do they fluoresce?
What's autofluorescence?
AF is the best way to image ONH Drusen
Is it? What about scan?
What about buried vs surface drusen?
What's the difference?
What is AF imaging?

Optic Nerve Head Drusen are made of calcium
Are they? How do they calcify?
Where does the calcium come from
Why does calcium form in the ONH?

AF is the best way to image ONH Drusen
Is it? What about scan?
What about buried vs surface drusen?
What's the difference?
What is AF imaging?

Ocular Disorders Found by Chance in Association with Optic Disc Drusen or “What I’m Not-Going To-Talk-About....”

- Aneurysm of the ophthalmic artery
- Astrocytic hamartoma
- Atrophy gyra
gyra
- Birdshot chorioretinopathy and Cacchi-Ricci syndrome
- Congenital night blindness
- Familial macular dystrophy
- Glaucoma
- Nanophthalmos
- Peripapillary central serous retinopathy
- Pigmented paravenous retinochoroidal atrophy
- Thick cornea

“Fine if you’re the smartest person in the room, find another room....”

Michale Dell, CEO
Dell Computers

Thank you Dr. William H. Spencer, MD
Author: Ophthalmic Pathology
My lifelong teacher of Ocular Anatomy

What This 30 Minutes Covers

- Historical Background
- Definition
- Pathogenesis
- Histopathology
- Evolution
- Clinical Signs & Symptoms
- Differential Diagnosis
- Definition: Fluorescence/ Autofluorescence
- Imaging: Fundus Autofluorescence

What’s in a Word?

- The term Drusen is originally a German word, singular druse, applying to a crystal lined, hollow space in a rock (or geode) widely used in the mining industry in the 16th century
- Hyaline (“resembling glass”) body
- Drusen is more appropriate here than hyaline or colloid (Colloidkugeln, or “spheres made of colloid”) bodies sometimes preferred by science writers.

Historical Background

- The initial description of the optic disk was a histological one made by Müller in 1652, 2 years before the invention of the ophthalmoscope by Helmholtz
- The initial description of drusen of the OD was a histological one. Müller described crystalline, fatty appearing granules in the ONH 5-1000 um in size, located extra- as well as intra-cellular
- Suggestion that drusen of the disc may be the product of long term pathologic alterations in the ONH was propounded in 1962 by Seitz and Karsten and again in 1968 by Seitz
What ARE Optic Nerve Head Drusen?

- Concentrically laminated, calcified acellular basophilic concretions/ globular aggregates of varying sizes and shapes
- They are extracellular
- About 5-1000 microns in diameter- they tend to collect in 2, 3 small nodules

Chemical Composition

- Drusen contain mucopolysaccharides, aminoacids,ribonucleic, deoxyribonucleic acid, calcium, and a small amount of iron....
- Drusen are not birefringent, but do show significant autofluorescence, which is very useful for clinical diagnosis, as will be shown later.

Etiology or “Fun Facts”

- 0.4-15% of population
- 70% in both eyes
- Primarily in Caucasians, autosomal dominant inheritance
- Usually present in childhood and develop with growth
- Initially thought to be static but increasingly apparent that they evolve slowly, often requiring decades
- Usually asymptomatic: discovered during routine eye exams
- Buried vs. Superficial; +/- asymmetry
- Typically extracellular and anterior to the Lamina Cribosa
- Classified as benign, but can cause trouble later in life by compromising the nerve fiber layers and vascular supply resulting in visual field loss (65-90% chance) and disc hemorrhages

Histological vs Clinical Observations

- Drusen are often seen in histologic sections as CHANCE observations, when they were not clinically observed
- Sometimes they lie deeper in the ONH ANTERIOR to the Lamina Cribosa
- Occasionally they are more superficial and overly the disc margin where they are visibly clinically

How & Why Do They Form:
First, an Anatomy Lesson!

Anatomy Lesson of Dr. Nicolaes Tulp, Rembrandt 1632

Prelaminar
Laminar
Post Laminar
Disruption of Axoplasmotic Transport

- Disruption of transport (ortho and retrograde) leads to rupturing of the axons, allowing mitochondria into the extracellular space. Lack of lysosomal digestion of the "schmutz" backing up creates Lipofuscin (a form of molecular garbage not taken out of the system).
- Then, deposition of needle-like calcium crystals continues to be deposited in the extracellular mitochondria. Calcium is continuously deposited on the surface of these nidi (focal point of a process), forming drusen.
- Although mitochondria naturally contain calcium, axons in the RNFL must be interrupted for a long time before progressive extracellular calcium deposition occurs (this will be important later).
- When this process exceeds the limits, degenerative changes begin which in the course of many years cause axonal death.
- As a general principle, chronic alterations in axonal transport from any cause seem to produce aggregates of swollen nerve fibers which impart a yellow-white appearance to the disc tissue, and account for the yellow-filled appearance of the disc.

Calcium in the Mitochondria

- Bruch's membrane acts as a constricting mechanical barrier to axoplasmic transport.
- Anatomy
  - Limitations of the rigid scleral shell
  - Abnormal disc vasculature
- Accounts for why disc drusen are typically observed at the margins of the disc which corresponds to the histopathology.

Anatomical Contributions

- Prelaminar
  - Born with a smaller scleral canal
  - Dysplasia: underdevelopment of the ONH in the >+4D hyperope
  - Short axial length, thick sclera, narrow scleral opening. No space for the wiring
ONH Drusen: Anatomical Facts

• ALWAYS located anterior to the Lamina Cribosa and within the scleral ring
• Usually located on the nasal side of the disc
• If they are of large size and well covered by bundles of optic nerve fibers they may mimic papilledema by exam
• Eventually yellow-white glistening structures become visible which vary in number and size

Buried vs Surface Drusen

All Grown Up…..

Fully Mature ONH Drusen

• Disc can become quite elevated in adulthood, leading to confusion with papilledema
• Visible optic disk drusen indicating a late stage of development are usually associated with visual field defects due to thinning of RNFL
• The larger the drusen and the more area of the optic canal occupied by drusen, the greater the associated retinal nerve fiber layer abnormalities.
• Slow, progressive atrophy of RNFL can occur; there are reports of blindness secondary to ONH drusen

ONH Drusen vs. Papilledema

• Papilledema is also a result of chronic blockage of axoplasmotic transport
• Their similarity to familial drusen may lead to diagnostic error!
• Papilledema is a true medical emergency where ONH drusen is not…. 

What is Luminescence?

• Luminescence is emission of light by a substance not resulting from heat; it is thus a form of cold body radiation. Forms are:
  • Fluorescence: photoluminescence as a result of singlet molecule relaxation (decay of radiation in the near IR light range)
  • Autofluorescence is the natural emission of light by biological structures such as mitochondria and lysosomes when they have absorbed light

What is Fluorescence?

• The property of absorbing light of short wavelength and emitting light of longer wavelength
• The phenomenon of fluorescence occurs when a high energy photon (the basic unit of light) impacts the fluorescent material (fluorophore) and excites the electrons of atoms into a higher energy level
• During this process, the excess energy can be released as another photon that carries less energy than the one that originally impacted the fluorophore (the glow or emission)
• The most striking examples of fluorescence occur when the absorbed radiation is in the ultraviolet or near ultraviolet region of the spectrum (blue light) and thus invisible to the human eye, and the emitted light is in the visible region.
**Fluorescence: a type of light emission**

- First observed from quinine by Sir J.F.W. Herschel in 1845

**What is a Fluorophore?**

- A part of a molecule which causes that molecule to fluoresce
- This part of the molecule absorbs energy of a specific wavelength and re-emits energy at a different wavelength
- A2-E Lipofuscin granules within the cell cytoplasm are a dominant fluorophore

**What is Lipofuscin?**

- Lipofuscin is material in the lysosomal compartment of non-dividing cells that cannot be degraded, and thus, it accumulates... *Molecular poop!*
- Lipofuscin contains fluorophores that glow
- Lipofuscin is found in the retina, the liver, kidneys, heart muscle, adrenals and nerve and ganglion cells

**Lipofuscin: Wear & Tear Pigment**

- RPE Lipofuscin contains at least 10 different fluorophores
- Lipofuscin has a broad excitation and emission range with excitation spectrum ranging from 300 to 600 emission spectrum ranging from 480 to 800
- A2E is 430 nm (that's our guy!)
- Maximal emission at 600-640nm.

**About All I can Handle on E&E....**

- By applying specific filters, of at least 450 nm to the illumination light the amount of fluorescent light emitted can be maximized (excitation)
- By using observation filters (500-800 nm) the large amount of illuminating light can be filtered out and the small amount of fluorescent light made to stand out and be more easily seen.
- Since lipofuscin have background autofluorescence (AF), pathological lesions may stand out compared with normal tissue when viewed in this manner by having a different light pattern than structures without lipofuscin

**Imaging of ONH Drusen**

**Origins of FAF Imaging**

- Really came into being around 1995 with the use of laser imaging
- Improvement in imaging devices and filters prompted more investigation in this area
- CLINICALLY available around late 1990's.

**No Fluorophore- No Fluorescence**

**Filters for Autofluorescence**
The cSLO technique uses a laser with an excitation wavelength of 488 nm and a barrier filter at 500 nm or 520 nm, the same wavelengths used for fluorescein angiography.

Because of this, cSLO FAF imaging must be done before angiography if both procedures are performed with a cSLO on the same visit.

Intravenous fluorescein will compromise the effectiveness of cSLO autofluorescence.

Modern filters have an excitation filter with a band-pass range of about 520-585 nm and a barrier filter with a band-pass range of about 605-715 nm.

These proprietary filters avoid excitation of both the crystalline lens and fluorescein, improve light transmission, and reduce noise.

FAF imaging with this filter combination can also be done either before or after fluorescein angiography.

ONH drusen calcium content is highly reflective and B scan is very sensitive to them.

Most useful for buried drusen where OCT or AF cannot reach.

However at 150 micron resolution there is limited information on the exact shape, size or location of the drusen.

Observation of outer structures of optic nerve may be impeded due to shadowing from dense overlying structures and greater level of penetration.

Exact composition of buried disc drusen remains unresolved.

We need better understanding of the nature of the coalescing materials.

B scan is a complementary technology particularly when drusen are buried.

ONH drusen are not very reflective and B scan is not very sensitive to them.

Most useful for buried drusen where OCT or AF cannot reach.

However at 150 micron resolution there is limited information on the exact shape, size or location of the drusen.

ONH drusen are not very reflective and B scan is not very sensitive to them.

Most useful for buried drusen where OCT or AF cannot reach.

However at 150 micron resolution there is limited information on the exact shape, size or location of the drusen.

Thank you for inviting me to beautiful Ann Arbor!
References

- XXXIV Edward Jackson Memorial Lecture Drusen of the Optic Disc and Alloplastic Axoplasmic Transport; William H. Spencer, MD; AAO Oct 1977
- Zimmerman LE: Bilateral optic atrophy associated with drusen of optic disk.