Ocular Disease: Part I

Presented by MBKU | SCCO

Live Interactive CE Webinar | Day One | PM Session

Saturday | July 10, 2021 | 12:10 p.m. - 4:00 p.m.

Marshall B. KETCHUM UNIVERSITY
Southern California College of Optometry

Department of Continuing Education

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Ocular Disease: Part II

Marshall B. KETCHUM UNIVERSITY
Southern California College of Optometry
Department of Continuing Education

Saturday, July 10

Pacific Time Zone | Live Webinar | COPE-Approved

8:00AM - 9:50AM
Comanaging Corneal Transplants: MD & OD Perspective
Presented by Lisa Wahl, OD & Asha Balakrishman, MD

10:00AM - 10:55AM
Thyroid Eye Disease: An Update on Clinical Management and Assessment
Presented by Jessica Yuen, OD

10:55AM - 11:50AM
Marine Omega-3s in Dry Eye Disease: Uncovering the Facts, Dispelling the Myths
Presented by Mark Roark, OD

11:50AM- 12:10PM
Lunch Break

12:10PM - 1:05PM
Evidence-Based Management of Retinal Artery Occlusions
Presented by Edward Chu, OD

1:05PM - 2:00PM
Neurotropic Keratitis: Rare, or Hiding in Plain Sight?
Presented by Douglas Devries, OD

2:10PM - 3:05PM
Anterior Segment Cases: OMD vs OD
Presented by David Sendrowski, OD & John Maher, MD

3:05PM - 4:00PM
Update on Cataract Work Up and Use of Multifocal IOLs
Presented by John Maher, MD & David Sendrowski, OD

Sunday, July 11

Pacific Time Zone | Live Webinar | COPE-Approved

8:00AM - 9:50AM
Oral Pharmaceuticals in Anterior Segment Disease
Presented by Blair Lonsberry, OD, MS, ME

10:00AM - 11:50AM
Legends of the Posterior Segment
Presented by Blair Lonsberry, OD, MS, ME

11:50AM- 12:10PM
Lunch Break

12:10PM - 1:05PM
Un-Nerved Conundrums of the Optic Disc
Presented by Mark Sawamura, OD

1:05PM - 2:00PM
PAMM, Plagues, and RAM: Uncommon Retinal Manifestations from Common Systemic Diseases
Presented by Xiao Xi Yu, OD

2:10PM - 3:05PM
Stargardt's Macular Dystrophy: A Family Affair
Presented by Ashley Deemer, OD

3:05PM - 4:00PM
Minimally Invasive Glaucoma Surgery (MIGS) Updates and Options
Presented by Igor Bussel, MD

This activity is supported by an unrestricted educational grant from the following education partners. We sincerely thank them for their support!

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Instructor Biographies

Lisa Wahl, OD

Assistant Professor, MBKU | SCCO
Clinic Co-Director, UECLA, MBKU | SCCO

Dr. Lisa Wahl is an optometrist practicing in Los Angeles, California and is an assistant professor at Marshall B. Ketchum University. She is the coordinator of Cornea and Contact Lens Services at University Eye Center Los Angeles and works predominately in clinical care with fourth-year optometry interns. Dr. Wahl graduated from UCLA with a B.S. in Biology and a minor in English Literature. She received her doctorate at Southern California College of Optometry, graduating Summa Cum Laude, and completed residency training in ocular disease at VA Los Angeles Ambulatory Care Center. Thereafter, she worked a prominent ophthalmology practice in Los Angeles, providing pre and postoperative care for patients undergoing refractive, cataract and corneal surgery. Her areas of interest are medically necessary contact lenses, dry eye and ocular pathology. She is an investigator in several research studies at Marshall B. Ketchum University and frequently lectures at continuing education seminars. In her free time, she enjoys lifting weights, traveling and exploring the local restaurant scene.

Asha Balakrishnan, MD

Surgeon, Dougherty Laser Vision

Dr. Asha Balakrishnan ("Bala") is a cataract, cornea, and refractive surgeon and a board-certified ophthalmologist. She joins DLV after having served as the Director of the Cornea and Refractive Surgery service and an Associate Professor of Ophthalmology at the University of Louisville. She was in private practice in the Los Angeles area prior to joining the DLV team. Dr. Balakrishnan specializes in all forms of cataract surgery, including manual & laser-assisted cataract surgery and premium intraocular lens implantation. She holds multiple certifications for a range of femtosecond laser platforms for cataract surgery. In addition to premium cataract surgery, Dr. Balakrishnan also has extensive experience in complex cataract surgery, sutured intraocular lens implantation, and intraocular lens exchanges. Dr. Balakrishnan is dedicated to providing the highest level of medical and surgical care to every patient.

Jessica Yuen, OD

Assistant Professor, MBKU | SCCO

Dr. Jessica Yuen graduated from the University of California, Berkeley with a Bachelor of Arts in Public Health and minor in Molecular Toxicology. She later returned to Berkeley to complete her Doctorate of Optometry. After receiving her OD degree, she completed a residency in Primary Care/Ocular Disease at the San Francisco VA Medical Center where she worked closely with UCSF ophthalmology in various sub-specialties including oculoplastics, cornea, glaucoma, and retina. In 2020, she joined the Southern California College of Optometry at Marshall B. Ketchum University as a full-time faculty with clinical and laboratory teaching responsibilities in the Primary Eye Care and Ocular Disease service. Dr. Yuen is a fellow of the American Academy of Optometry and member of the American Optometric Association and California Optometric Association.

Mark Roark, OD

Private Practice, Allisonville Eye Care Center

Dr. Mark Roark enjoys full-scope optometry utilizing advanced technology and has extensive experience in the management of ocular conditions including Macular Degeneration and Dry Eye Disease. He has a special interest in ocular nutrition and has lectured frequently to other Eye Care Professionals, both nationally and internationally, on the importance of macular nutrition in reducing the risk of ocular disease and enhancing visual performance, especially contrast sensitivity. Dr. Roark was honored to speak at the 2018 Brain and Ocular Nutrition Conference at Cambridge University and recently co-authored a peer-reviewed article published in a special edition of the Molecular Nutrition and Food Research journal on "Nutrition for the Eye and Brain".

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Instructor Biographies

Edward Chu, OD

Staff Optometrist | Residency Coordinator, Long Beach VA Medical Center

Dr. Edward Chu has worked in the VA system his entire career. After graduating from Berkeley Optometry in 2008, he completed a residency in Primary Care at the San Francisco VA Hospital. After residency, he accepted a staff optometrist position at the Salisbury VA in North Carolina, where he spent 5 years. In April 2014, Edward moved back to Southern California where he began his new job at the Long Beach VA serving as the residency and externship coordinator.

Douglas K. Devries, OD

Co-Founder, Eye Care Associates of Nevada

Dr. Douglas Devries co-founded Eye Care Associates of Nevada in 1992 and since that point has limited his practice to diseases of the eye and surgical co-management. His specific area of interest has been in ocular surface disease, which makes up the majority of his clinical practice. He is the director of the optometric residency program and is an Associate Clinical Professor of Optometry. Dr. Devries graduated with a degree in financial management from the University of Nevada and received his doctor of optometry degree from Pacific University. He has served as President of the Nevada Optometric Association as well as the Great Western Counsel of Optometry. He lectures nationally and internationally on anterior segment eye disease.

David Sendrowski, OD

Professor, MBKU | SCCO
Chief, Opthalmology Consultation & Special Testing Service, Ketchum Health

Dr. Sendrowski is a Professor at the Southern California College of Optometry. He is presently the Chief of the Ophthalmology Consultation and Special Testing Service at the University Eye Center at Ketchum Health. He was residency trained in the area of Hospital-based primary care optometry in 1986 and he has lectured extensively in the area of ocular disease diagnosis and management at the college and continuing education venues. He has co-authored a textbook called “Differential Diagnosis in Primary Eye Care” as well as the Thyroid Chapter is the last four editions of “Clinical Ocular Pharmacology” by Bartlett and Jaanus. He has also published several papers in the area of ocular disease and is a fellow in the American Academy of Optometry. Dr. Sendrowski is a member of the Prospect Medical Group surgical consultation board. He also has consulted for the California Optometric Association Legislative and Education Committees. Dr. Sendrowski is a speaker for Alcon and Allergan Pharmaceuticals. He works toward the advancement of the profession and practice of Optometry.

John Maher, MD

Adjunct Faculty, MBKU | SCCO

John Maher entered medical school with a case of nearsightedness. Although he originally intended to study internal medicine, after being fitted for glasses – and later for contact lenses – he was filled with fascination for the human eye. He took a part time job in the ophthalmology clinic, introducing him to what he came to see as the most fascinating and beautiful part of the human body. In 1981, Dr. Maher graduated from Loyola University, Chicago, Illinois where he completed his residency in ophthalmology. Upon achievement of his medical degree, Dr. Maher returned to California where he accomplished his fellowship training at the University of California, San Diego. He began his practice in ophthalmology in Torrance, California in 1986. Today, Dr. Maher is a board-certified ophthalmologist with fellowship training in Cornea and External Diseases. He maintains memberships in Loyola University’s Foreign Ophthalmologic Care from the United States, the Los Angeles County Medical Association, the California Medical Association, the Los Angeles Society of Ophthalmology and the Orange County Society of Ophthalmology.

Evidence-Based Management of Retinal Artery Occlusions

Presented by Edward Chu, OD

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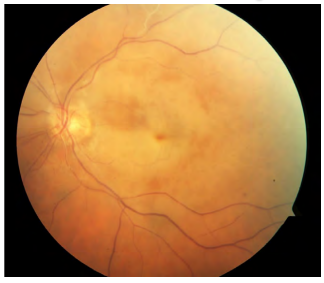
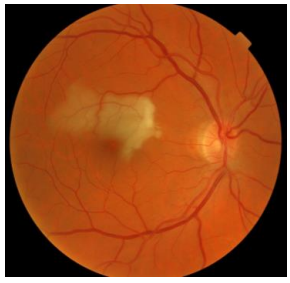
Evidence Based Management of Retinal Artery Occlusions

Edward Chu, OD, FAAO
Long Beach VAMC – Residency/Externship Coord.
MBKU – Assistant Professor
Ocular Disease Part II
July 10, 2021

No Financial Disclosures

1

Questions to ponder today…

What clinical signs/symptoms help me identify a retinal artery occlusion (RAO)? Past RAO?

What is my responsibility to patient when I diagnose a RAO? Lab test? Imaging?

If my patient has a RAO, what is his/her risk for stroke? How urgently do I need to refer?

2

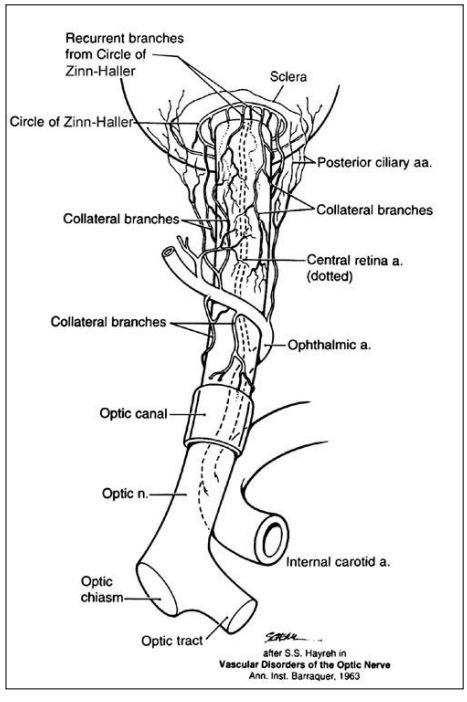
Retinal Artery Occlusion (RAO)

- Interrupted blood flow
  - Embolic occlusion retinal vasculature
  - Non-obstructive hypoperfusion
- Analogous to cerebral infarction
  - Thromboembolus ischemic CVA
  - Blockage blood, no O^2 →brain vs retina
  - Irreversible tissue injury/death 2-3 hours
  - Neuro deficit vs vision loss
  - Overlapping systemic risk factors

3

Vascular supply to ON
-ICA
-Ophthalmic
-Central Retinal

Brain/Retina same arterial blood supply!



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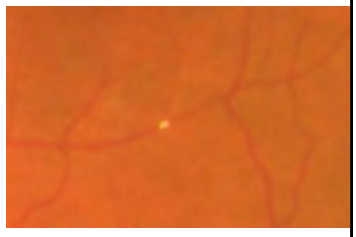
Retinal Emboli Composition

- 70 patients
- Emboli composition
  - Cholesterol 74% - migrate
  - Calcified material 10.5% - rough, stationary
  - Platelet-fibrin 15.5% - smooth, migrate
- TMVL - cholesterol
- Permanent occlusion (RAO) - Calcific

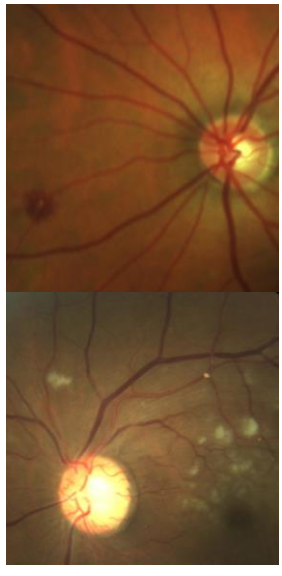


Arruga J, Sanders MD. Ophthalmologic findings in 70 patients with evidence of retinal embolism. Ophthalmology 1982; 89: 1336-1347

5

Cholesterol Plaques

- AKA Hollenhorst Plaques
- Refractile
- Yellow, white, copper color
- Round, rectangular
- Endothelial damage → Hemes
- **TMVL**
- **Carotid Ultrasound**



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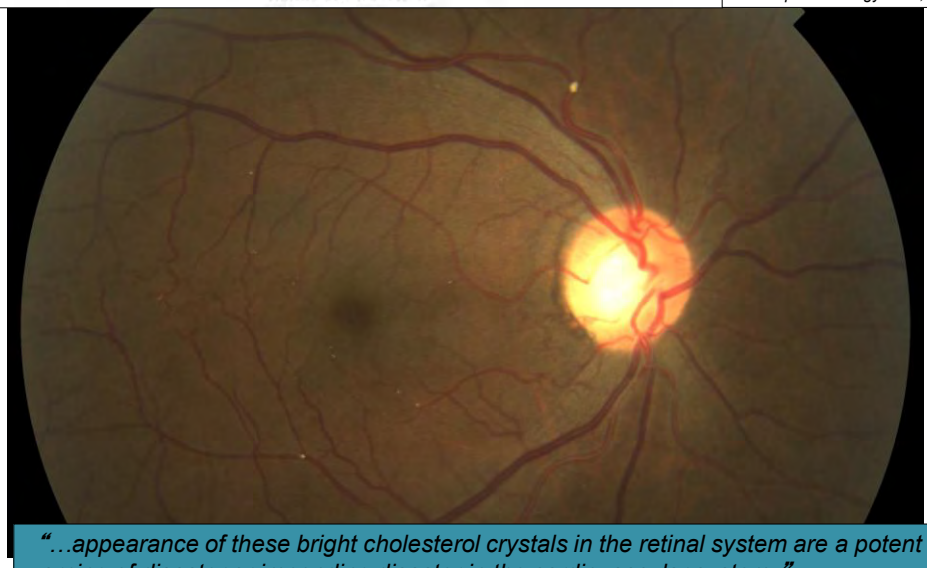
VASCULAR STATUS OF PATIENTS WHO HAVE CHOLESTEROL EMBOLI IN THE RETINA*

ROBERT W. HOLLENHORST, M.D.
Rochester, Minnesota

Am J Ophthalmology 1966; 61: 1159-1165

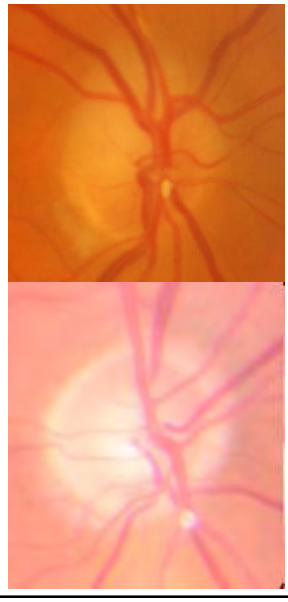


"…appearance of these bright cholesterol crystals in the retinal system are a potent warning of disaster or impending disaster in the cardiovascular system."

7

Calcific Emboli

- Damaged heart valve
  - Calcific aortic stenosis
  - Mitral and aortic valve disease
- Flat and white
- Optic nerve BV
- **Retinal Arterial Occlusion**
- Electrocardiogram
- Echocardiogram



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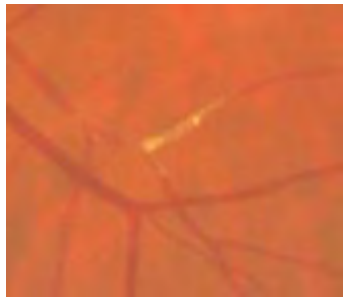
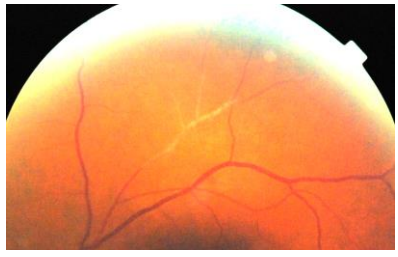
Fibrinoplatelet Plaque

- Dull gray/white plugs
- Mobile
- Long, smooth shape
- Carotid artery disease
- Heart valves
  - Rheumatic disease
  - Floppy mitral valve
  - Systemic Lupus





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Central Retinal Artery Occlusion

- Most serious RAO
- Term, branch Oph. artery, no collaterals
- Acute, painless, monocular vision loss
- Retinal whitening/opacity
  - Ischemia, giant CWS, swollen NFL
- Retinal arteriole attenuation
- Segmental blood flow (box-car)
- Cherry red spot

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FUNDUS CHANGES IN CENTRAL RETINAL ARTERY OCCLUSION

SOHAN SINGH HAYREH, MD, MS, PHD, DSC, FRCS, FRCOPHTH,*
M. BRIDGET ZIMMERMAN, PHD†

240 CRAOs
Main findings during initial examination

Cherry Red Spot	**90%**
Opacity in posterior pole	**58%**
Optic Nerve Pallor	39%
Retinal arterial attenuation	32%
Optic Disk Edema	22%
Box-Carring	19%

Emboli seen only 20% of cases

Retina 27: 276-289, 2007

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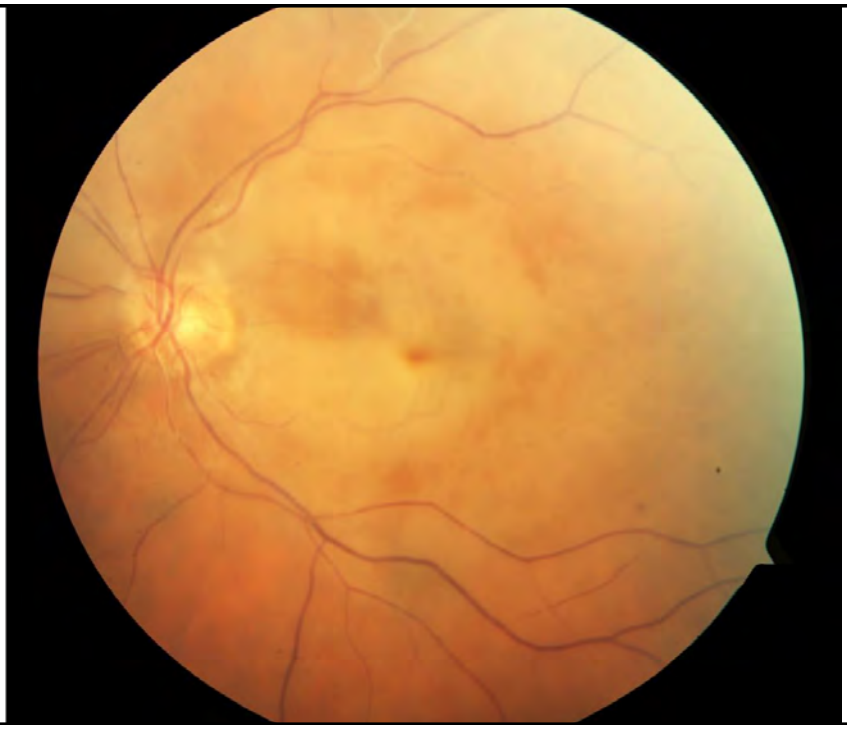

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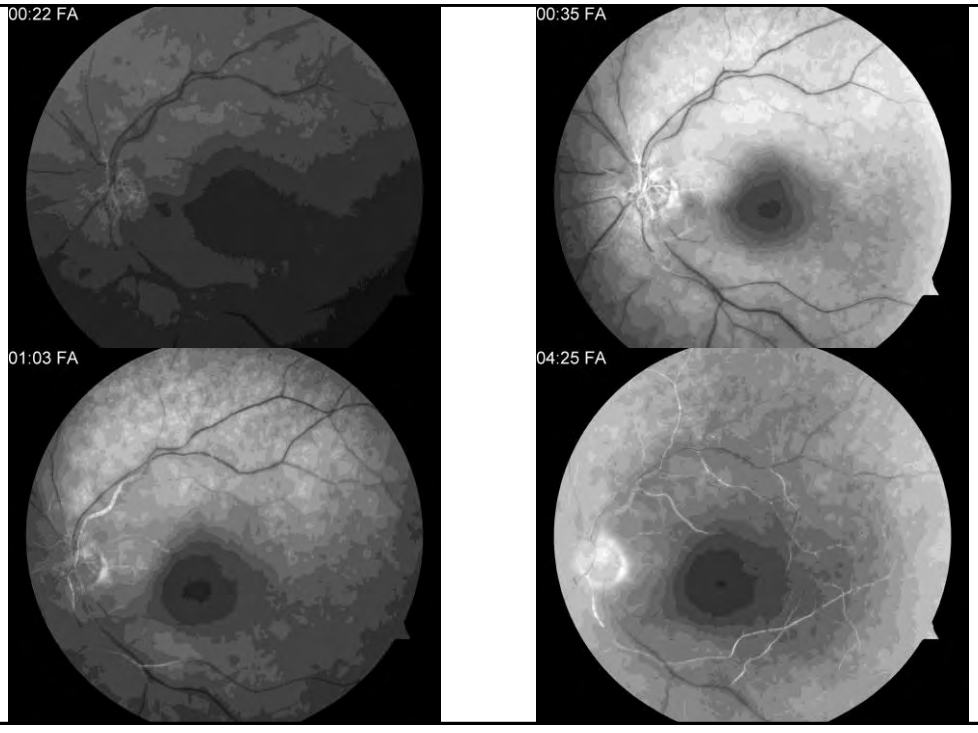

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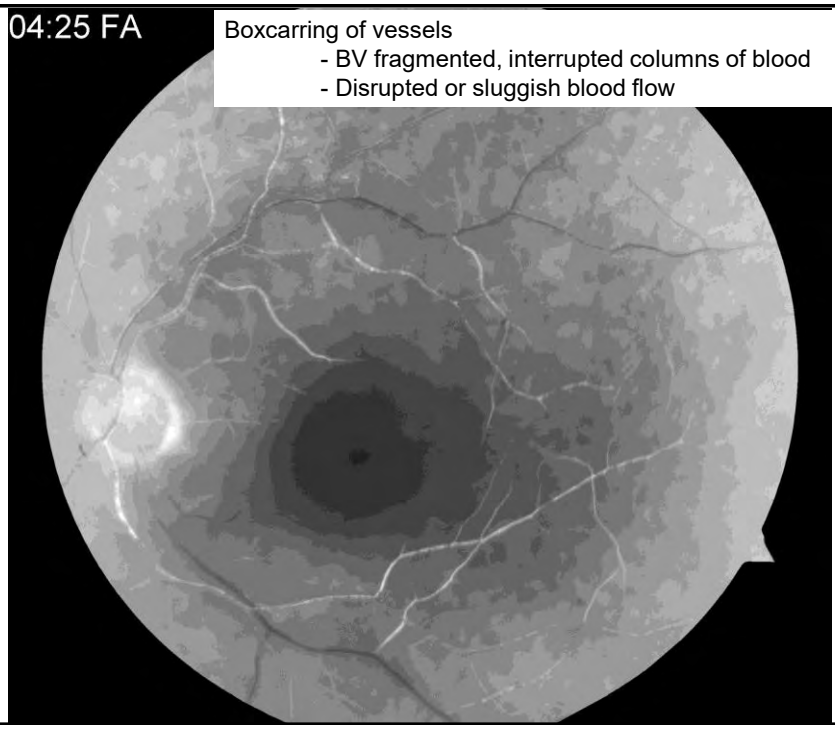

Boxcarring of vessels
- BV fragmented, interrupted columns of blood
- Disrupted or sluggish blood flow

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Central Retinal Artery Occlusion: Visual Outcome

SOHAN SINGH HAYREH, MD, MS, PHD, DSC, FRCS, FRCOPHTH, AND M. BRIDGET ZIMMERMAN, PHD

244 patients CRAO
VA and VF improved primarily first 7 days

74.2% present CF or worse vision

Initial visual acuity	20/40 better	CF/worse
NA-CRAO (66.9%)	None	**93.2%**
NA-CRAO w/ cilioretinal sparing (14.3%)	20%	60%
Transient NA-CRAO (16%)	37.9%	37.9%
Arteritic CRAO (4.5%)	None	75%

Am J Ophthalmol 2005; 140: 376-391

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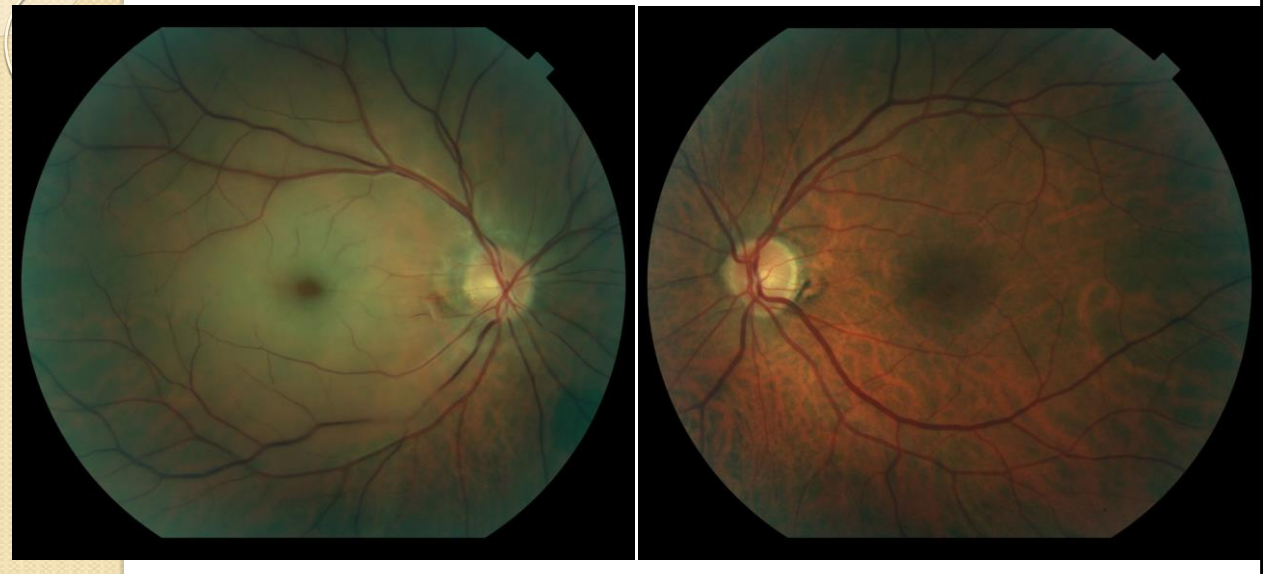

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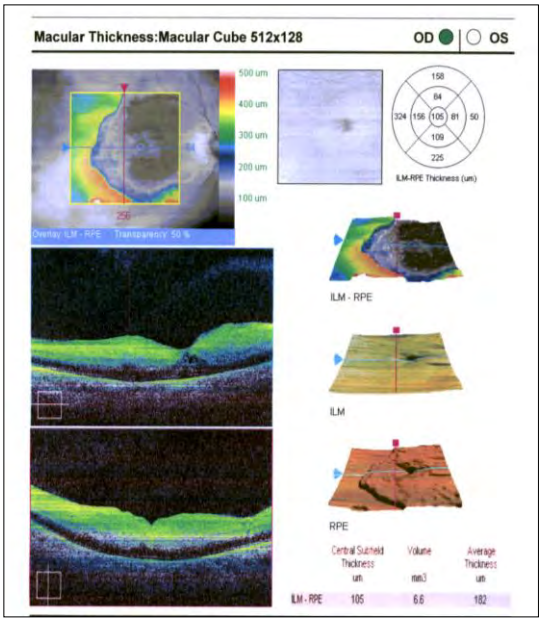

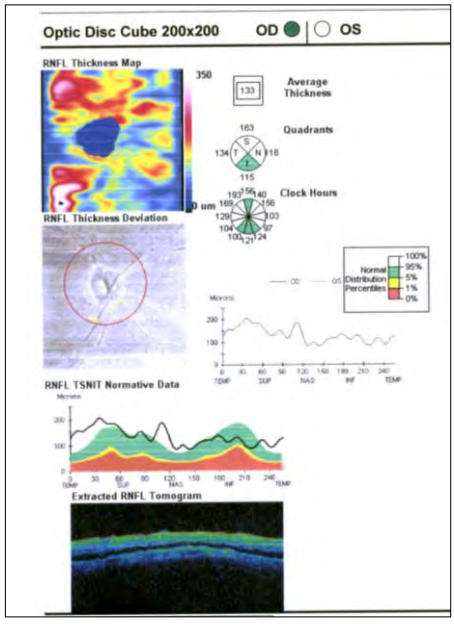

OCT shadowing due to severely swollen NFL

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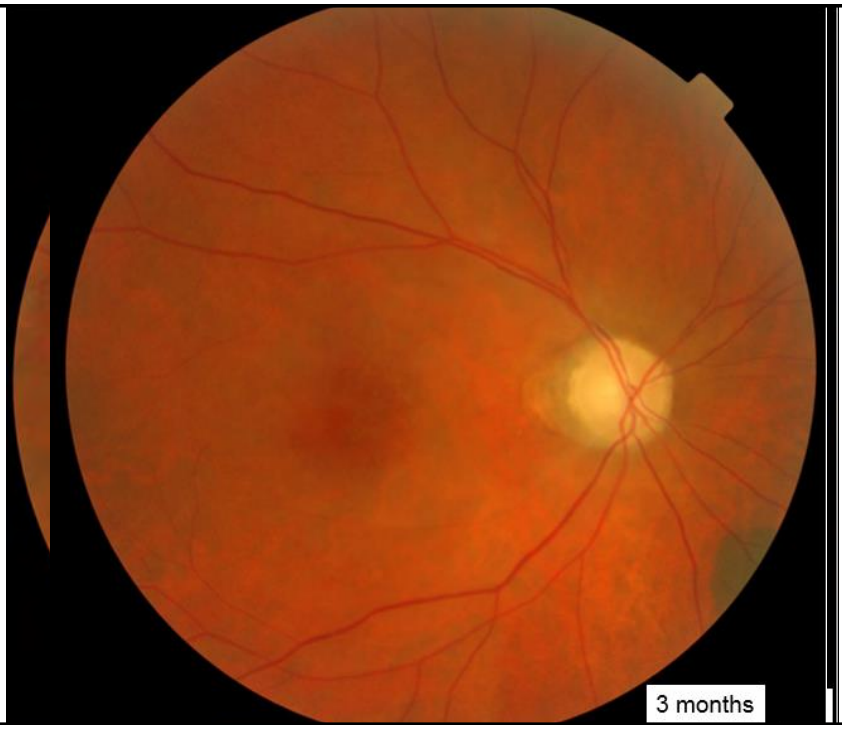

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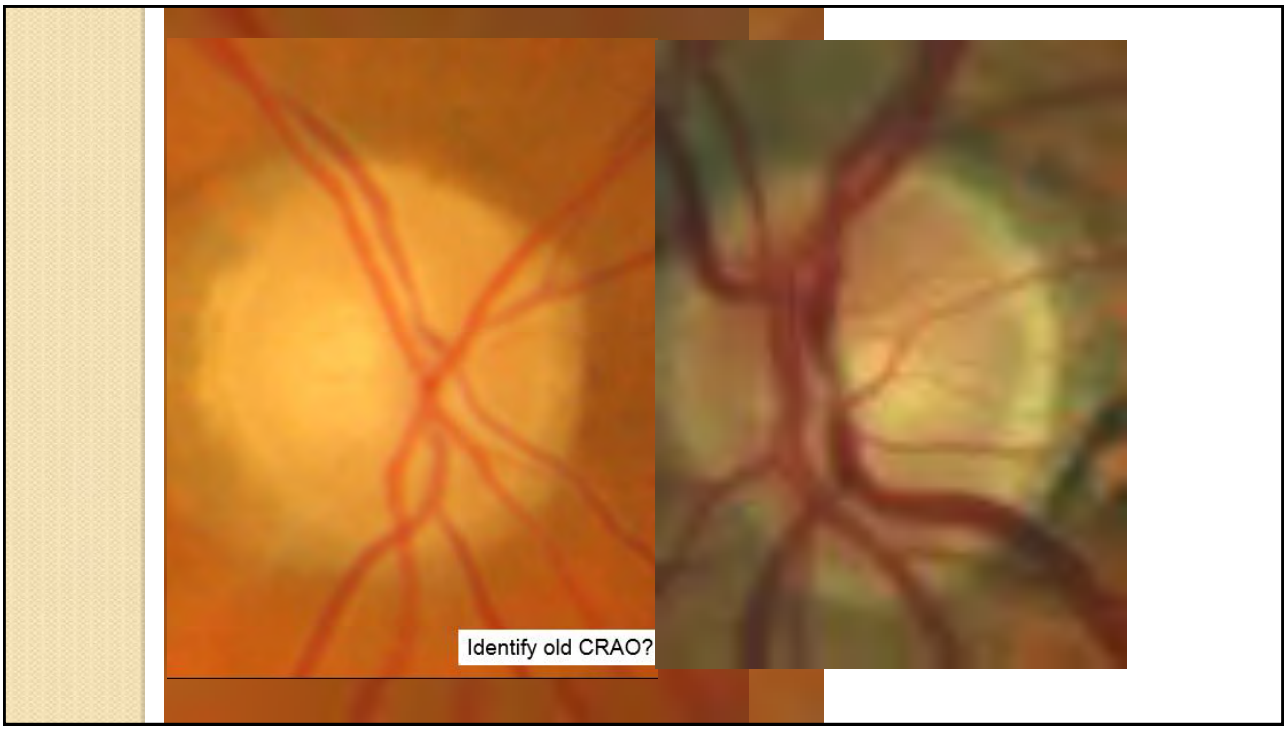

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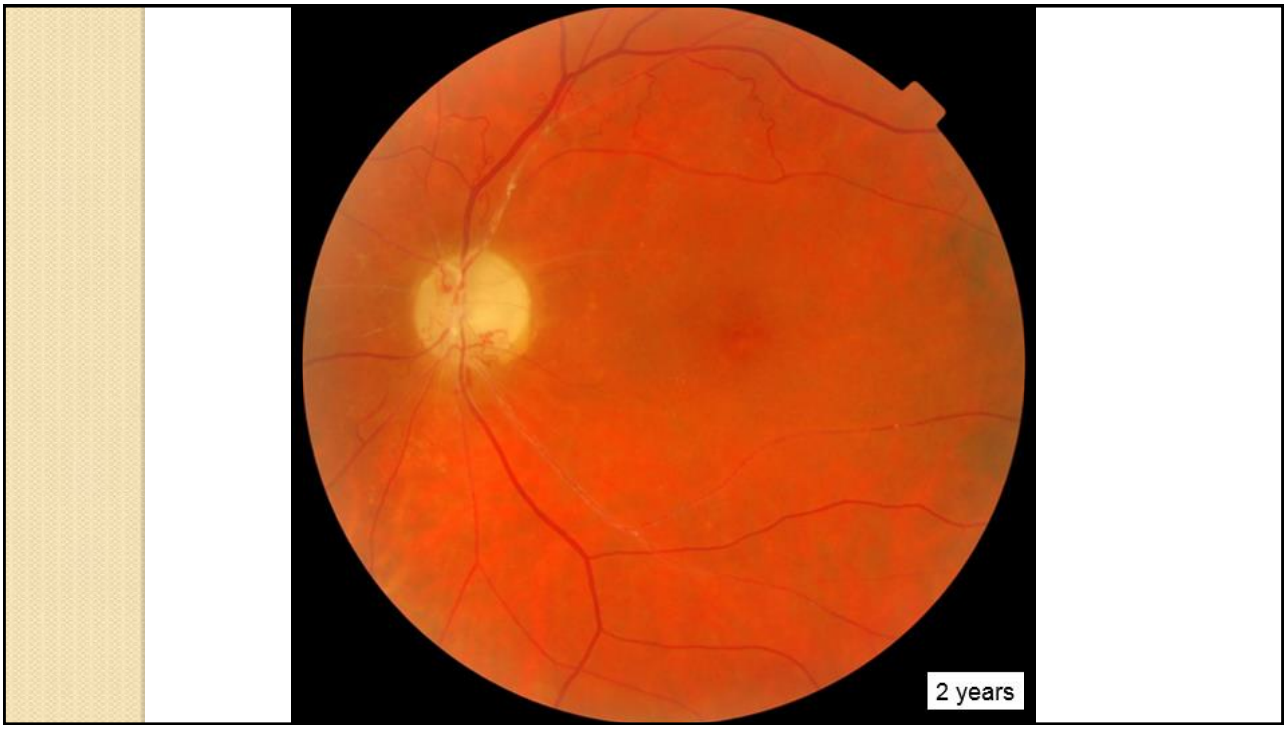

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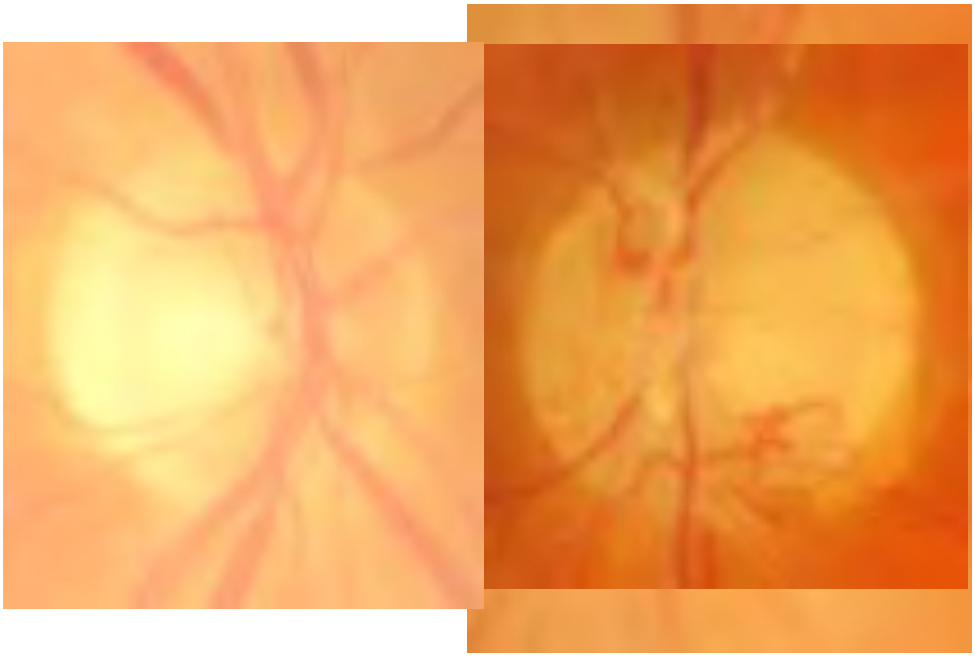

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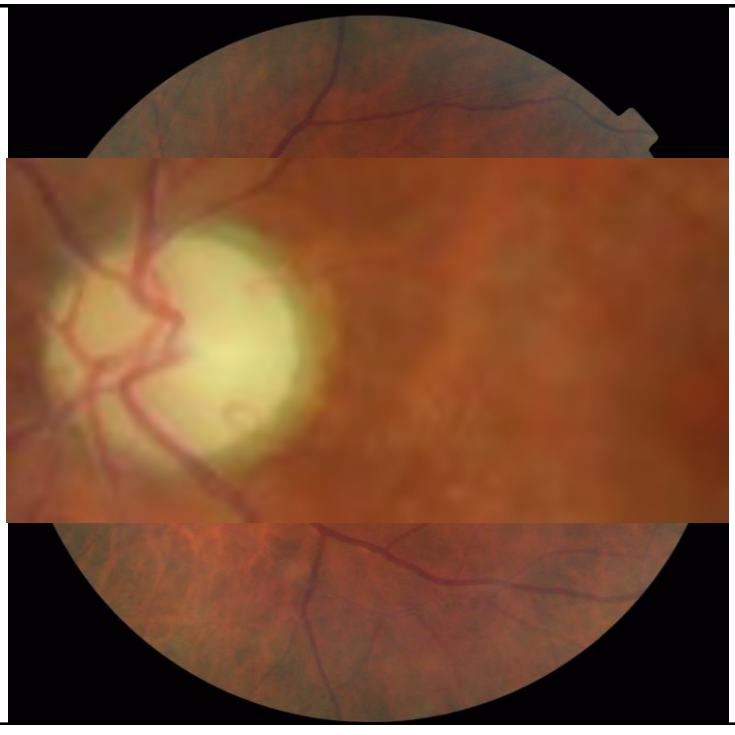


Outside Dx:
NA-AION 2/2 ED Medication 2001

Medical Hx
-Sleep apnea
-DM II
-HTN
-Hyperlipidemia

BCVA: 20/70

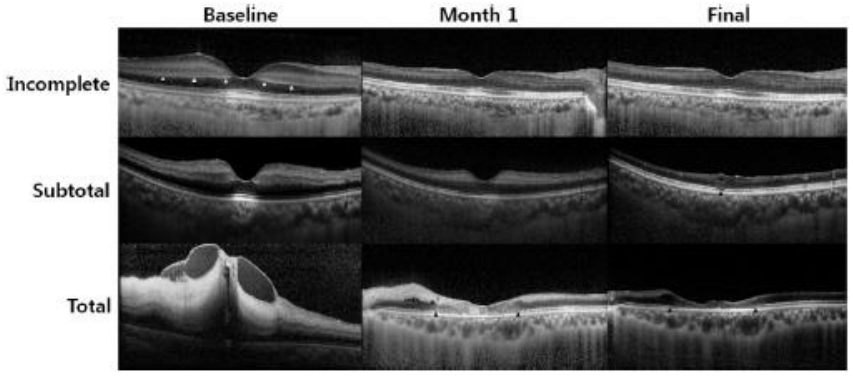
CRAO w/ cilio—retinal sparing?

22

Retinal and Choroidal Changes and Visual Outcome in Central Retinal Artery Occlusion: An Optical Coherence Tomography Study

Stage by extent edema (shadowing), VA

Ahn et al. Am J Ophthalmol 2015; 159: 667-676



Prognosis → Acute Phase: extent ME, layer structure/organization
Retinal thinning final (worse w/ subfoveal choroidal thinning)

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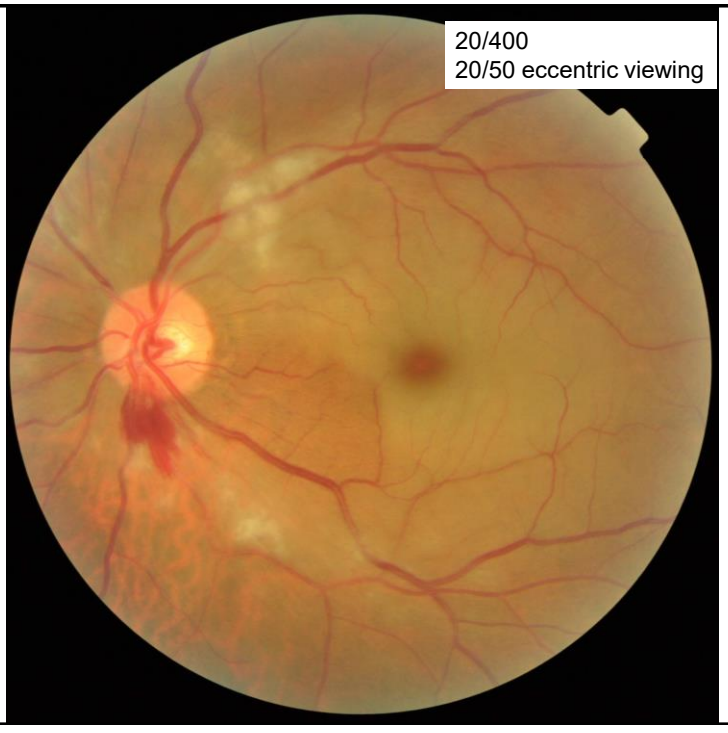

20/400
20/50 eccentric viewing

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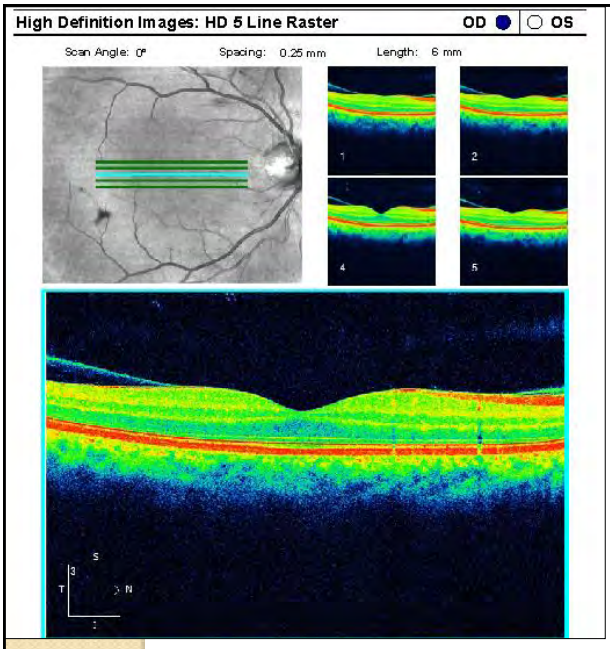

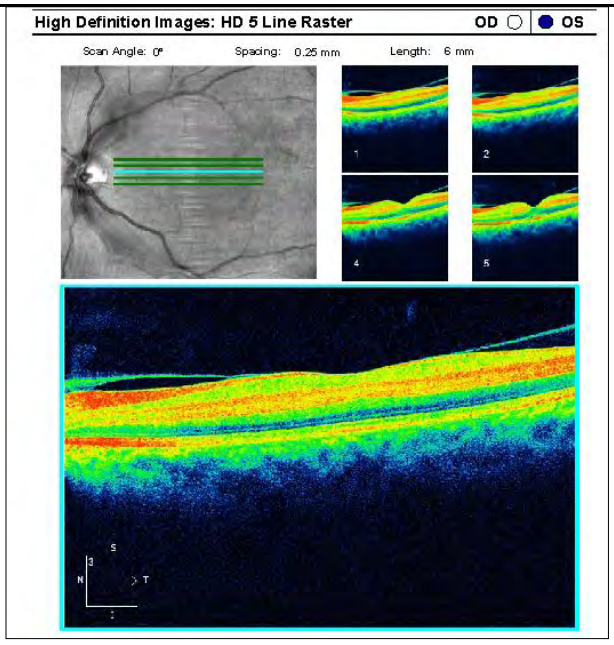

Mild shadowing, preserved layers
retinal structure

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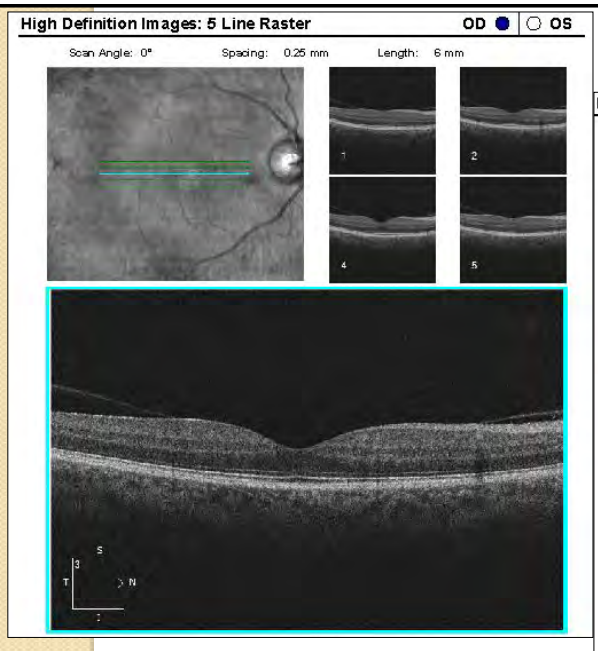
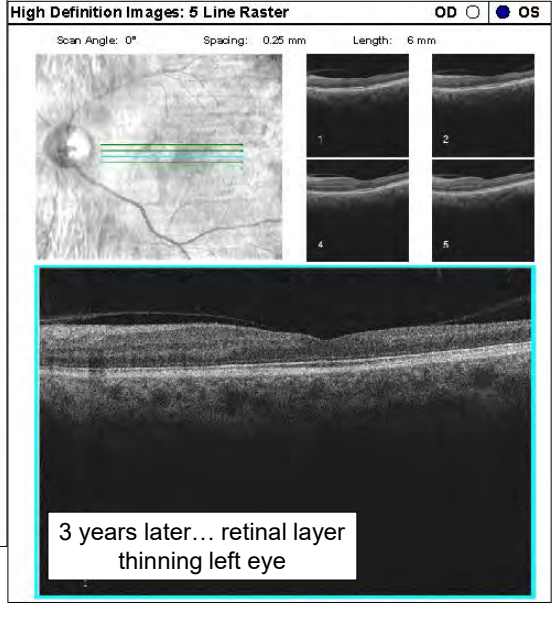


Final Acuity: 20/300
EV: 20/50-



3 years later… retinal layer
thinning left eye

26

Acute CRAO: Dislodge Embolus??

- Ocular massage
- A/C Paracentesis: IOP down to zero
- Breath into paper bag: Increase CO^2
- Thrombolysis: IV thrombolytic agent or locally via ophthalmic artery
  - Fibrinolytic agents only dissolve **fibrino**-platelet embolus, not cholesterol/calcific
  - CRA blocked – little chance fibrinolytic agent reaching thrombus

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Central Retinal Artery Occlusion

- Hayreh Primate Studies
  - No detectable damage CRAO ~97 min
  - After ~ 100 minutes → longer CRAO, more extensive + irreversible damage
  - 240 minutes (4 hours) → Retina dead
- "Parking Lot or Waiting Room CRAO"
- ***"CRAO a classic case of a disease without any treatment that has many treatments"*** – SS Hayreh

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Arteritic CRAO

- 5% of all CRAOs
- 2/2 Giant Cell Arteritis
  - ESR, CRP, Platelets
- GCA w/ ocular involvement
  - 10 % CRAOs
- Steroid treatment
  - Fellow eye involvement within days
  - **TIME SENSITIVE!**
- **CRAO REQUIRES R/O GCA**

Hayreh, et al. Am J Ophthalmol 1998; 125: 509-520

Hayreh, et al. Am J Ophthalmol 1998; 125: 521-526

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Occult Giant Cell Arteritis:
Ocular Manifestations

SOHAN SINGH HAYREH, MD, PHD, DSC, PATRICIA A. PODH
AND BRIDGET ZIMMERMAN, PHD

Evaluating the Incidence of Arteritic Ischemic Optic Neuropathy and Other Causes of Vision Loss from Giant Cell Arteritis

John J. Chen, MD, PhD,[1] Jacqueline A. Leavitt, MD,[1] Chengbo Fang, MD,[1,2] Cynthia S. Crowson, MS,[3,4] Eric L. Matteson, MD, MPH,[3,4] Kenneth J. Warrington, MD[3]

~21.2% GCA patients + visual loss

NO SYSTEMIC SYMPTOMS GCA

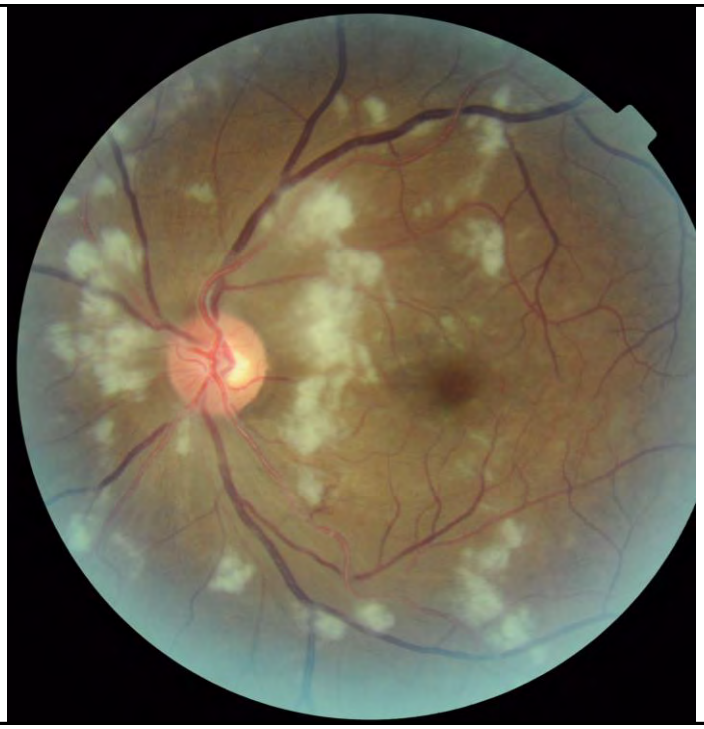
Headache, scalp tender, fever, fatigue, weight loss, jaw claudication, neck pain

CRAO requires r/o GCA even when NO SYMPTOMS

Am J Ophthalmol 1998; 125: 521-526

Ophthalmology 2016; 123: 1999-2003

30



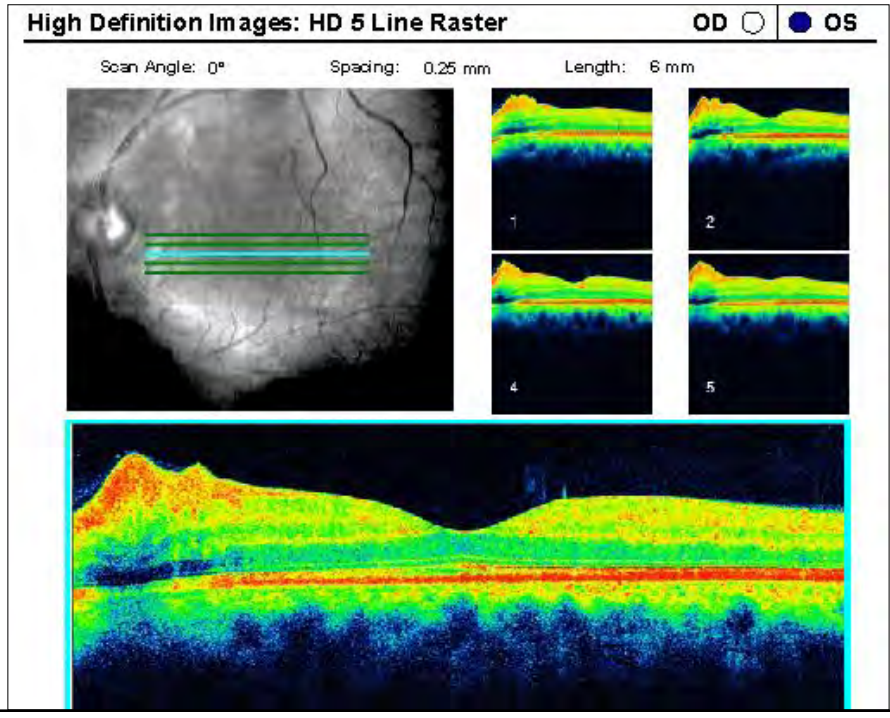
51 year old male
-blurry vision OS x 2 weeks
-3 days ago, vision completely dark x several hours
-vision slowly returned but blur persists

ER 2 days ago
-BP 70/40

OS: 20/70
2+ APD

Photos courtesy of Dr. Diana Vivirito

31



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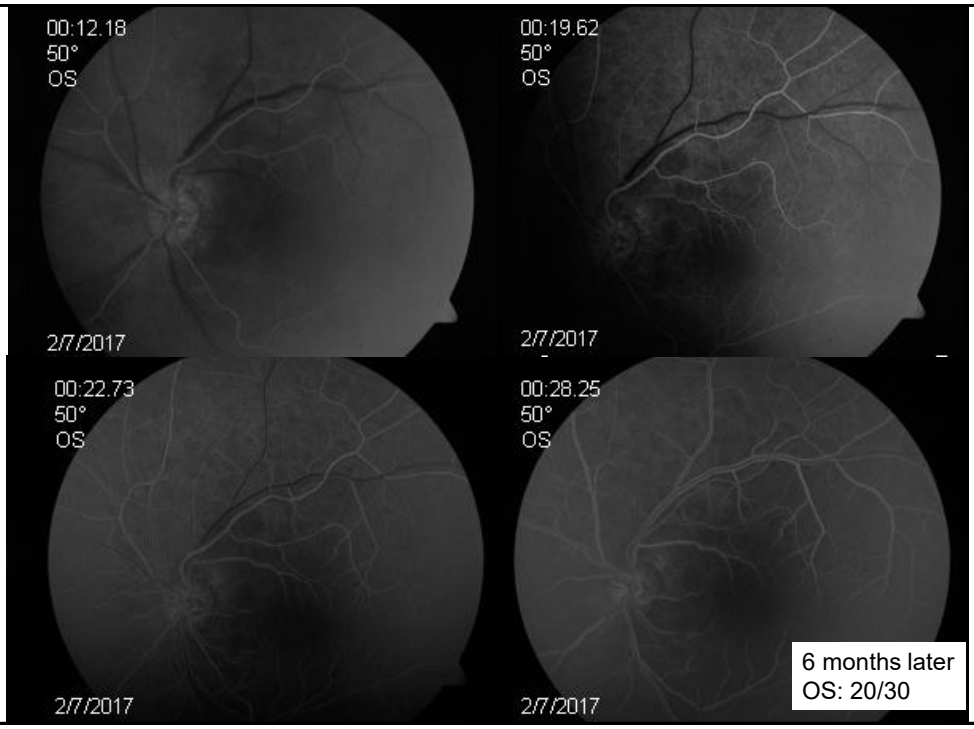
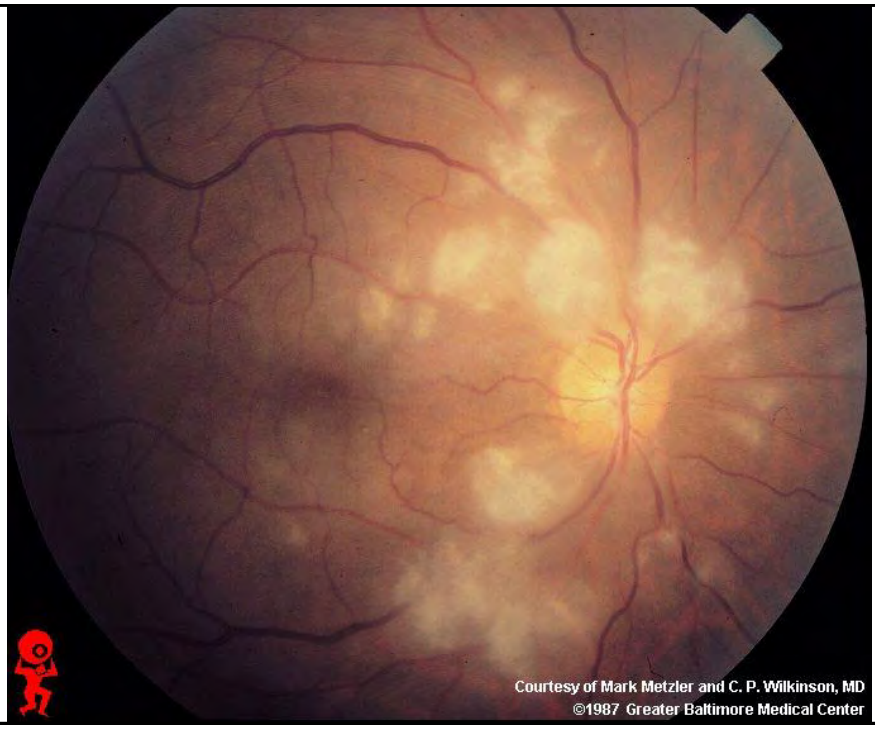


33

Transient CRAO

- Occlude CRA temporarily, then dislodge
- Non-Obstructive Hypoperfusion
  - **Fall perfusion pressure**
  - **Drop blood pressure (nocturnal)**
  - Surgery, Dialysis, Shock
- Rise IOP
- Vasospasm of CRA
- Carotid Artery Stenosis

34



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Retinal Artery Occlusion

Associated Systemic and Ophthalmic Abnormalities

Sohan Singh Hayreh, MD, PhD,[1] Patricia A. Podhajsky, BSN,[1] M. Bridget Zimmerman, PhD[2]

Ophthalmology 2009; 116: 1928-1936

DM 2, HTN, ischemic heart disease, smoking, **Stroke/TIA**
all significantly higher than prevalence in matched US population

Carotid Doppler/Angiography
Ipsilateral ICA >50% stenosis — **Plaque present**
31% NA-CRAO — **71% NA-CRAO**

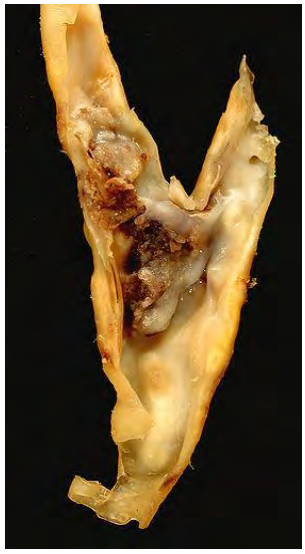
Abnormal echocardiogram of an embolic source
52% of NA-CRAO — mostly calcified valve

CRAO require HEART + CAROTID evaluation

36

Embolic Work-up

- Carotid U/S
  - Evaluates hemodynamically significant stenosis → carotid endarterectomy?
  - Plaque may be present w/ or w/o any significant carotid stenosis
- Absence stenosis **does not** rule out carotid as source of embolism



37

Embolic Work-Up

- Heart Disease
- Electrocardiography (EKG)
  - Record heart electrical activity
  - Heart arrhythmias - Afib
  - Weaknesses different parts of heart muscle
- Echocardiography ("Echo")
  - Heart Sonogram/Ultrasound
  - Valve dysfunction
  - Chamber abnormalities

38

Retinal Artery Occlusion and the 3-Year Risk of Stroke in Taiwan: A Nationwide Population-Based Study

YUH-SHIN CHANG, REN-LONG JAN, SHIH-FENG WENG, JHI-JOUNG WANG, CHUNG-CHING CHIO, FU-TSUNG WEI, AND CHIN-CHEN CHU

Am J Ophthalmol 2012; 154: 645-652

3248 patients: 464 RAO, 2784 Control
- 19.61% patients w/ RAO suffered stroke
- 10.05% patients control group suffered stroke

Stroke risk highest 1st month (9.5x higher) vs controls
- Most strokes first 6 months
- CRAO >> BRAO stroke risk/incidence

RAO increases risk subsequent stroke
- **Early neuro eval, stroke prevention needed**

39

Cardiovascular Risk Factors in Central Retinal Artery Occlusion

Results of a Prospective and Standardized Medical Examination

Callizo et al. Ophthalmology 2015; 122: 1881-1888

European Assessment Group for Lysis in Eye (EAGLE) study

77 patients complete medical examination
- **Carotid Doppler**, Echocardiography, Electrocardiography, BP
- Pulse rate, urine analysis, BMI analysis, Labs

Ipsilateral significant carotid artery stenosis ~ 40%
Only 3% diagnosed pre-CRAO → **order Carotid U/S!**

Previously <u>undiagnosed</u> vascular factors <u>78%</u> CRAO
- **Recommend comprehensive diagnostic work-up**

40

Stroke Risk and Risk Factors in Patients With Central Retinal Artery Occlusion

PATRICK LAVIN, MORGAN PATRYLO, MATTHEW HOLLAR, KIERSTEN B. ESPAILLAT, HOWARD KIRSHNER, AND MATTHEW SCHRAG

Am J Ophthalmol 2018; 196: 96-100

103 CRAO patients, "Stroke Belt"
-expedited inpatient evaluation CVA risk (labs/MRI)

36.7% critical carotid disease
37.3% coincident acute stroke
33% hypertensive emergency
20% myocardial infarction, critical structural cardiac disease
93% change medication due to evaluation

CRAO significant risk future cardio/cerebrovascular events + undiagnosed modifiable risk factors

CRAO = High Risk TIA (future stroke, MI, Death)

41

Co-occurrence of Acute Retinal Artery Occlusion and Acute Ischemic Stroke: Diffusion-Weighted Magnetic Resonance Imaging Study

JUNWON LEE*, SEUNG WOO KIM*, SUNG CHUL LEE, OH WOONG KWON, YOUNG DAE KIM, AND SUK HO BYEON

Am J Ophthalmol 2014; 157: 1231-1238

33 consecutive acute RAO patients, MRI within 7 days

Acute ischemic stroke Dx **24.2%** (8 total of 33)
5 CRAO, ipsilateral brain lesion ALL

37.5% suffered silent stroke, no neuro signs/symptoms

Acute cerebral infarctions accompany RAO
→ Recommend MRI

42

Risk and Risk Periods for Stroke and Acute Myocardial Infarction in Patients with Central Retinal Artery Occlusion

Sang Jun Park, MD, MSc,[1,4] Nam-Kyong Choi, PhD,[2,3,4] Bo Ram Yang, PhD,[2] Kyu Hyung Park, MD, Ph
Joongyub Lee, MD, PhD,[5] Sun-Young Jung, PhD,[6] Se Joon Woo, MD, PhD[1]

ORIGINAL RESEARCH

Ischemic Stroke Risk in Medicare Beneficiaries with Central Retinal Artery Occlusion: A Retrospective Cohort Study

Dustin D. French · Curtis E. Margo · Paul B. Greenberg

Risk for stroke after CRAO
- **HIGHEST incidence FIRST WEEK**
- Korea: Incident Rate Ratio = 44.51
- USA: 28-33 fold increased incidence 1st week

Incident CRAO → IMMEDIATE neuro evaluation
preventative stroke Tx

Ophthalmology 2015; 122: 2336-2343

Ophthalmol Ther (2018) 7: 125-131

43

2011: CRAO = Stroke Equivalent

- American Heart Association (AHA), American Stroke Association (ASA) definition of CNS infarction:

*"Brain, spinal cord, or **retinal cell death** attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury"*

- **CRAO = medical emergency**
  - IMMEDIATE referral stroke center/ER
  - Establish relationship w/ 24/7 stroke center

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Ocular Arterial Occlusive Disorders and Carotid Artery Disease

Sohan Singh Hayreh, MD, PhD,[1] M. Bridget Zimmerman, PhD[2]

Ophthalmology Retina 2017; 1: 12-18

203 Central Retinal Artery Occlusions

Carotid Artery Stenosis > 50%	29%
Presence Plaques	**74%**
Echocardiography (embolic)	**61%**
Myocardial Infarction	21%
TIA/Stroke before/after RAO	7%

TIA/Stroke absolute incidence **within 3 months** RAO

CRAO only 1% incidence

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AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Protecting Sight. Empowering Lives.™

Retinal and Ophthalmic Artery Occlusions Preferred Practice Pattern®

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AAO Practice Pattern: RAOs

- **50 years old → r/o GCA** (BEST)
  - ESR, CRP, Platelets
- Systemic evaluation vasculitis, hypercoag state → younger patients
- **Embolic workup older patients**
  - Heart (EKG/Echo), Carotid Artery
- **RAO 2/2 embolic etiology → IMMEDIATE referral stroke center**
- **Urgent ID risk factors, preventative measures in timely manner**

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Life after CRAO

- Lifetime reduced ave 10 years vs healthy
- 30% RAO died after average 4.2 years
- Stroke risk 10 times higher vs general population 3.5 years
- Increased stroke risk up to 10 years
- **Stroke Education**
- Risk Factors: DM, HTN, Hyperlipidemia
- Additional ocular sequelae
  - NV, NVI, NVA, NVG

Rim et al. Stroke 2016

Bruno et al. Ann Intern Med 1995

Lorentzen SE. Acta Oph 1969

Hankey et al. BMJ 1991

48

Ocular neovascularization following central retinal artery occlusion: prevalence and timing of onset

Adam K. Rudkin[1], Andrew W. Lee[2], Celia S. Chen[1]

Incidence and Clinical Features of Neovascularization of the Iris following Acute Central Retinal Artery Occlusion

Young Ho Jung[1,2], Seong Joon Ahn[3], Jeong-Ho Hong[4], Kyu Hyung Park[1], Moon-Ku Han[5], Cheolkyu Jung[6], Se Joon Woo[1]

ORIGINAL RESEARCH

Ocular neovascularization in eyes with a central retinal artery occlusion or a branch retinal artery occlusion

10.9 - 18.2% developed neovascularization
6.4 - 15.2% developed neovascular glaucoma

Ave time Dx neo: 1-3 months (range 2-16 weeks)

Follow CRAO regular intervals 2 weeks → 4 months

Eur J Ophthalmol 2010; 20 (6): 1042-1046 | *Korean J Oph 2016; 30 (5): 352-359* | *Mason et al. Clin Ophthalmology 2015: 9 995-1000*

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Ocular Neo 2/2 CRAO?

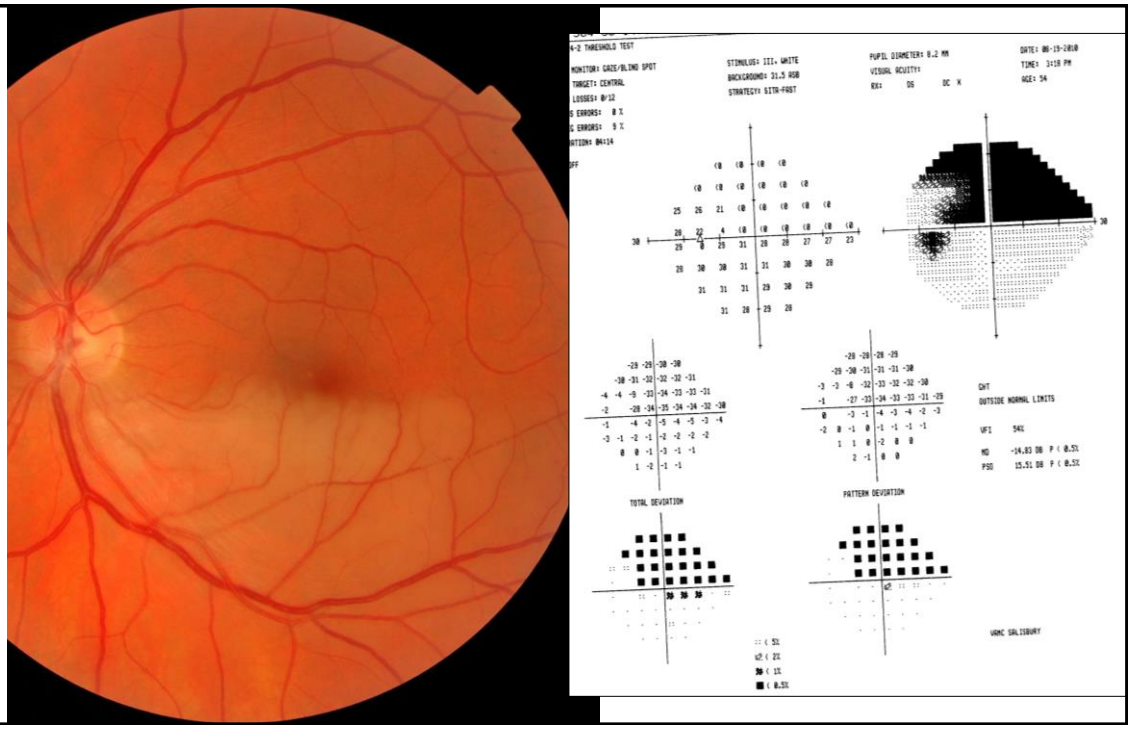
- VEGF released 2/2 CHRONIC retinal hypoxia (CRVO, PDR, OIS)
- CRAO = ACUTE retinal hypoxia
- Ocular Ischemic Syndrome
  - Internal Carotid Artery Disease – Plaque presence >> Stenosis
  - Embolus source CRAO
- Carotid Doppler limitations

50

ER Referral to Optometry

- 54 year old male
- Painless loss upper visual field OS upon awakening this morning
- VA
  - OD: 20/20
  - OS: 20/25
- 2+ APD OS
- Confront. VFs: superior/nasal defect OS

51



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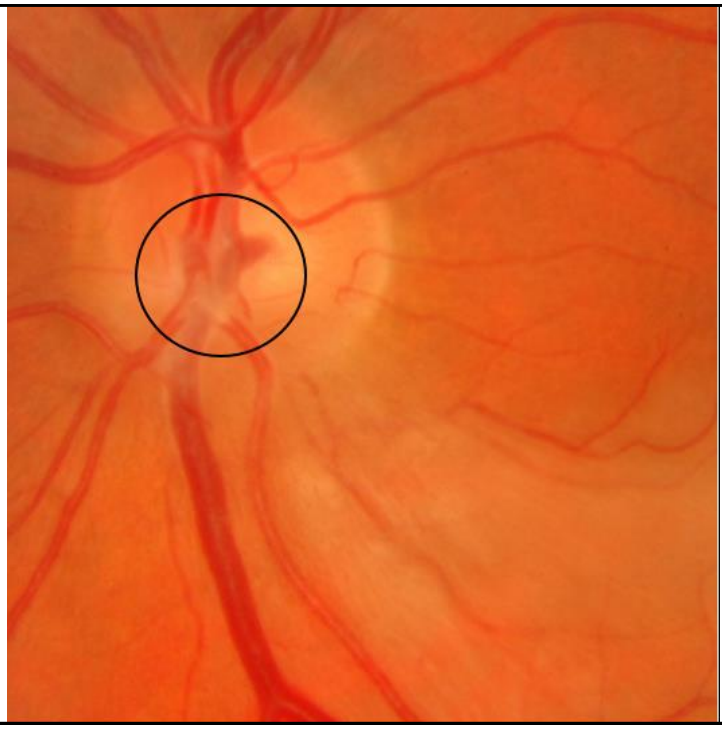

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Branch Retinal Artery Occlusion

- 38% RAOs
- 98% temporal artery
- Embolus at vessel bifurcation
- Corresponding VF loss
  - Improvement first 7 days
- Compared to CRAO
  - Emboli visible 65% BRAO vs 20%
  - Similar risk factors, better vision, + APD

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Visual Outcome in Central Retinal and Branch Retinal Artery Occlusion

Daisuke Yuzurihara[1,2] and Hiroyu

Branch Retinal Artery Occl

Natural History of Visual Outcome

Sohan Singh Hayreh, MD, PhD,[1] Patricia A. Podhajsky, BSN,[1] M. Bridget Zimmerman, PhD[2]

Branch Retinal Artery Occlusion: Visual Prognosis

JOHN O. MASON III, AMI A. SHAH, RACHEL S. VAIL, PETER A. NIXON, EDGAR L. READY, AND JAMES A. KIMBLE

212 BRAO, initial visual acuity > 20/40 in **74%** patients
Visual acuity > 20/40, 89% eyes retain vision

BRAO < 20/40 initially, **79%** improved 3 lines or more

Visual acuity better than 20/40 final visit
80-89% permanent BRAO
100% CLRAO

Jpn J Ophthalmol 2004; 48: 490-492 | *Am J Oph 2008; 146: 455-457* | *Ophthalmology 2009; 116: 1188-1194*

55

FUNDUS CHANGES IN BRANCH RETINAL ARTERIOLAR OCCLUSION

SOHAN S. HAYREH, MD, MS, PHD, DSC, FRCS, FRCOPHTH (HON),* M. BRIDGET ZIMMERMAN, PHD†

Retina 35: 2060-2066, 2015.

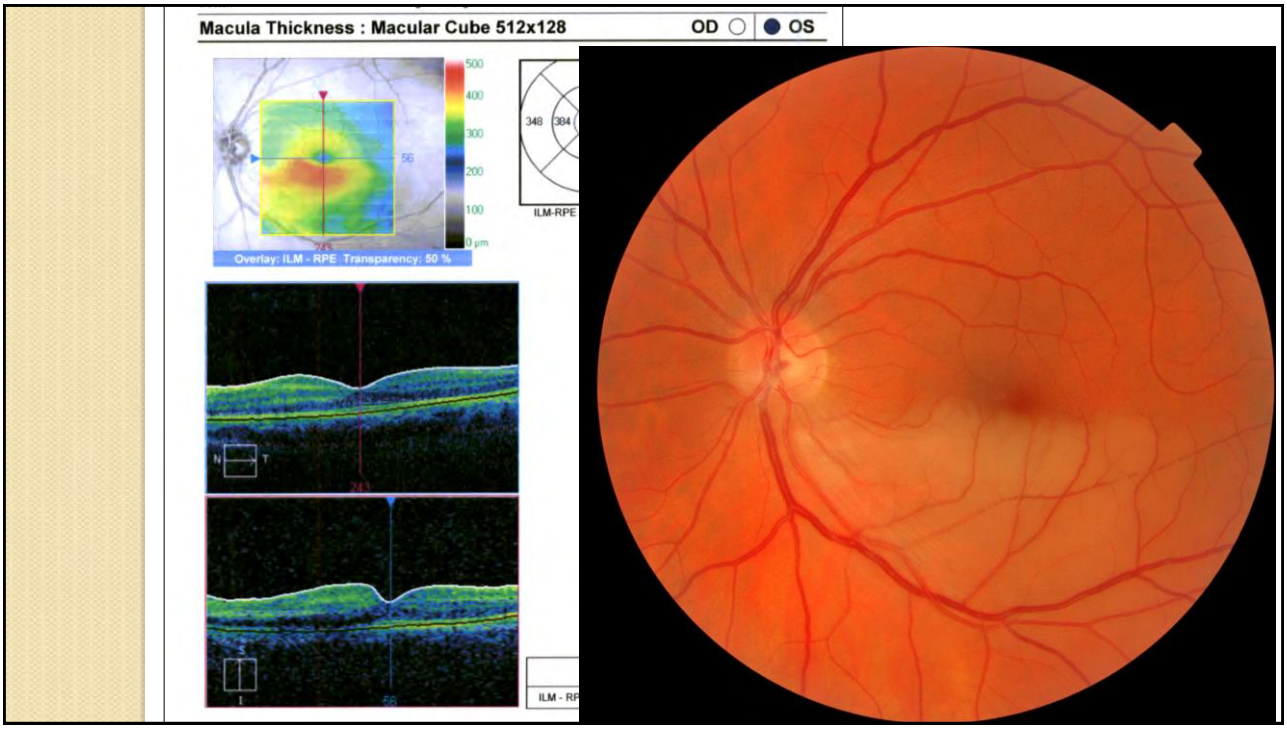
123 consecutive BRAO patients

Retinal infarct
Ave resolution 4-6 weeks, 13% at 3 months

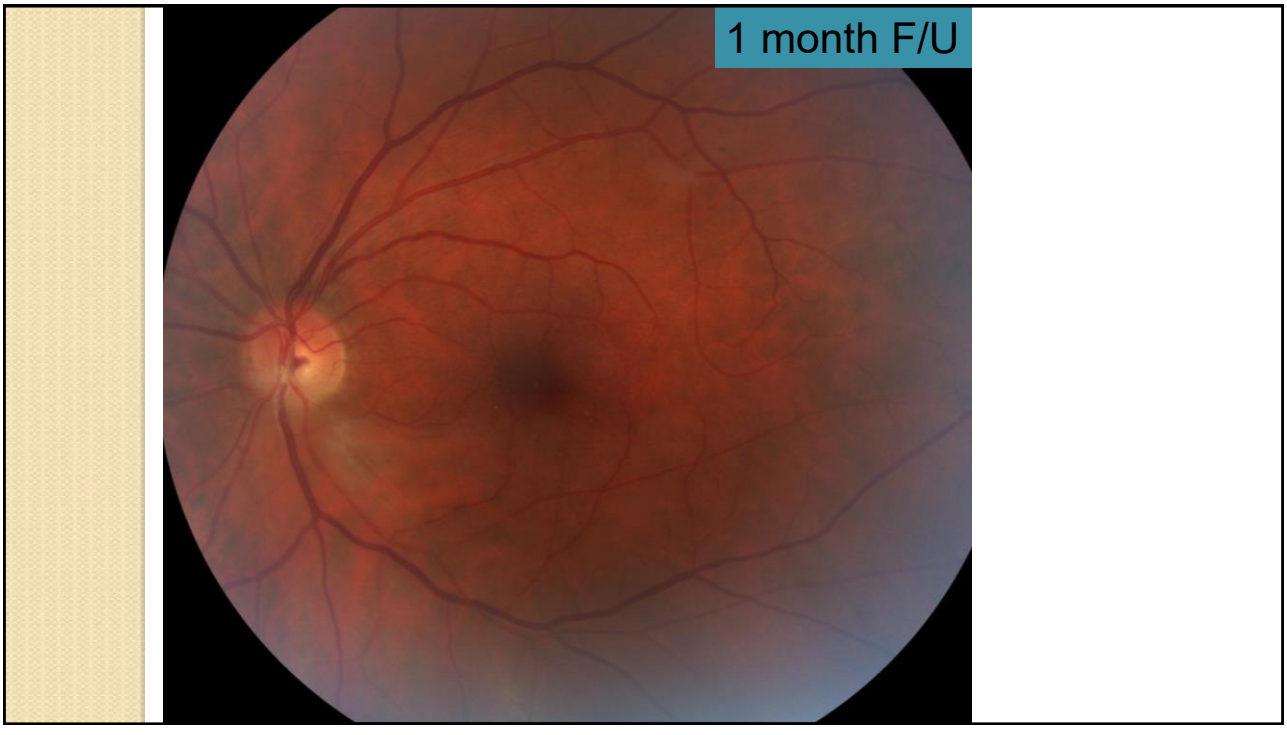
Optic Nerve Pallor→ 65% at 3 months

Initial: OCT increased **thickening** inner layers
F/U: Destruction inner retinal layers → **thinning**

56

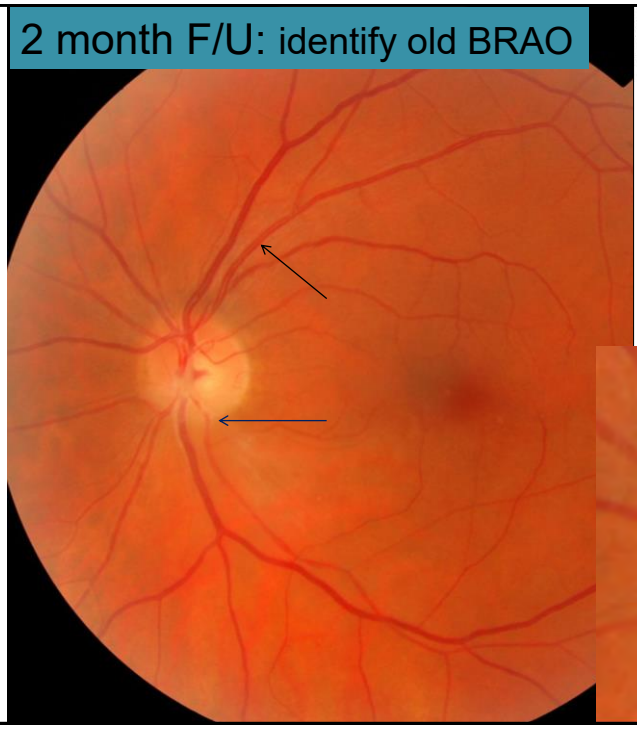

Macula Thickness : Macular Cube 512x128
OD
OS
500
400
300
200
100
0 µm
348
384
ILM-RPE
Overlay: ILM - RPE Transparency: 50 %

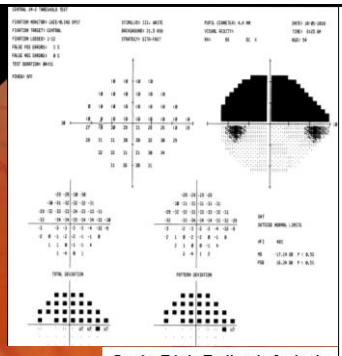
57


1 month F/U

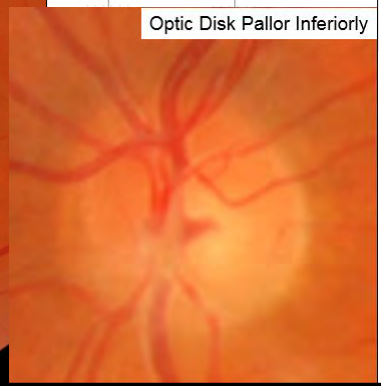
58

2 month F/U: identify old BRAO





Optic Disk Pallor Inferiorly



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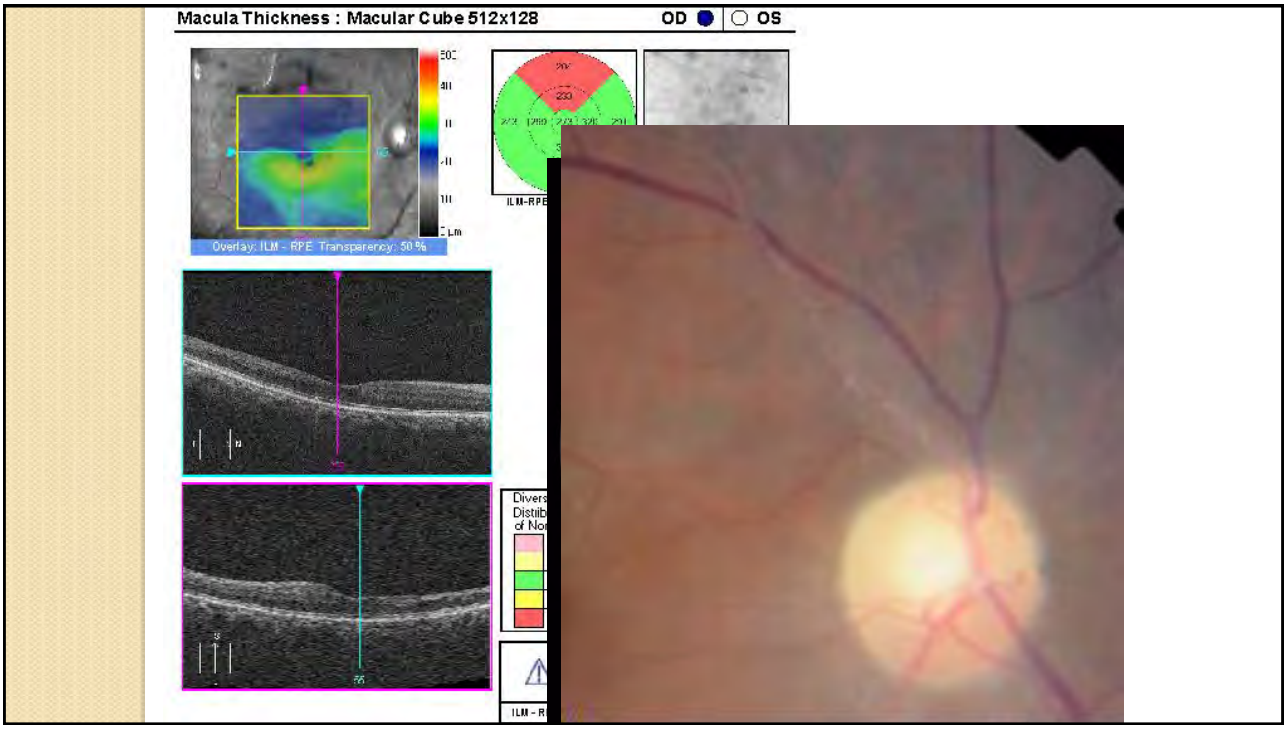

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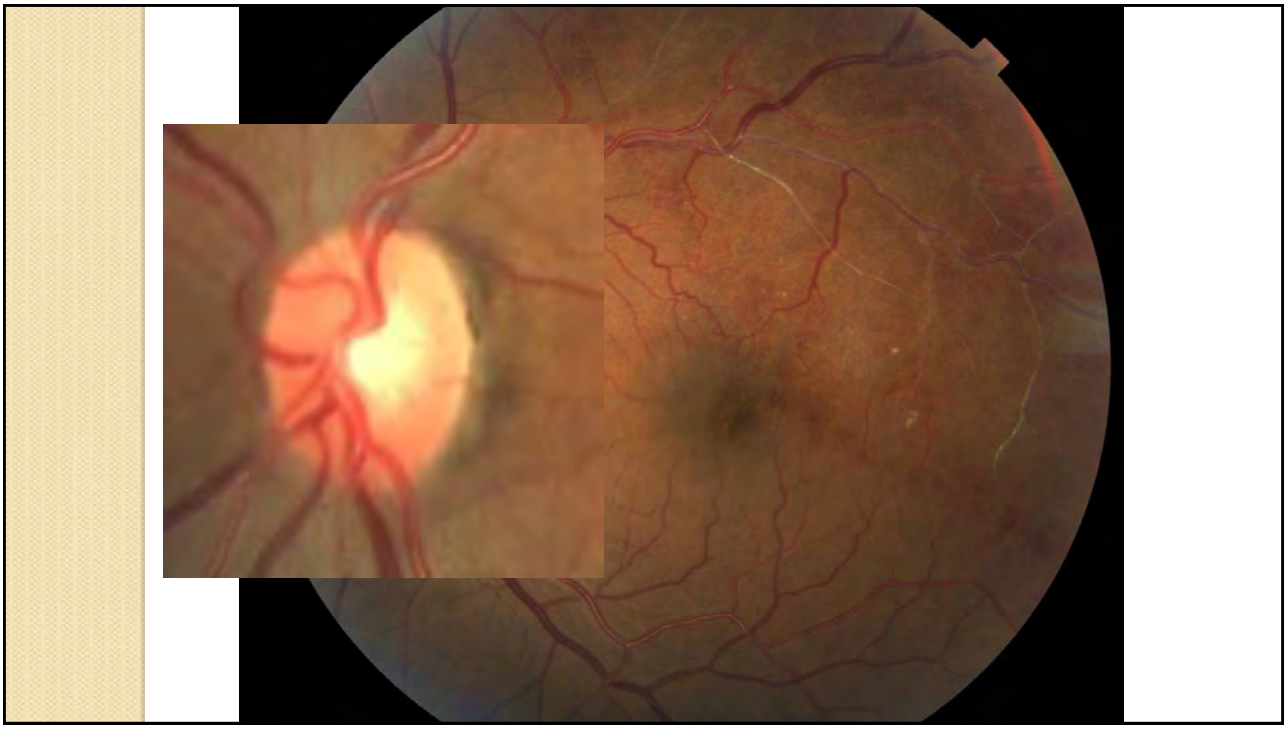

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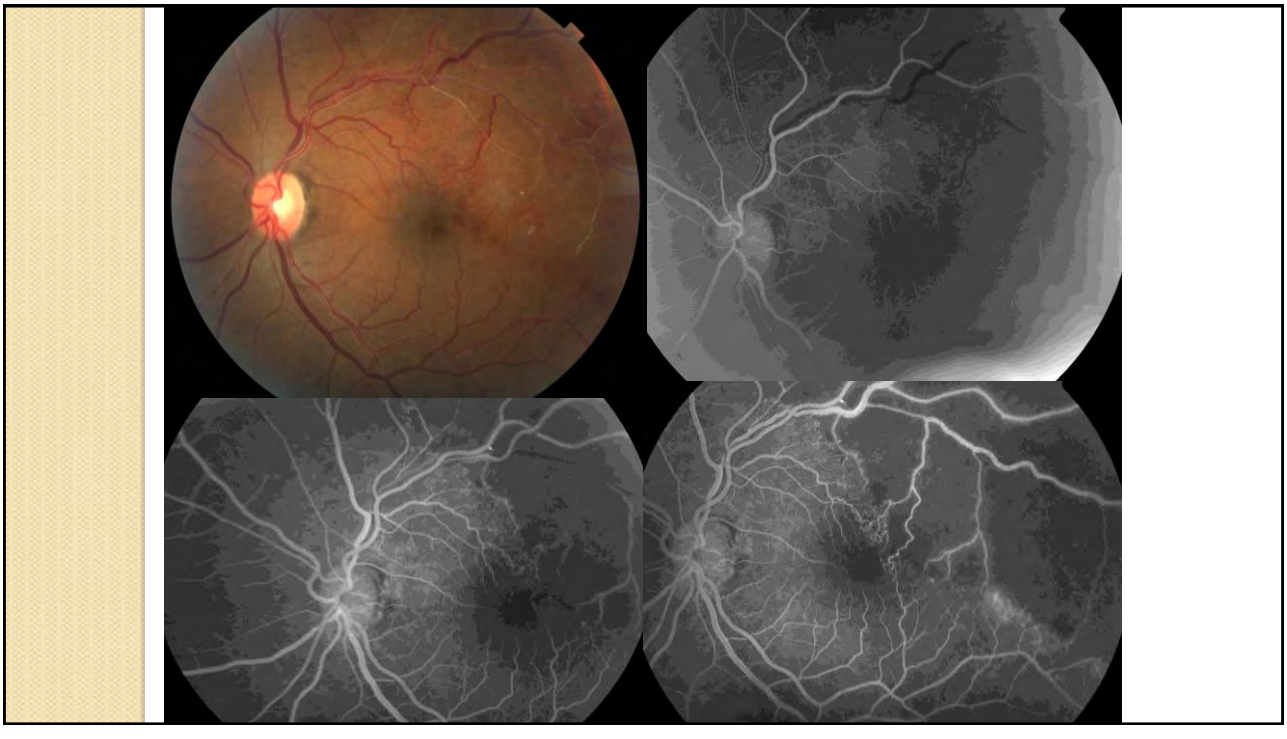

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Retinal Artery Occlusion
Associated Systemic and Ophthalmic Abnormalities

Sohan Singh Hayreh, MD, PhD,[1] Patricia A. Podhajsky, BSN,[1] M. Bridget Zimmerman, PhD[2]

Ophthalmology 2009; 116: 1928-1936

Carotid Doppler/Angiography	
Ipsilateral ICA >50% stenosis	**Plaque present**
30% BRAO	**66% BRAO**

Abnormal echocardiogram embolic source
42% of BRAO mostly calcified valve

BRAO/CLRAO require HEART + CAROTID evaluation

63

Ocular Arterial Occlusive Disorders and Carotid Artery Disease

Sohan Singh Hayreh, MD, PhD,[1] M. Bridget Zimmerman, PhD[2]

Ophthalmology Retina 2017; 1: 12-18

127 BRAO

Carotid Artery Stenosis > 50%	31%
Presence Plaques	**64%**
Echocardiography (embolic)	**53%**
Myocardial Infarction	22%
TIA/Stroke before/after RAO	3%

TIA/Stroke absolute incidence within 3 months RAO
BRAO – only 2 patients over 5 years

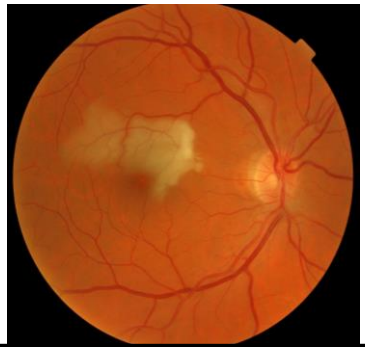
64

Open Access Full Text Article ORIGINAL RESEARCH

Ocular neovascularization in eyes with a central retinal artery occlusion or a branch retinal artery occlusion

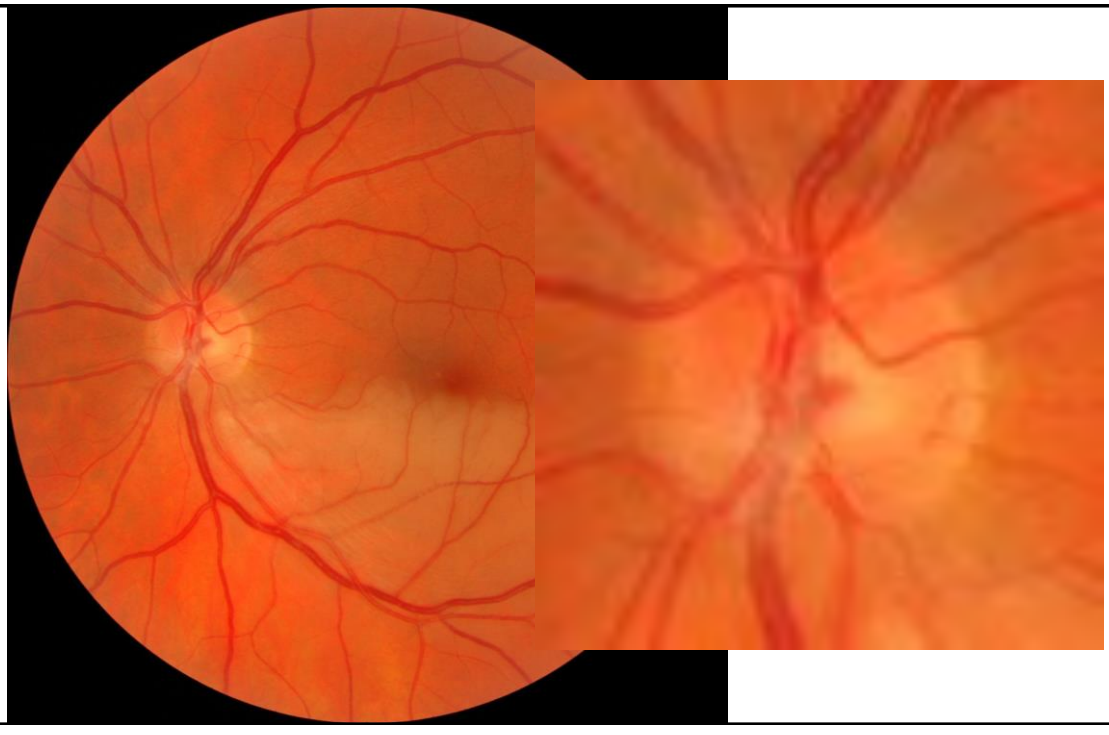
Mason et al. Clin Ophthalmology 2015: 9 995-1000

Ocular neovascularization
< 1% BRAO (ave 4.5 months)



BRAO Risk TIA/Stroke and NV SIGNIFICANTLY less vs CRAO

65



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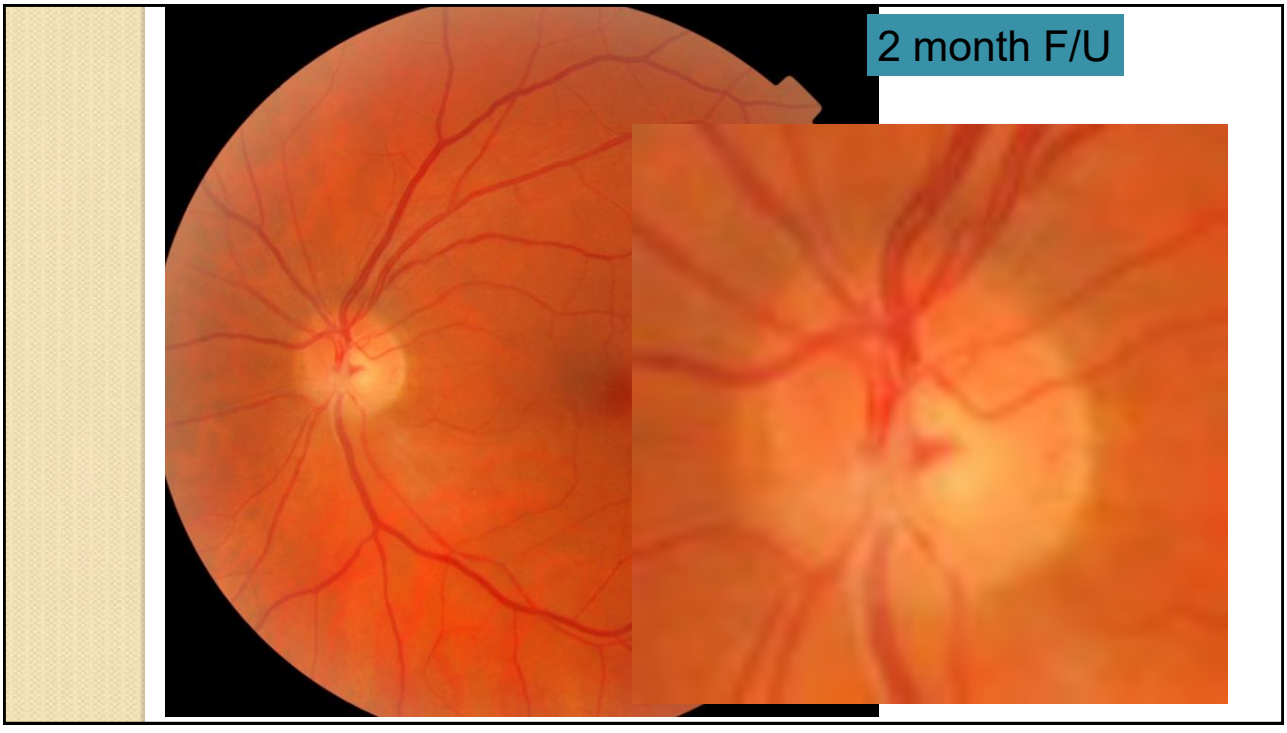

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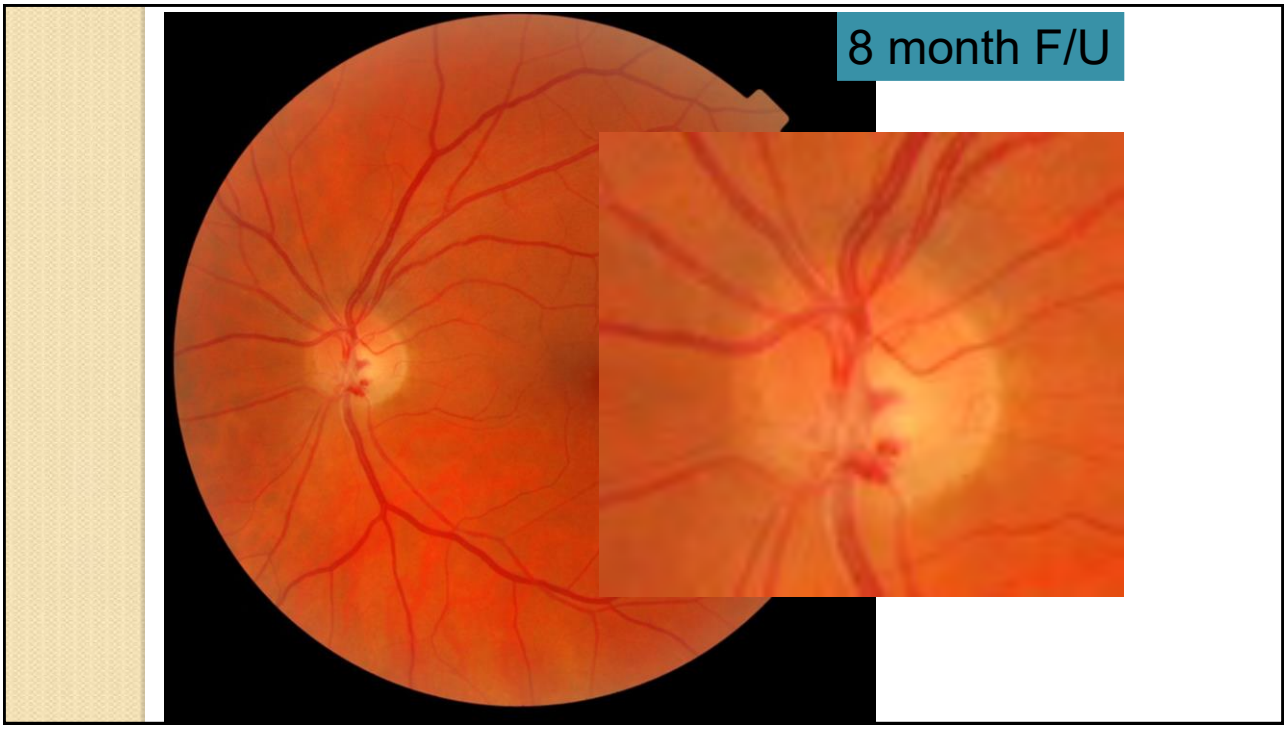

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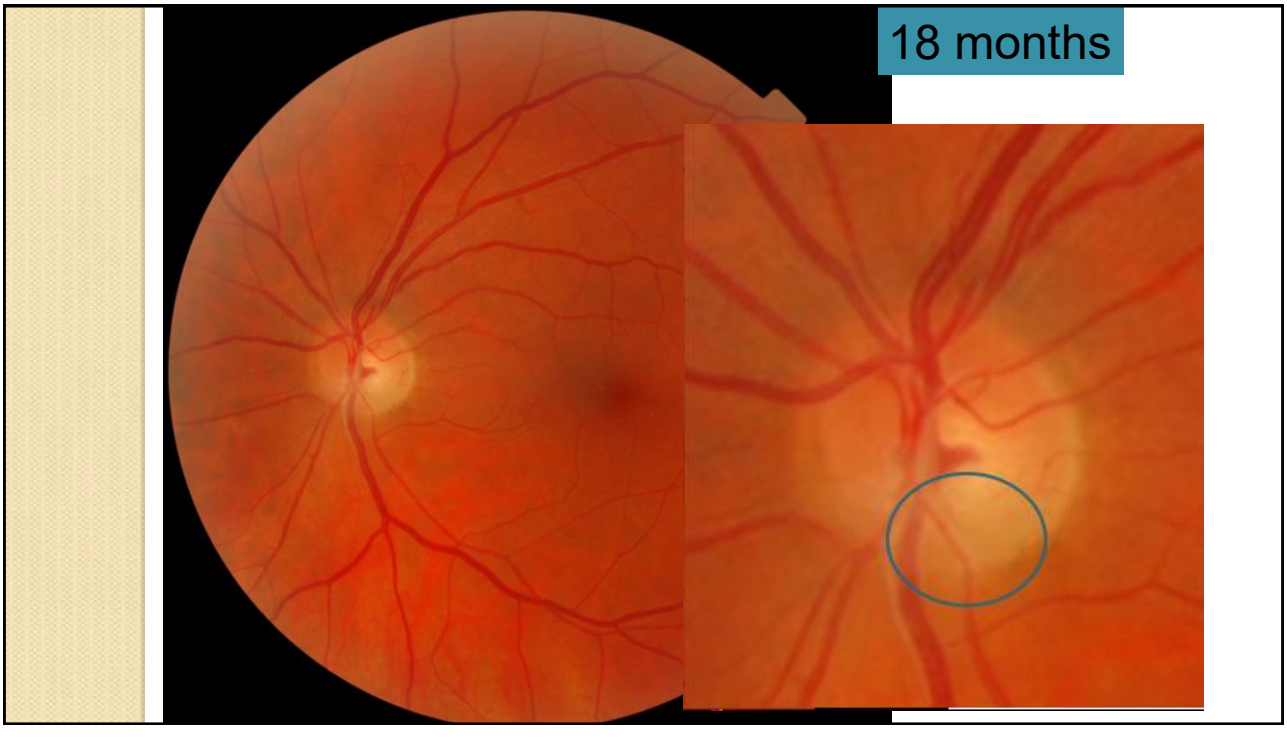

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Cilioretinal Artery

- Normal anatomical variant
- Choroidal blood supply
  - FA: CLR artery fills during choroidal flush
- Present ~ 32% eyes
- Hook-like appearance, temporal
- 88% cilioretinal arteries supply macula

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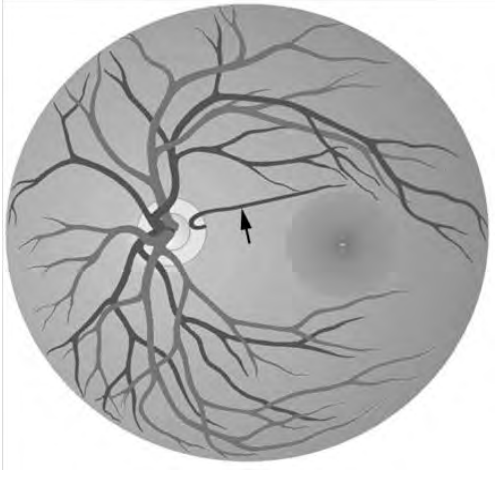
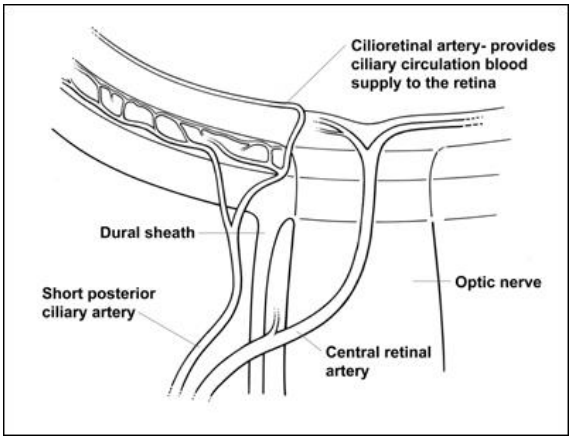
Cilioretinal Artery

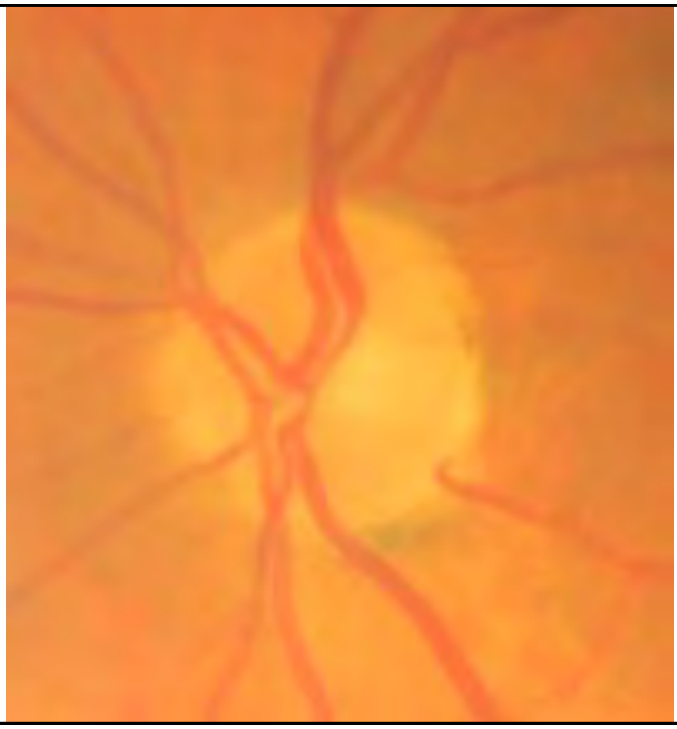


Exits optic nerve separate from CRA



Derived from short posterior ciliary arteries

72



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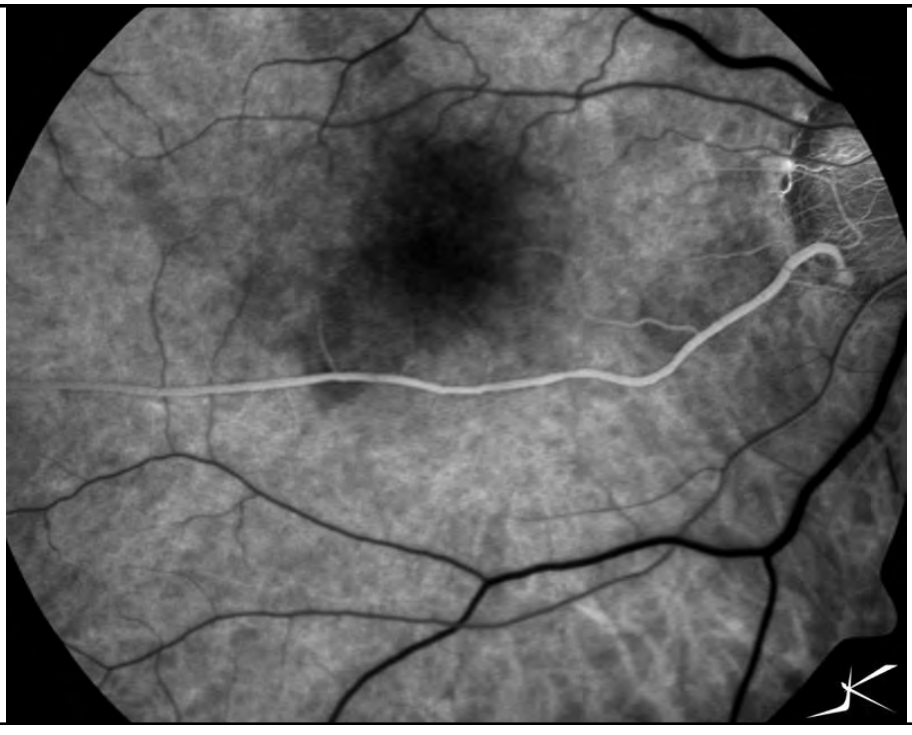

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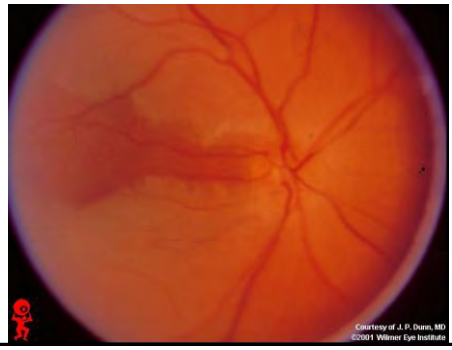
Cilioretinal Artery in CRAO

- Patent cilioretinal artery improves visual prognosis CRAO
- Bypass occlusion, supply macula
- Spare macula/central vision 25% CRAO



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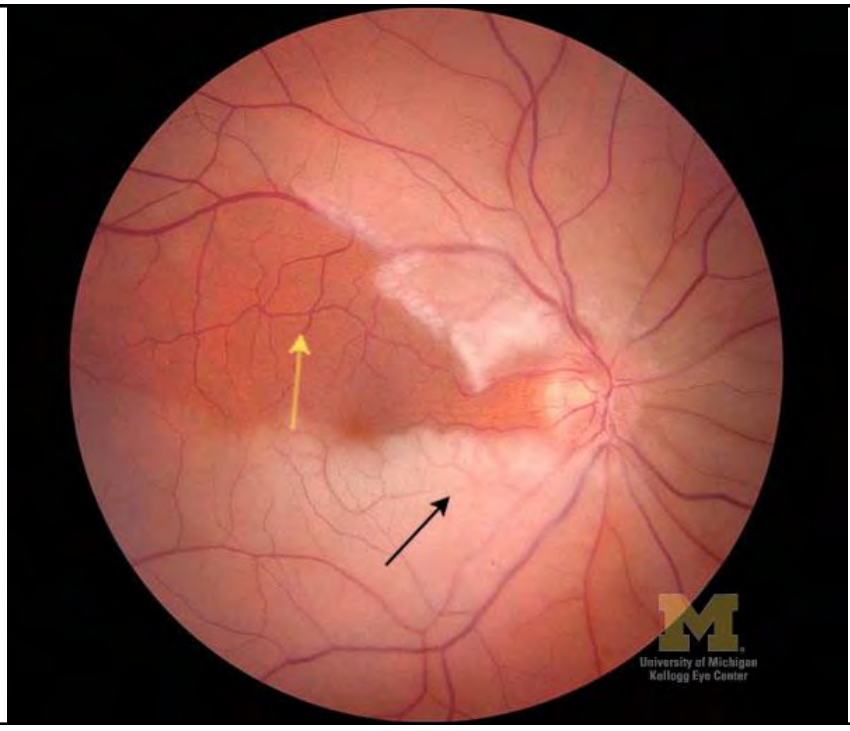

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Cilioretinal Artery Occlusions

- Cilioretinal artery occluded w/ associated vision loss
- 5% RAOs
- Isolated → GIANT CELL ARTERITIS
- 3 clinical variants:
  - Isolated CLRAO (40%)
  - CLRAO + CRVO (40%)
  - CLRAO + AION (20%) – arteritic vs non-art

Brown G et al. Cilioretinal Artery Obstruction. Retina 3: 182-187, 1983.

77

Primary Care Referral

- 53 year old Caucasian male
- Intermittent sudden loss right/lower vision OD
  - 8 am yesterday: lost lower right quadrant vision x 10-15 minutes, then spontaneously returned
  - 2 PM: repeat episode
- Today: Grey area, looking through veil

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Baseline Exam Findings

- Medical History: Hypercholesterolemia
- Medication: Simvastatin
- OD: 20/25 OS: 20/20
- No APD
- Screening visual field normal
- Mild vessel tortuosity OD
- Carotid U/S ordered
  - No hemodynamically significant stenosis

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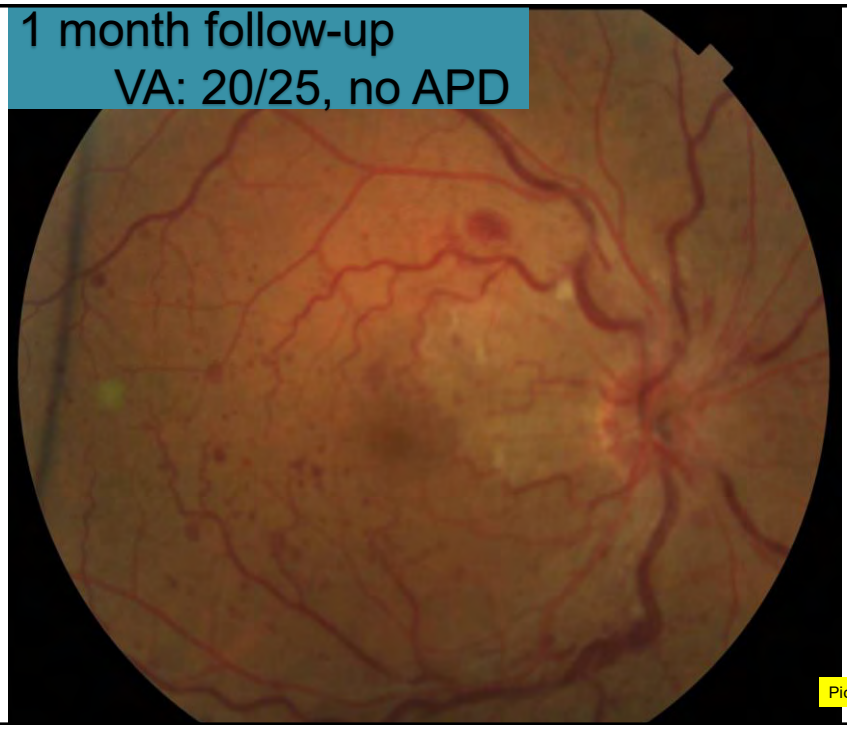

Pictures courtesy Dr. Brandy Augustine

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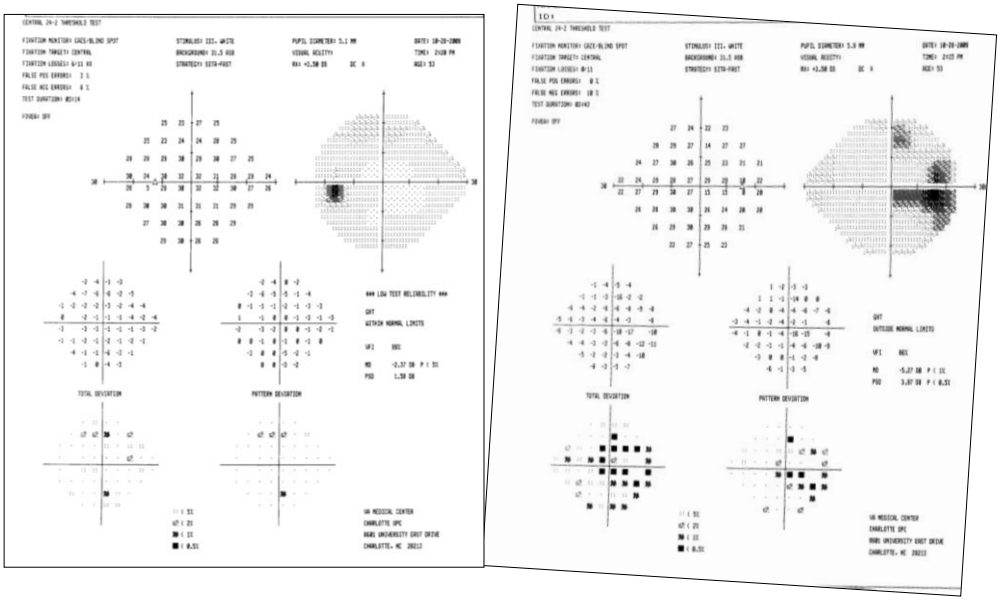
Centrocecal Defect



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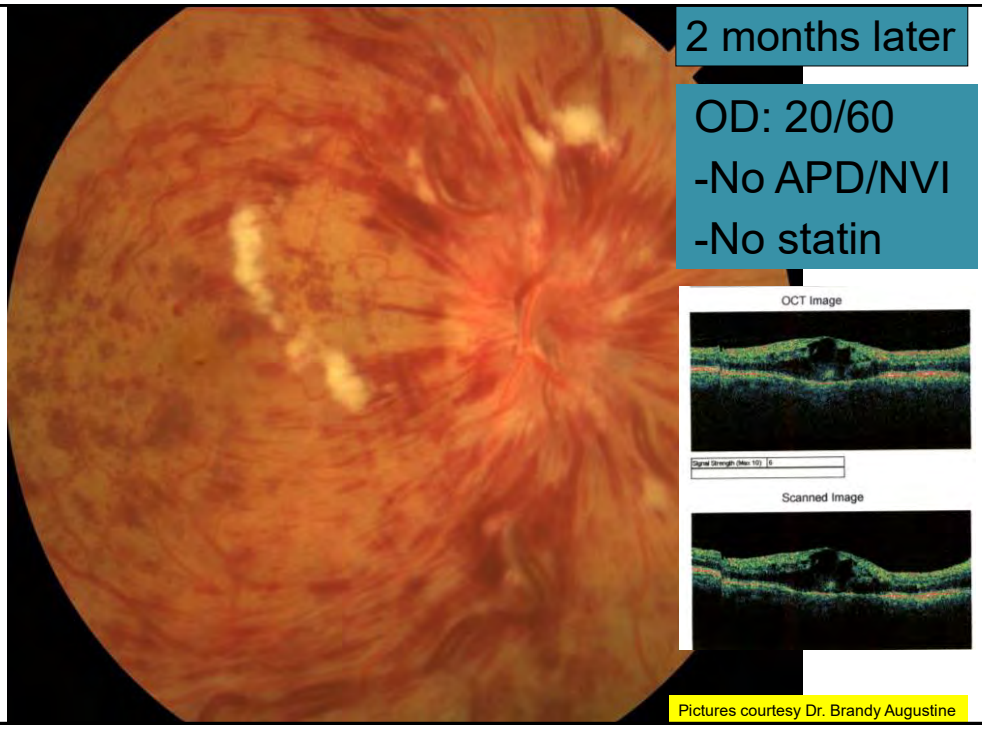
Work-up

- EKG: no abnormalities
- Coagulopathy labs: normal
- ESR/CRP/Platelets normal
- Hemoglobin A1c – 5.1
- Blood pressure: 140/90
- **Triglycerides** elevated
  - 285 w/ ref 0-200 → poor statin compliance

82



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CRVO associated w/ CLRAO

- 1/3 transient visual blur before constant blurred vision
- Centrocecal defect most common
- Hemodynamic Block
  - Venous pressure > Arterial pressure
  - Choroidal blood supply no autoregulation
  - Lower perfusion pressure
  - FA: Oscillating blood column

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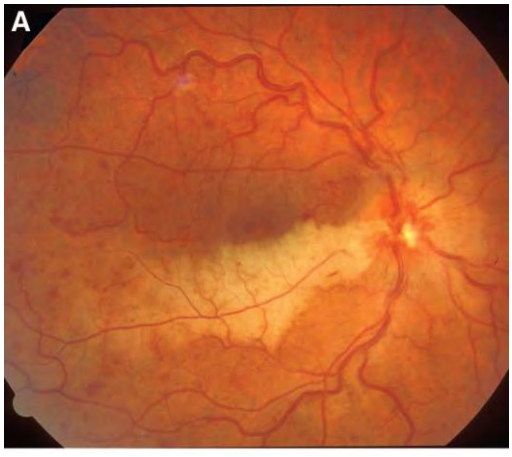
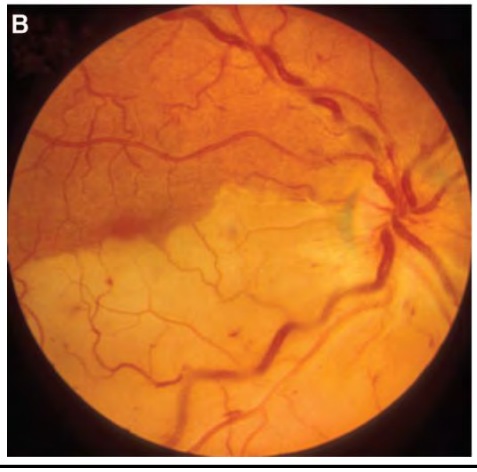
CENTRAL RETINAL VEIN OCCLUSION ASSOCIATED WITH CILIORETINAL ARTERY OCCLUSION

SOHAN SINGH HAYREH, MD, PHD, DSC, FRCS, FRCOPHTH,*
LYNN FRATERRIGO, MD,* JOST JONAS, MD†

Retina 28: 581-594, 2008





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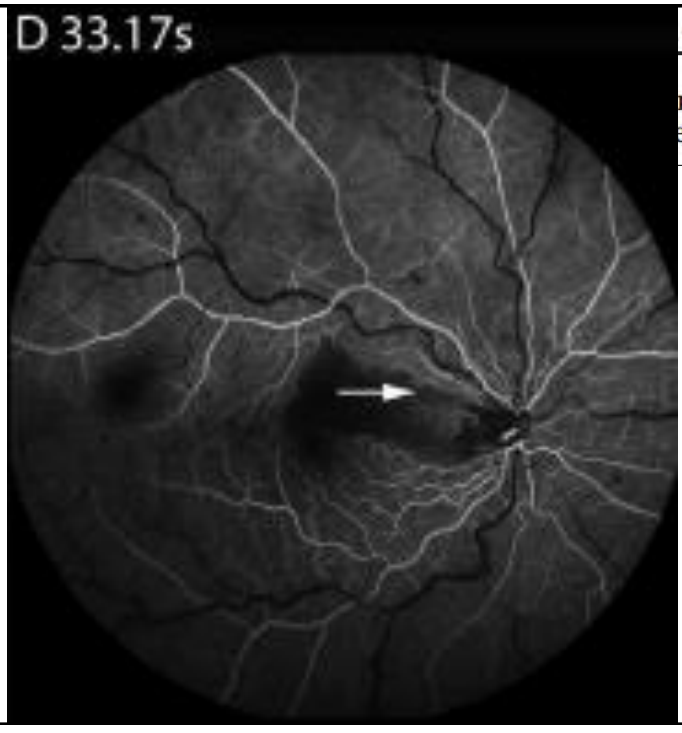


Toth with Michael I. Seider and Xi Chen

nal Artery
ein Occlusion

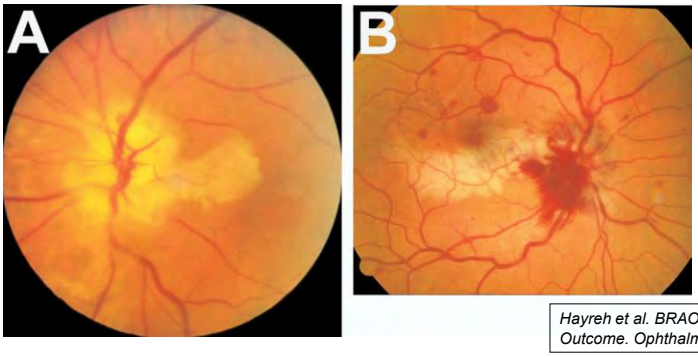
Oscillating Blood Column
-Systole = fill
-Diastole = retract

Retina 2016 May; 36 (5): e33-35

86

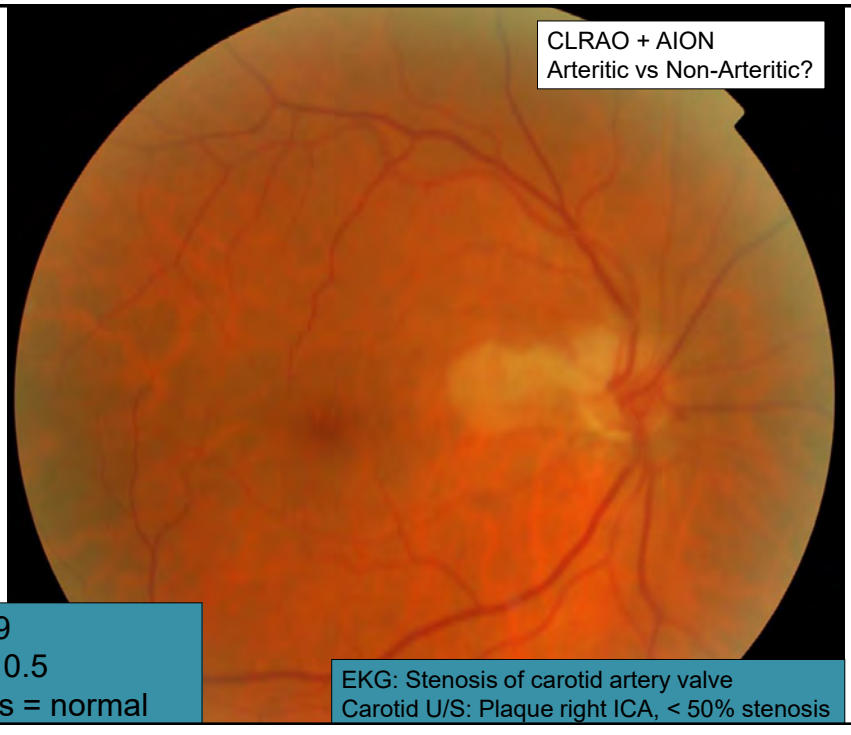
CLRAO – Giant Cell Arteritis

- Choroidal → Posterior ciliary arteries
- Simultaneous CLRAO + AAION
- **Need r/o GCA: ESR, CRP, Platelets**



Hayreh et al. BRAO Natural History of Visual Outcome. Ophthalmology 2009; 116: 1188-1194

87



ESR = 9
CRP = 0.5
Platelets = normal

EKG: Stenosis of carotid artery valve
Carotid U/S: Plaque right ICA, < 50% stenosis

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BRAO/CLRAO Management

- Embolic Work-up: Heart (EKG/ECG),CA R/O Giant Cell Arteritis
  - GCA disease medium/large arteries only
    - Branch retinal arteries = arterioles
  - **CLA supplied by posterior ciliary artery → need ESR/CRP/Platelets**
- Ocular Neovascularization, visual field
- AAO Preferred Practice Pattern
  - No strong evidence ASYMPTOMATIC BRAO
  - Referral to Stroke Center?? Triage?

89

Triage Stroke Risk w/ ABCD^2

- **A**ge > 60 = 1 point
- **B**lood Pressure
  - Systolic > 140 and/or diastolic > 90 = 1 point
- **C**linical symptoms
  - Unilateral weakness/numbness = 2 points
  - Speech disturbance w/o weakness = 1 point
- **D**uration
  - 0 < x < 10 minutes = 0 points
  - 10 < x < 59 minutes = 1 point
  - > 60 minutes = 2 points
- **D**iabetes = 1 point

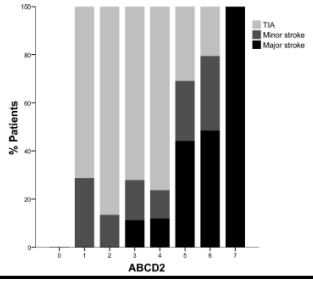
90

Multicenter external validation of the ABCD^2 score in triaging TIA patients

Tsivgoulis et al. Neurology 2010; 74: 1351-1357

ABCD^2-score	7-day stroke risk (95% CI)	90-day stroke risk (95% CI)
0-3	3% (0-7%)	4% (0-9%)
4-5	9% (1-17%)	21% (10-33%)
6-7	24% (6-42%)	43% (22-64%)

Low risk: ABCD^2 = 0-3; moderate risk: ABCD^2 = 4-5; high risk: ABCD^2 = 6-7.



ABCD^2 predicts **severity** recurrent events
-Disability
-Hospital stay length
-Hospital costs

Chandratheva et al. ABCD^2 Score Predicts Severity Rather Than Risk of Early Recurrent Events After TIA. Stroke. 2010; 41: 851-856

91

ABCD^2 for TIA

- Current international guidelines per
  - American Heart Association
  - American Stroke Association

Immediate hospitalization *+ diagnostic evaluation TIA patients* ***ABCD^2 score 3 or above within 24 hours*** *of symptom onset*

92

RAO = Stroke Education

- Many having stroke, DO NOT KNOW they are having a stroke!
- **Signs/Symptoms**
- Decision to call ambulance ~ 40%
  - Stroke = **SERIOUS + TREATABLE**
- Tissue Plasminogen Activator (TPA) ~ 4%
  - Principal impediment to Tx = LATE ARRIVAL (3 hours)
- **Time sensitive**!!

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Treatment (Un)Awareness

- *"Suppose you were having a stroke. Do you know of any medication your doctor could give you to increase your chance of recovering from stroke?"*

3.6% → T-PA or "clot buster"

EDUCATION NEEDED

Stroke public awareness campaigns →
NO IMPROVEMENT

Kleindorfer et al. Temporal Trends in Public Awareness of Stroke. Stroke. 2009; 40: 2502-2506

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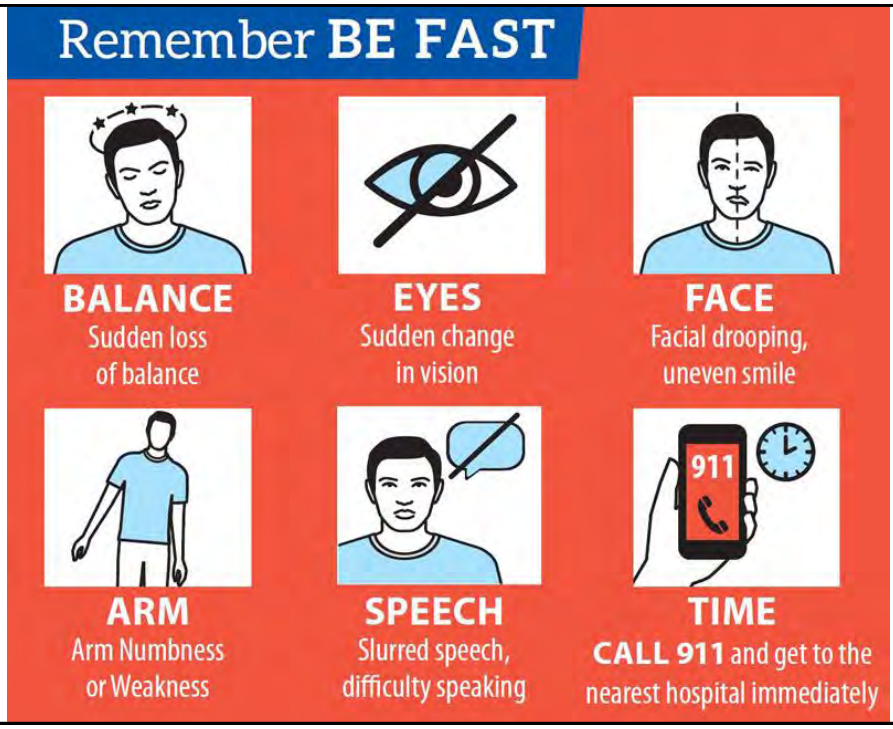

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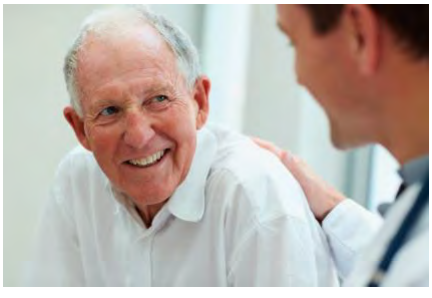
STROKE EDUCATION

-SIGNS

-URGENT

-TREATABLE



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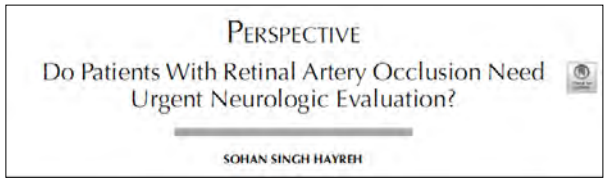
Only 1/3 OMD transfer acute CRAO → ER immediate evaluation

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Management of Acute Retinal Ischemia

Follow the Guidelines!

Valérie Biousse, MD,[1,2] Fadi Nahab, MD,[2,3] Nancy J. Newman, MD[1,2,4]



PERSPECTIVE

Do Patients With Retinal Artery Occlusion Need Urgent Neurologic Evaluation?

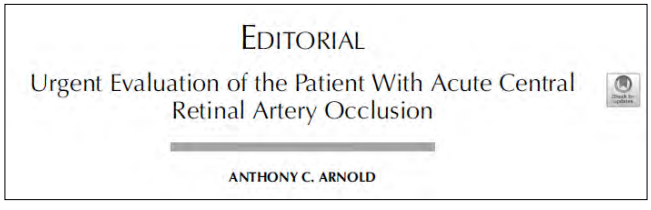
SOHAN SINGH HAYREH

Biousse,[4] a neuro-ophthalmologist, advocated that all patients with presumed transient or permanent retinal ischemia undergo urgent brain imaging and etiologic testing, like patients with cerebral ischemia. According to her, this is recommended by the guidelines by the National Stroke Association,[5] American Heart Association/American Stroke Association,[6] and other international organizations.[7] Yet a review of those publications showed that the report of the National Stroke Association[5] dealt with TIA only; the one by the American Heart Association/American Stroke Association[6] made no mention of retinal artery occlusion; and Uehara and

"My basic and clinical studies on retinal ischemia showed that… it is not logical for the American Heart Association/ American Stroke Association to lump retinal ischemia with TIA and stroke" – SS Hayreh

Am J Oph 2018; 196: 53-56

97



EDITORIAL

Urgent Evaluation of the Patient With Acute Central Retinal Artery Occlusion

ANTHONY C. ARNOLD

Does it make a difference how quickly evaluation is performed? YES!
To focus on differences in study population is to miss the point:

Urgent evaluation is necessary in CRAO to *characterize* those differences and *identify* more severely involved patients immediately because they are at risk for new events within 24-72 hours

Am J Oph 2018 Dec; 196

The paradigm for management of acute retinal ischemia has changed.
Dr. Hayreh's approach is outdated and potentially dangerous – Biousse V

Am J Oph 2019 Mar; 199: 262-263

98

RAO Management

- **Urgent R/O Giant Cell Arteritis**
  - CRAO, CLRAO, BRAO
- **Urgent Referral Stroke Center**
  - CRAO, BRAO
- **Embolic work-up (Heart, Carotid)**
  - CRAO, BRAO, CLRAO

  **Hayreh most important
- **Stroke Triage (ABCD^2)** BRAO/CLRAO?
- **Risk Factor Work-Up**
- **Stroke Education – ALL RAOs**

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Neurotropic Keratitis: Rare, or Hiding in Plain Sight?

Presented by Douglas Devries, OD

Marshall B.
KETCHUM UNIVERSITY
Southern California College of Optometry
Department of Continuing Education
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Neurotrophic Keratitis: Rare? Or Just Hiding in Plain Sight?

Douglas K. Devries, O.D.
Eye Care Associates of Nevada
July 2021

1

Douglas K. Devries, O.D. Financial Disclosures

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- **Eyes 4 Lives**
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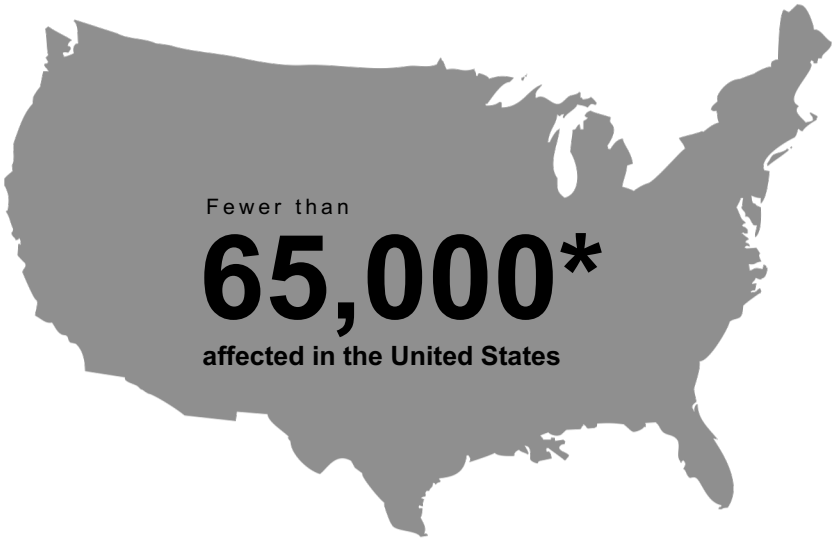
2

NK Is Classified as a Rare Disease



*Adapted number based on the United States population.
Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579.

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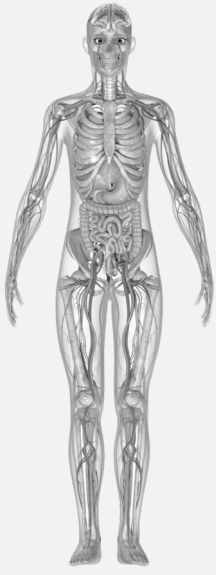

Etiologies of NK

NK is caused by impairment of trigeminal innervation, and several conditions can lead to this impairment…

OCULAR

SYSTEMIC

CENTRAL NERVOUS SYSTEM

GENETIC

- **Infections** (eg, post-herpes)
- **Ocular surgery** (eg, post-laser vision correction)
- **Contact lens wear**
- Chemical and physical burns
- Abuse of topical anesthetics
- Drug toxicity
- Chronic ocular surface injury

Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131.

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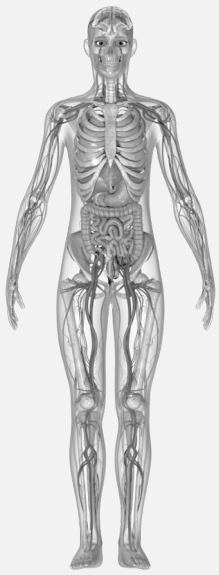

Etiologies of NK

NK is caused by impairment of trigeminal innervation, and several conditions can lead to this impairment…

OCULAR

SYSTEMIC

CENTRAL NERVOUS SYSTEM

GENETIC

- **Diabetes**
- Multiple sclerosis
- Vitamin A deficiency
- Leprosy
- Amyloidosis

Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131.

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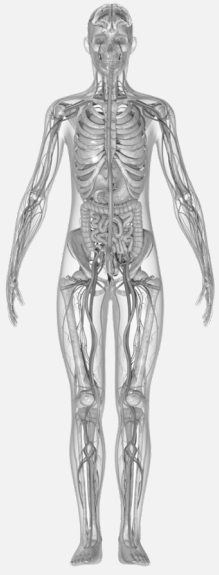

Etiologies of NK

NK is caused by impairment of trigeminal innervation, and several conditions can lead to this impairment…

OCULAR

SYSTEMIC

CENTRAL NERVOUS SYSTEM

GENETIC

- **Post-neurosurgical procedures**
- **Stroke**
- Neoplasm
- Aneurysms
- Degenerative disorders of the CNS

Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131.

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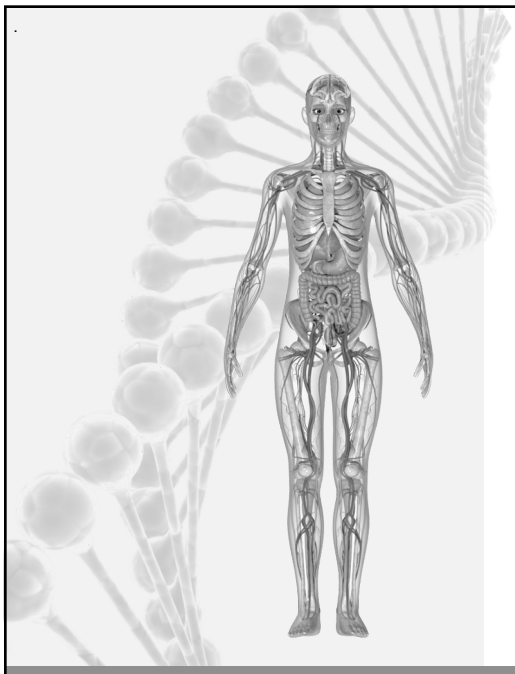

Etiologies of NK

NK is caused by impairment of trigeminal innervation, and several conditions can lead to this impairment…

OCULAR

SYSTEMIC

CENTRAL NERVOUS SYSTEM

GENETIC

- **Riley-Day syndrome**
- Goldenhar-Gorlin syndrome
- Mobius syndrome
- Familial corneal hypoesthesia

Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131.

7

7

Etiologies Associated with NK

Ocular
- Herpes (simplex or zoster) infection
- Other infections e.g acanthamoeba
- Chemical or physical burn
- Abuse of topical anaesthetics
- Drug toxicity
- Chronic ocular surface injury or inflammation
- Ocular surgery
- Cataract surgery
- LASIK, PRK
- PK and DALK
- Collagen crosslinking for keratoconus
- Vitrectomy for retinal detachment
- Photocoagulation for diabetic retinopathy
- Postsurgical or laser treatment
- Routine laser for proliferative diabetic retinopathy
- Contact lenses
- Orbital neoplasia
- Corneal dystrophies

Central nervous system
- Neoplasm
- Aneurysms
- Stroke
- Degenerative CNS disorders
- Post-neurosurgical procedures
  - For acoustic neuroma
  - For trigeminal neuralgia
- Other surgical injury to trigeminal nerve

Systemic
- Diabetes mellitus
- Leprosy
- Vitamin A deficiency
- Amyloidosis
- Multiple sclerosis

Genetic
- Riley-Day syndrome (familial dysautonomia)
- Goldenhar-Gorlin syndrome
- Mobius syndrome
- Familial corneal hypoaesthesia

DALK=deep anterior lamellar keratoplasty; LASIK=laser in situ keratomileusis; PK=penetrating keratoplasty; PRK=photorefractive keratectomy

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003.

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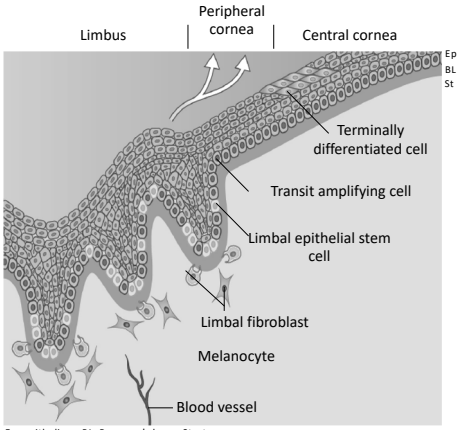
Corneal epithelial cells



Ep: epithelium; BL: Bowman's layer; St: stroma

Adapted from 1. StemBook. Available at: http://www.stembook.org/node/588.html. Accessed July 2018.

- Corneal integrity and function depends on a constant replenishment of epithelial cells
- Stem cells located in the limbus divide asymmetrically to produce:
  - More stem cells
  - Cells that differentiate into epithelial cells as they migrate out of the limbus
- In the healthy cornea, production of new epithelial cells is sufficient to replace cells lost at the epithelial surface

- Corneal epithelial cells and keratocytes regulate the survival, differentiation and maturation of nerve fibres by releasing neurotrophins and growth factors, such as:

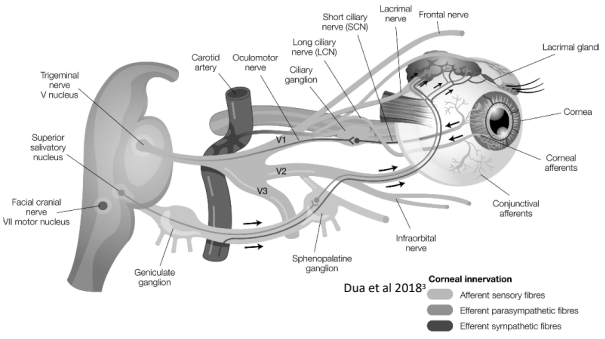
NGF	BDNF
NT-3	CNTF
NT-4	GDNF
EGF	

Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24; 2. Adapted from Shaheen B, et al. Surv Ophthalmol. 2014;59:263–85.

9

Cornea: Richest innervation of all body tissues[1]

- Healthy cornea contains no blood vessels and is extremely sensitive to pain[1]
- Corneal sensory nerves originate from the ophthalmic branch of the fifth cranial nerve[1]
- Trigeminal nerve bundles lose their perineurium and myelin sheaths where they enter the corneal stroma at the corneoscleral limbus, thus maintaining transparency of the cornea[1,2]
- The cornea also receives some sympathetic innervation from the superior cervical ganglion[2]

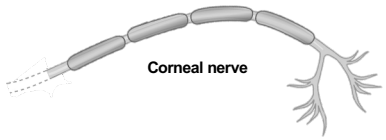


Dua et al 2018[3]

1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:521–42; 3. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print].

10

Role of corneal nerves



Corneal nerves react to injury at the ocular surface by registering pain and irritation and triggering **protective reflexes**, such as **tear production** and **blinking**[1]

They also release neuromediators that provide **trophic support** to corneal epithelial cells and keratocytes[1,2]

When corneal sensory nerves are damaged, these mechanisms are altered leading **to impaired corneal renewal and healing**, and reduced tear formation[1]

Neuromediators[1]

- Substance P
- Neurokinin A
- Calcitonon gene-related peptide
- Acetylcholine
- Cholecystokinin
- Galanin
- Noradrenaline
- Serotonin
- Neuropeptide Y
- Vasointestinal peptide
- Met-enkephalin
- Brain natriuretic peptide
- Vasopressin
- Neurotensin
- Beta endorphin

Images by kind permission of Prof. Dua

1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:521–42.

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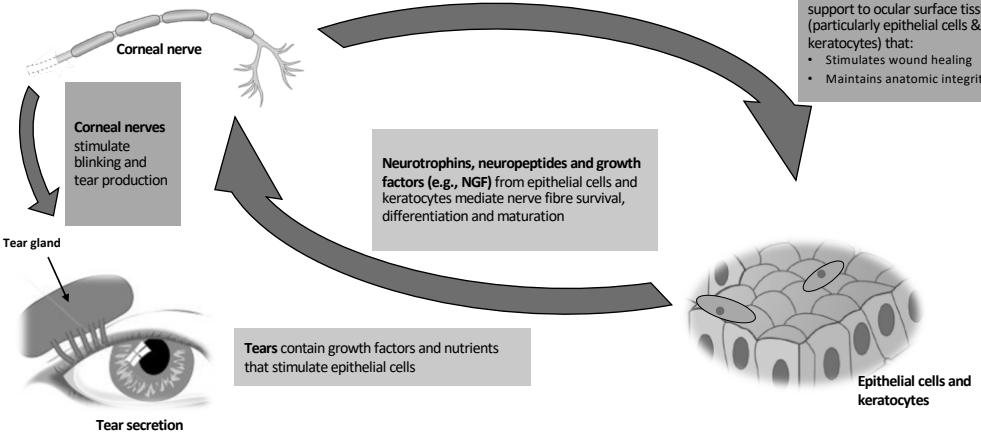
Corneal homeostasis

Interaction between corneal nerves and epithelial cells/keratocytes mediates corneal homeostasis



Adapted from Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24.

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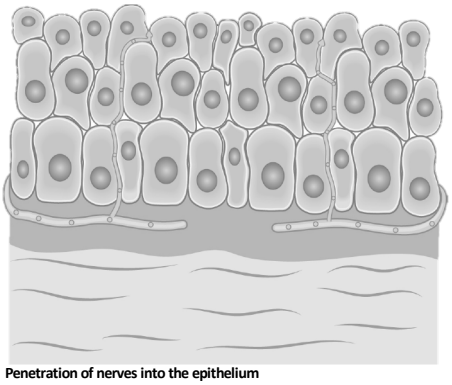
Pathophysiology of NK[1]

- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neuromediators that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomic integrity
- Impairment of corneal sensitivity also affects tear film production and blink rate due to the reduction of trigeminal reflexes
- Impairment of trigeminal innervation leads to decreased corneal epithelium renewal and healing rate, and ultimately the development of NK



Penetration of nerves into the epithelium

1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:521–42.

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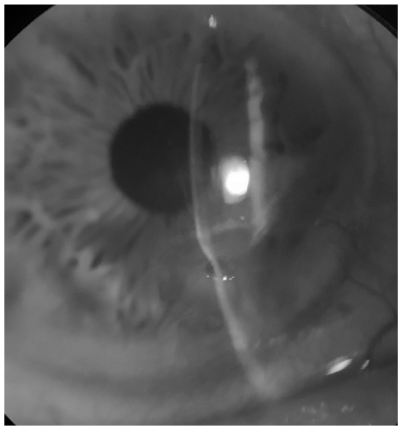
Neurotrophic keratitis (NK): Defined

Impairment of trophic supply and trigeminal reflexes

Epithelial alterations, impaired healing, reduced tear production, reduced blink rate

Spontaneous corneal epithelial breakdown

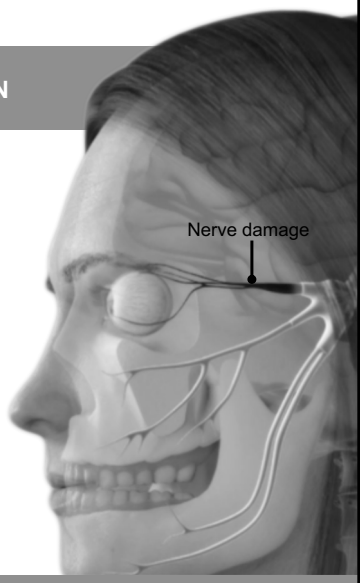


Mastropasqua L, et al. J Cell Physiol. 2017;232:717-724
Image courtesy of Elizabeth Yeu, MD

14

Nerve Malfunction: Central to NK

IMPAIRED CORNEAL TRIGEMINAL INNERVATION



Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017;232(4):717-724.

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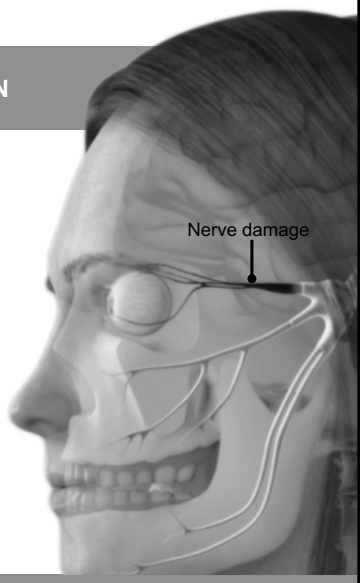
15

Nerve Malfunction: Central to NK

IMPAIRED CORNEAL TRIGEMINAL INNERVATION

- Impairment of trophic supply
- Impairment of trigeminal reflexes



Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017;232(4):717-724.

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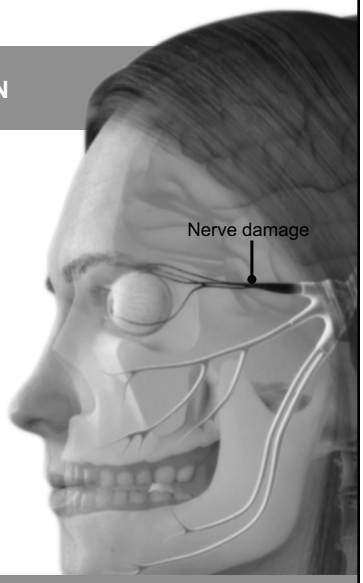
Nerve Malfunction: Central to NK

IMPAIRED CORNEAL TRIGEMINAL INNERVATION

- Impairment of trophic supply
  - Corneal epithelial alterations
  - Impairment of corneal healing
- Impairment of trigeminal reflexes



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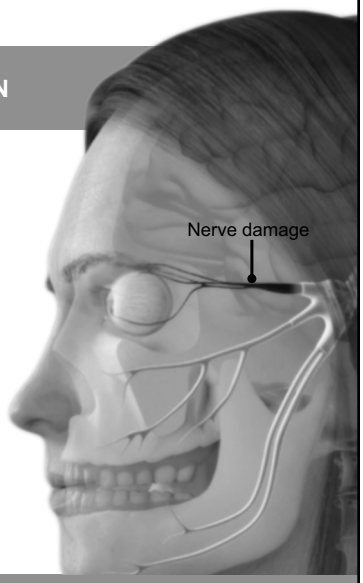
17

17

Nerve Malfunction: Central to NK

IMPAIRED CORNEAL TRIGEMINAL INNERVATION

- Impairment of trophic supply
  - Corneal epithelial alterations
  - Impairment of corneal healing
- Impairment of trigeminal reflexes
  - Reduced tear film production & blink rate



Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017;232(4):717-724.

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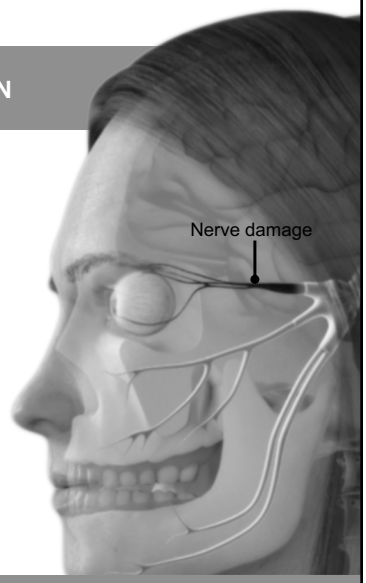
18

Nerve Malfunction: Central to NK

IMPAIRED CORNEAL TRIGEMINAL INNERVATION

- Impairment of trophic supply
  - Corneal epithelial alterations
  - Impairment of corneal healing
- Impairment of trigeminal reflexes
  - Reduced tear film production & blink rate

→ Spontaneous corneal epithelial breakdown



Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017;232(4):717-724.

19

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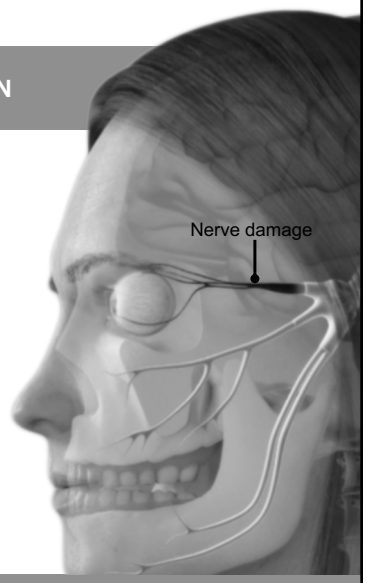
Nerve Malfunction: Central to NK

IMPAIRED CORNEAL TRIGEMINAL INNERVATION

- Impairment of trophic supply
  - Corneal epithelial alterations
  - Impairment of corneal healing
- Impairment of trigeminal reflexes
  - Reduced tear film production & blink rate

→ Spontaneous corneal epithelial breakdown

→ **NEUROTROPHIC KERATITIS**

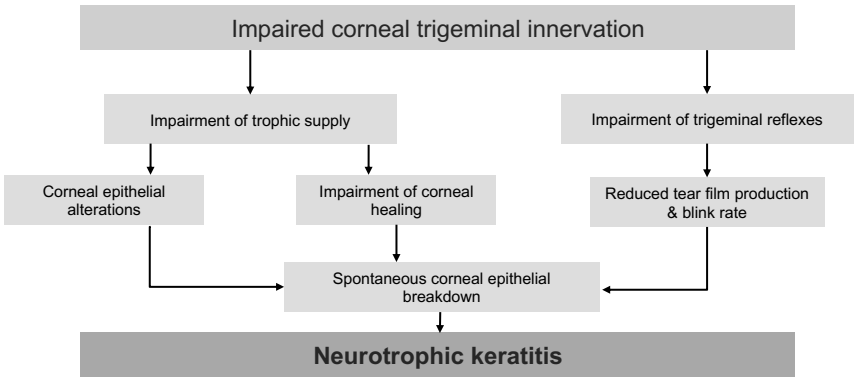


Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017;232(4):717-724.

20

20

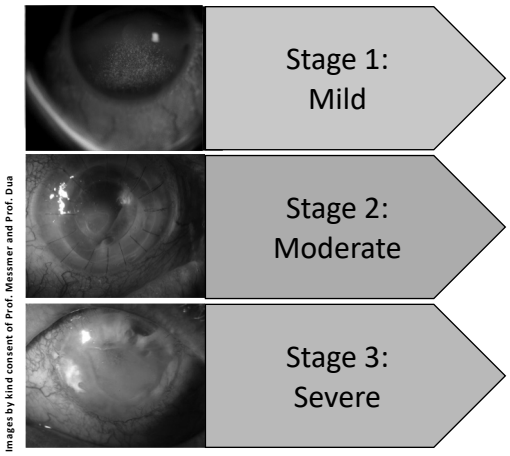
Trigeminal nerve damage leading to NK[1]



Adapted from 1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24.

21

NK classification



Images by kind consent of Prof. Messmer and Prof. Dua

Stage 1: Mild

(Epithelial changes only without epithelial defect):
Epithelial irregularity without frank epithelial defect, tear film instability and symptoms (hyper-aesthesia) with reduced or absent sensations in one or more quadrants of the cornea

Stage 2: Moderate

(Epithelial defect without stromal defect):
Frank persistent epithelial defect and corneal hypo-aesthesia/ anaesthesia

Stage 3: Severe

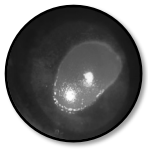
(Stromal involvement):
Stromal involvement from corneal ulcer to lysis to perforation, with corneal hypo-aesthesia/anaesthesia

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]. 2. 1. Semarero F, et al. Ophthalmologica 2014;231:191–7; 2. Sacchetti M & Lambiase A. Clin Ophthal 2014:8 571–9.

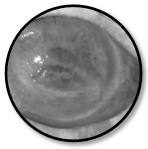
22

Neurotrophic keratitis (NK): Stages

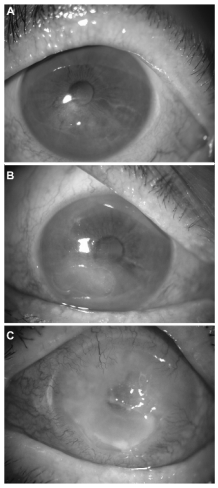
Mild: Staining, SPK, decreased TBUT, superficial neovascularization, corneal epitheliopathy
Epithelial changes but no defect



Moderate: Persistent epi defect with smooth/rolled edges, Descemet's folds, stromal edema
Epithelial defect but no stromal defect



Severe: Corneal ulcer, perforation, stromal melting
Stromal involvement

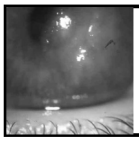


Sacchetti M, Lambiase A. Clin Ophthalmol. 2014;8:571-579
Dua HS, et al. Prog Retin Eye Res 2018;66:107-131
Versura P, Giannaccare G, Pellegrini M, Sebastiani S, Campos EC. Eye and brain. 2018;10:37

23

NK Is a Degenerative Disease[1]

The Mackie Classification Represents One Way to Assess NK Progression[2-4]



STAGE 1 (Mild)
Punctate epithelial keratopathy (PEK)

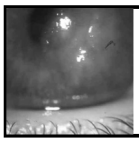
1. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res.* 2018;66:107-131. **2.** Semararo F, et al. Neurotrophic Keratitis. *Ophthalmologica.* 2014;231:191-197.
3. Bonini S, Lambiase A, Rama P, et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology.* 2018;125:1332-1343.
4. Roussel T, Grutzmacher R, Coster D. Patterns of superficial keratopathy. *Aust J Ophthalmol.* 1984;12(4):301-316.

24

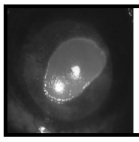
24

NK Is a Degenerative Disease[1]

The Mackie Classification Represents One Way to Assess NK Progression[2-4]



STAGE 1 (Mild)
Punctate epithelial keratopathy (PEK)



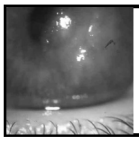
STAGE 2 (Moderate)
Persistent epithelial defect (PED)

1. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res.* 2018;66:107-131. **2.** Semararo F, et al. Neurotrophic Keratitis. *Ophthalmologica.* 2014;231:191-197.
3. Bonini S, Lambiase A, Rama P, et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology.* 2018;125:1332-1343.
4. Roussel T, Grutzmacher R, Coster D. Patterns of superficial keratopathy. *Aust J Ophthalmol.* 1984;12(4):301-316.

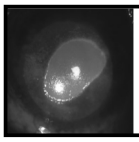
25

NK Is a Degenerative Disease[1]

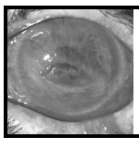
The Mackie Classification Represents One Way to Assess NK Progression[2-4]



STAGE 1 (Mild)
Punctate epithelial keratopathy (PEK)



STAGE 2 (Moderate)
Persistent epithelial defect (PED)



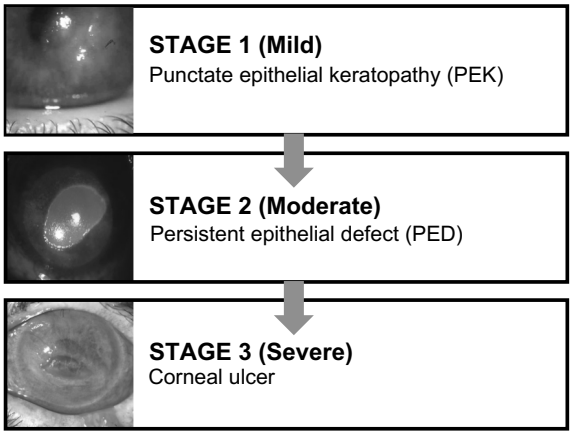
STAGE 3 (Severe)
Corneal ulcer

1. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res.* 2018;66:107-131. **2.** Semararo F, et al. Neurotrophic Keratitis. *Ophthalmologica.* 2014;231:191-197.
3. Bonini S, Lambiase A, Rama P, et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology.* 2018;125:1332-1343.
4. Roussel T, Grutzmacher R, Coster D. Patterns of superficial keratopathy. *Aust J Ophthalmol.* 1984;12(4):301-316.

26

NK Is a Degenerative Disease[1]

The Mackie Classification Represents One Way to Assess NK Progression[2-4]

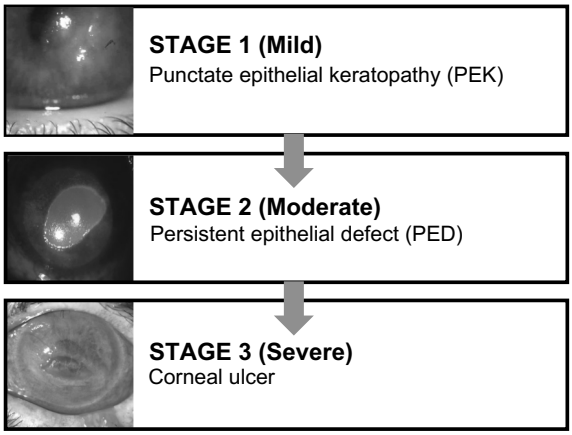


- Some vision loss can potentially be seen **in all stages of NK[3]**

1. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res.* 2018;66:107-131. **2.** Semararo F, et al. Neurotrophic Keratitis. *Ophthalmologica.* 2014;231:191-197.
3. Bonini S, Lambiase A, Rama P, et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology.* 2018;125:1332-1343.
4. Roussel T, Grutzmacher R, Coster D. Patterns of superficial keratopathy. *Aust J Ophthalmol.* 1984;12(4):301-316.

NK Is a Degenerative Disease[1]

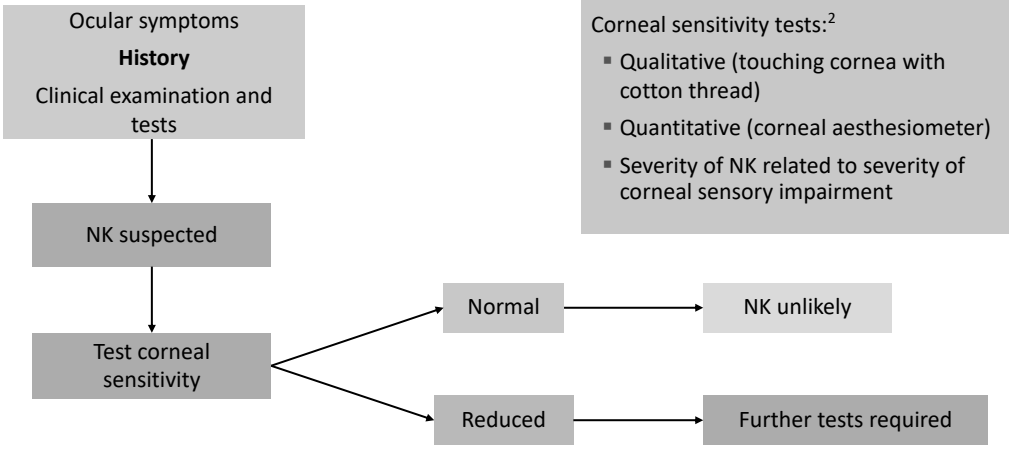
The Mackie Classification Represents One Way to Assess NK Progression[2-4]



- Some vision loss can potentially be seen **in all stages of NK[3]**
- If untreated, **moderate NK progresses to severe disease** with associated risks of **profound vision loss** resulting from scarring and corneal perforation[3]

1. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res.* 2018;66:107-131. **2.** Semararo F, et al. Neurotrophic Keratitis. *Ophthalmologica.* 2014;231:191-197.
3. Bonini S, Lambiase A, Rama P, et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology.* 2018;125:1332-1343.
4. Roussel T, Grutzmacher R, Coster D. Patterns of superficial keratopathy. *Aust J Ophthalmol.* 1984;12(4):301-316.

Assessment of corneal sensitivity is essential to confirm NK diagnosis[1]



Adapted from 1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]; 2. Sacchetti M & Lambiase A. Clin Ophthal 2014:8 571–9.

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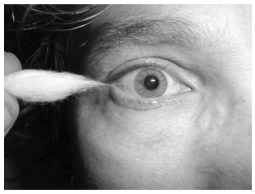
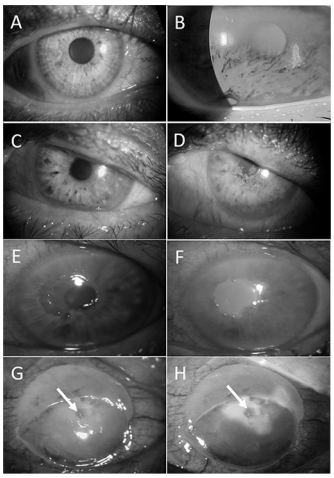
Neurotrophic keratitis (NK): Diagnosis

- Exam and history
- Vital dye staining
- Lid function and blink rate
- Corneal sensitivity
  - Cotton wisp contact test
  - Cochet-Bonnet esthesiometry
  - Bilateral comparison





Sheha H, Tighe S, Hashem O, Hayashida Y. Clinical Ophthalmology (Auckland, NZ). 2019;13:1973

30

Neurotrophic keratitis (NK): Patient Presentation

- "Stain without pain"
- Can be significant asymmetry
- Common presentations
  - Older, only has blurred vision, but exam reveals 5-mm defect!
  - Hx of HSV, c/o light sensitivity → epi breakdown

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Testing Corneal Sensitivity: A Key Step in Diagnosing NK

QUALITATIVE

- **Examples:** cotton swab, cotton wisp, dental floss, tip of a tissue
- Basic scoring systems may be developed using simple tests for sensation
- Descriptive scales: normal, hypoesthesia, anesthesia

QUANTITATIVE

- **Example:** Cochet-Bonnet esthesiometer
- Often used in basic research and clinical trial settings
- May be limited in general clinical practice

Milner M, Beckman K, Luchs J. Dysfunctional Tear Syndrome: Dry Eye Disease and Associated Tear Film Disorders - New Strategies for Diagnosis and Treatment. *Current Opinion in Ophthal.* Volume 28, Supplement 1. January 2017.

32

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Corneal Sensitivy Testing

33

Chronic Comorbidities May Worsen the Prognosis of NK

- Dry Eye
- Blepharitis
- Exposure Keratitis
- Topical Drug Toxicity
- Mild Chemical Injury
- Contact Lens-Related Disorder
- Limbal Cell Deficiency

They can also confound the diagnosis of NK, increasing the need for a thorough diagnostic workup, including a confirmatory test

Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579.

34

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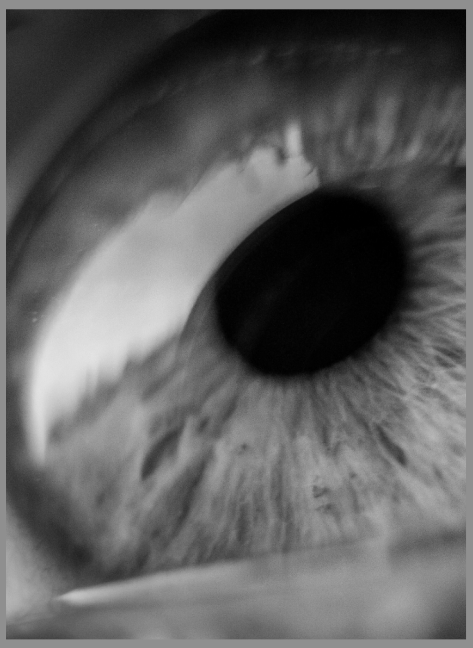
LET'S TALK TREATMENT



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NK Treatment Options[1-3]

Treatments are typically used according to NK stage/severity but are not mutually exclusive of one another.
The table is not an exhaustive list of all available treatment options.

Topicals	In-Office Procedures	Surgical Intervention
• Artificial tears	• Therapeutic contact lenses	• Tarsorrhaphy
• Corticosteroids	• Punctal occlusion	• Conjunctival flap
• Autologous serum eye drops	• Non-surgical eyelid closure	• Corneal transplant
• Antibiotics	• Amniotic membranes	• Direct neurotization
• OXERVATE (cenegermin-bkbj ophthalmic solution 0.002% [20 mcg/mL])	• Tissue adhesives	• Sutured AMT

1. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res.* 2018;66:107-131;
2. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017;232:717-724.
3. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579;

36

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Neurotrophic keratitis (NK): Therapeutic Bandage CL

PROS

- Inexpensive
- Mechanical protection
- Surface hydration

CONS

Risks

- Infection
- Hypopyon formation
- Reactive iritis

Requires frequent follow-up

- Use with caution!

Allen VD, Malinovsky V. Management of NK. Contact Lens Ant Eye 2003;26:161-5
Weissman BA, Mondino BJ. Contact Lens Ant Eye 2002;25:3-9

37

Amniotic Membrane

- Self-retaining or in O.R.
- Single or multi-layer graft or patch
- Heal acute defect
- Restore stromal thickness
- Re-establish epithelial integrity
- Consider amniotic membrane extract

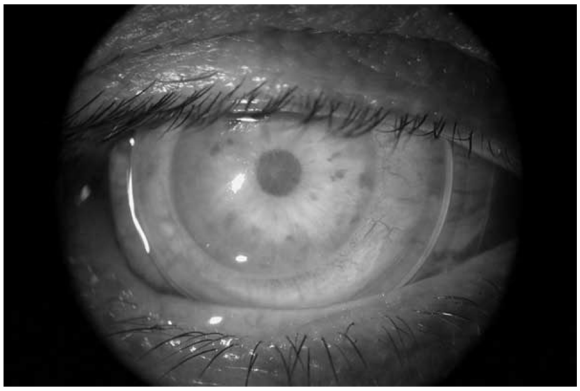
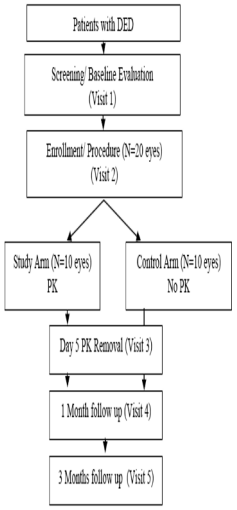


Image courtesy of Elizabeth Yeu, MD

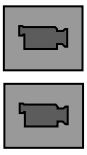
38

PROKERA® **ACCELERATE LASTING** HEALING IN DRY EYE BY PROMOTING **CORNEAL NERVE REGENERATION**

- A **prospective, controlled study** to compare self-retained amniotic membrane (ProKera® Slim, Bio-Tissue, Miami, FL) and conventional treatment in patients with **moderate to severe DED (DEWS 2-4)**.
- Twenty subjects were enrolled and randomized to receive ProKera Slim (PKS) or conventional treatment.
- Changes in signs and symptoms, corneal topography, corneal sensitivity, and corneal nerve density were evaluated a
1 month and 3 months



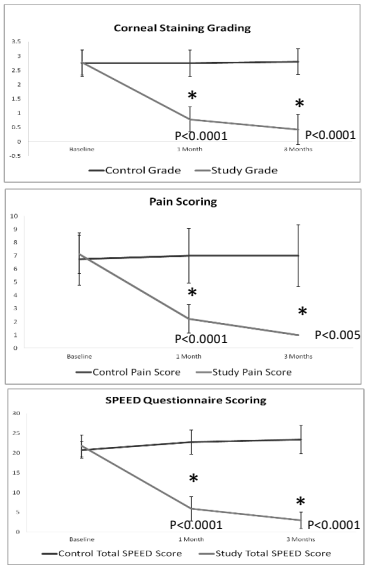
Dr. Thomas John

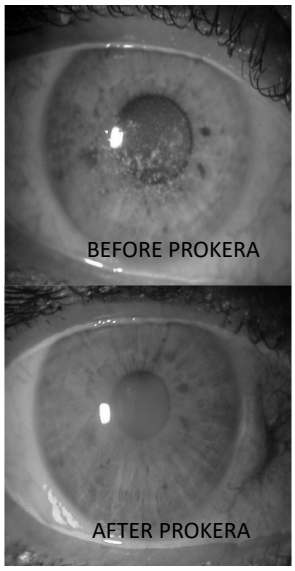


John et al, *Ophthalmol*, submitted, 2017

39

RAPID REDUCTION OF SYMPTOMS, PAIN, AND CORNEAL STAINING

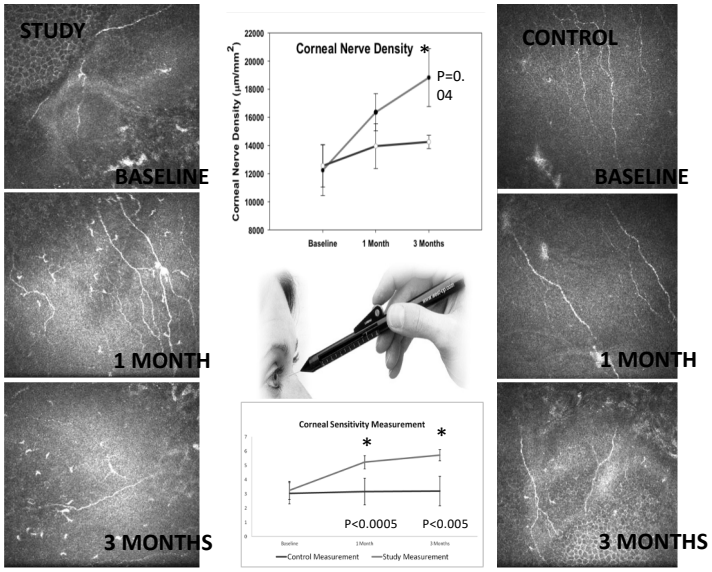




John et al, *Ophthalmol*, submitted, 2017

40

PROKERA®PROMOTING A **LASTING EFFECT** BY **INCREASING CONREAL NERVE DENSITY**



John et al, *Ophthalmol*, submitted, 2017

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New Therapies for Managing Neurotrophic Keratitis

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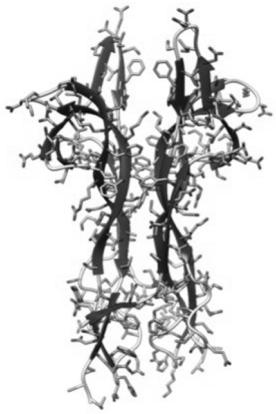
Cenegermin (Oxervate)

- Novel recombinant human nerve growth factor that is structurally identical to the NGF protein produced in ocular tissues
  - NGF plays a role in neuron development and survival, trophic support, epithelial cell proliferation & differentiation, & stromal healing[1]
  - First application of human NGF
  - First topical biologic medication in ophthalmology



Dua HS, et al. Prog Retin Eye Res 2018;66:107-131

43

Cenegermin-bkbj: Recombinant human NGF (rhNGF) Proprietary treatment developed by Dompé

~10x more potent than murine NGF based on in vitro studies

Phase I study (74 healthy subjects)

- Favorable safety and tolerability
- No immunogenicity and no significant changes in serum NGF

BioDrugs (2014) 28:275–283
DOI 10.1007/s40259-013-0079-5

ORIGINAL RESEARCH ARTICLE

Safety and Pharmacokinetics of Escalating Doses of Human Recombinant Nerve Growth Factor Eye Drops in a Double-Masked, Randomized Clinical Trial

Mauro P. Ferrari · Flavio Mantelli · Marta Sacchetti · Maria Irene Antonangeli · Franca Cattani · Gaetano D'Anniballe · Francesco Sinigaglia · Pier Adelchi Ruffini · Alessandro Lambiase

Resulting product: A more potent, patient-compatible NGF

Safety and pharmacokinetics of escalating doses of human recombinant nerve growth factor eye drops in a double-masked, randomized.Ferrari MP, Mantelli F, Sacchetti M, et al. clinical trial. BioDrugs. 2014;28(3):275e283

44

OXERVATE™ (cenegermin-bkbj 20 mcg/ml) was studied in the Largest Combined Population of NK Patients in Controlled Trials

	NGF0212 (REPARO) (n=156)	NGF0214 (n=48)
Geography	Europe 6 Countries (Italy, Germany, UK, France, Spain, Poland) 32 Clinical Centers	USA 11 Clinical Centers
Design	3 treatment arms: (vehicle, cenegermin 10 mcg/mL, cenegermin 20 mcg/mL)	2 treatment arms: (vehicle, cenegermin 20 mcg/mL)
Vehicle & cenegermin composition	Without antioxidant	With antioxidant (methionine)
Duration of follow up	48 weeks	24 weeks
Uni/bilateral disease	Unilateral	Unilateral and bilateral
Endpoints	Week 8 (based on a post-hoc analysis) Complete corneal healing (defined as 0.0 mm maximum diameter of fluorescein staining in the lesion area) *Primary analysis was <0.5 mm maximum diameter of fluorescein staining in the lesion area at Week 4	Week 8 Complete corneal healing (defined as 0.0 mm maximum diameter of fluorescein staining in the lesion area)

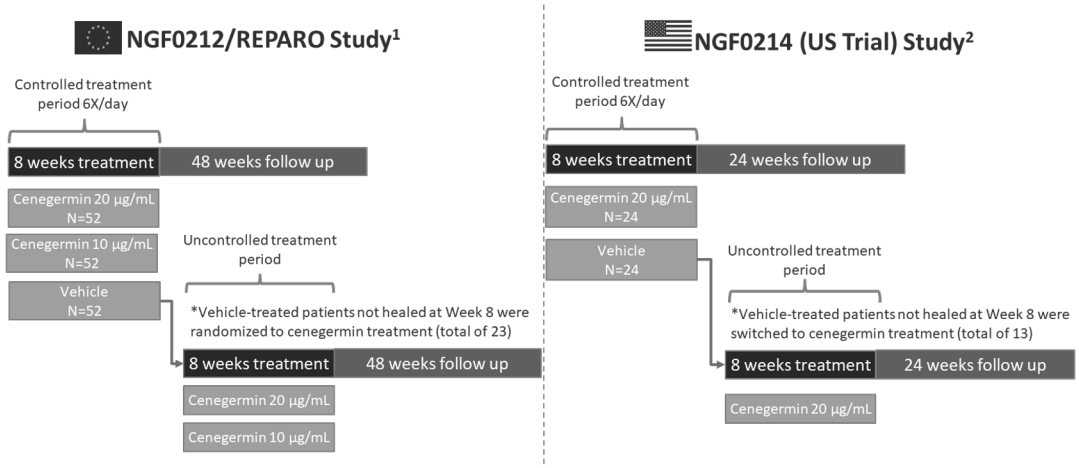
FDA approval was based on complete corneal healing defined as absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of treatment.

1. Bonini S, Lambiase A, Rama P *et al.* Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343. 2. OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

45

Clinical Trials: Study Design

OXERVATE™ (cenegermin-bkbj 20 mcg/ml)



The formulation that was tested in REPARO (Study NGF0212) did not include the antioxidant methionine and is not the final formulation that is marketed as OXERVATE™. Methionine is an excipient added to the commercial formulation to improve its stability. More than one study was conducted with the final commercial formulation. No difference in safety was seen in either of the trials.

46

1. Bonini S, Lambiase A, Rama P *et al.* Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343. 2. Chao W, J. BDC, R. D *et al.* Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE) 10–13 June, 2017, Barcelona, Spain. 2017.

46

Clinical Trials: Study Criteria

OXERVATE™ (cenegermin-bkbj 20 mcg/ml)

Main inclusion criteria

- Adult NK patients with stage 2 or 3 NK
  - Unilateral NK only in NGF0212/REPARO
  - Unilateral or bilateral NK permitted in NGF0214
- Evidence of decreased corneal sensitivity (<40mm by Cochet-Bonnet aesthesiometer) within the area of the PED or corneal ulcer and outside of the area of the defect, in at least 1 corneal quadrant
- Refractory to ≥ 1 nonsurgical treatment
- No improvement in in 2 weeks prior to enrollment

Main exclusion criteria

- Infection, inflammation, other ocular disease requiring topical treatment
  - Glaucoma patients were switched to systemic meds during the study
- Severe blepharitis or MGD
- Prior surgical treatment for NK
  - Exception for AMT performed > 6 weeks prior or membrane disappeared > 2 prior
- Stromal involvement in posterior third, corneal melting, or perforation in study eye

1. ClinicalTrials.gov Identifier: NCT01756456. 2. ClinicalTrials.gov Identifier: NCT02227147

47

Clinical Trials: History of NK

OXERVATE™ (cenegermin-bkbj 20 mcg/ml)

NGF0212/REPARO Study[1,3]

	OXERVATE™ (n=52)	Vehicle (n=52)
Primary NK diagnosis, no. (%)		
Stage 2 (moderate)	**27 (51.9)**	**28 (53.8)**
Stage 3 (severe)	**25 (48.1)**	**24 (46.2)**
Underlying cause, no. (%)		
Herpetic eye disease	11 (21.2)	18 (34.6)
Neurosurgical procedure	8 (15.3)	7 (13.4)
Ocular surgery or procedure	5 (9.6)	7 (13.4)
Dry eye disease	6 (11.5)	5 (9.6)
Ocular surface injury/inflammation	5 (9.6)	5 (9.6)
Other	5 (9.6)	3 (5.8)
Topical medication (glaucoma)	1 (1.9)	1 (1/9)
Stroke	2 (3.8)	0
Unknown origin	1 (1.9)	0
Systemic medication	0	0

NGF0214 (US Trial) Study[2,3]

	OXERVATE™ (n=24)	Vehicle (n=24)
Primary NK diagnosis, no. (%)		
Stage 2 (moderate)	**15 (62.5)**	**18 (75.0)**
Stage 3 (severe)	**9 (37.5)**	**6 (25.0)**
Underlying cause, no. (%)		
Herpetic eye disease	9 (37.5)	8 (33.3)
Neurosurgical procedure	1 (4.2)	5 (20.8)
Ocular surgery or procedure	3 (12.5)	4 (16.7)
Dry eye disease	3 (12.5)	3 (12.5)
Ocular surface injury/inflammation	2 (8.3)	1 (4.2)
Other	2 (8.3)	1 (4.2)
Topical medication (glaucoma)	1 (4.2)	1 (4.2)
Stroke	0	1 (4.2)
Unknown origin	2 (8.3)	0
Systemic medication	1 (4.2)	0

The formulation that was tested in REPARO (Study NGF0212) did not include the antioxidant methionine and is not the final formulation that is marketed as OXERVATE™. Methionine is an excipient added to the commercial formulation to improve its stability. More than one study was conducted with the final commercial formulation. No difference in safety was seen in either of the trials.

48

1. Bonini S, Lambiase A, Rama P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology. 2018;125:1332-1343. 2. Chao W, J. BDC, R. D *et al.* Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE) 10–13 June, 2017, Barcelona, Spain. 2017. 3. Drug Approval package; OXERVATE (Cenegermin-bkbj). Accessdata.fda.gov. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761094Orig1s000SumR.pdf. Published 2018. Accessed November 13, 2018

48

Clinical Trials: Pooled Safety Report

OXERVATE™ (cenegermin-bkbj 20 mcg/ml)

- No serious adverse reaction related to the treatment occurred in any clinical trials
- The majority of adverse reactions were mild and transient ocular reactions that did not require treatment discontinuation or any corrective treatment

16%

The most common adverse reaction was **eye pain** following instillation, which was reported in approximately 16% of patients.

12/75= 16%
7/23=30.4% (US trial)
5/52= 9.6% (REPARO)

1-10%

Other adverse reactions occurring in 1%-10% of patients taking OXERVATE and more frequently than in the vehicle-treated patients included **corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation**, and **tearing.**

Source: Data on file, pooled analysis of NGF0212/REPARO and NGF0214

1. Bonini S, Lambiase A, Rama P, et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343. 2. OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

49

OXERVATE™ (cenegermin-bkbj 20 mcg/ml) was approved by FDA in August 2018

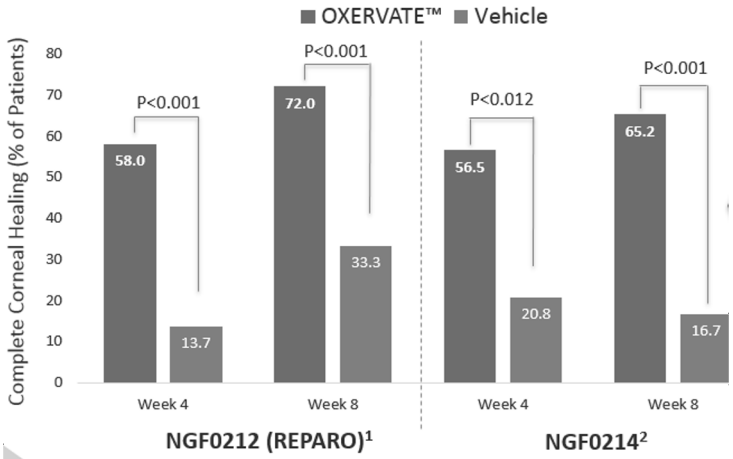
- Approved for the treatment of neurotrophic keratitis in adults and children age 2 and older
- Available for ordering since January 2019 through a specialty pharmacy
- Developed by Dompé pharmaceuticals

1. Bonini S, Lambiase A, Rama P *et al*. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343. 2. OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

50

Cenegermin FDA Clinical Trial Results

- Efficacy Established as Early as Week 4



51

Summary of New Therapies for Managing Neurotrophic Keratitis

- Neurotrophic keratitis has historically been very challenging to manage, with significant associated morbidity
- Existing treatment options are aimed to close epi defect or close eyelids
- New therapies offer the promise of corneal healing and nerve regeneration

52

Anterior Segment Cases: OMD vs OD

Presented by John Maher, MD and David Sendrowski, OD

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Anterior Segment Cases: OMD vs OD

Dr. John Maher, FACS

Dr. David Sendrowski, FAAO

1

Financial Disclosure Information

Lecture Bureau for:

- *Alcon Pharm.*
- *Allergan Pharm.*
- *VSP*
- *Ista Pharm. (now B&L)*

Nor do I or We or any immediate family member have any personal business interests, affiliation or activity with any entity in the Optometric health care field that would give rise to a Conflict of Interest in this lecture

No animals were harmed during the development of this lecture!

2

Case #1

A 48 year old patient reported that they experienced itchiness and burning of at first, the right eye and then at times the left. Usually it was the right eye and the patients reported sleeping on their right side, so it made sense. Strangely, adjusting pillows and sleep modification positions did not seem to alleviate the problem. Sleeping pills made the symptoms worse. The patients surmised that the mild itchiness arising in middle age was indicative of allergy, and several anti-allergy OTC drops including Visine were used. At first, they seemed efficacious because they "got the red out", but strangely the itchiness persisted. Dietary changes were made including a cessation of sugar, and gluten containing foods. The itching and burning continued and seemed to worsen as the day progressed, especially at work, where long periods were spent viewing a computer screen in a pharmaceutical factory, under clean conditions. The patients were convinced that stress was a factor and therefore convinced their PCP to Rx an anxiolytic, but they only continued to have the symptoms while being very relaxed and sleepy.

3

Case #1

On the supposition that this was an allergy, to something, somewhere, somehow, and on the advice of family, friends, and clergy who also felt that this was allergy, the patient consulted a busy ophthalmologist, who listened to the fourteen minute narrative history, with magnificent detachment. A brief and efficient exam followed. To the query from the patients as to whether surely this was simply a distressing allergy, the ophthalmologist simply replied: "Yeh, could be". He shrugged the shoulders of his immaculately starched white coat, and thoughtfully gazed momentarily at the gleaming, complicated sculpture of mirrors, lights and lenses that was his slit lamp. Then he wrote out a RX for a very expensive antihistamine, with a similar generic name to that that the patients took OTC. However this one needed only to be taken once every other day, if either of the patients could get straight which day that was. The price of the bottle of drops was equivalent to that of a pair of prescription spectacles, but with the coupon that the doctor handed out the price was reduced 20%. No follow-up was scheduled. The ophthalmologist's parting words were: Come on back whenever you feel…", or perhaps "come on back whenever you get real…..", or something.

4

Case #1

The medication afforded little relief from itching, although there was a temporary relief from burning after the drop was instilled, much like the relief from an artificial tear drop.

The patient was convinced that they had a recurrent infection that would worsen as the day went on. Their eyes seemed infected because they were red. When smoking marijuana, their eyes were also red, but the idea that they were infected then only seemed humorous; perhaps because they were high.

The frustrated patient took themselves to another ophthalmologist and told their story of allergy. They asked: "Could it be an allergy to make-up which one of us uses?". The ophthalmologist listened with magnificent detachment with her index finger poised at her right cheek, and then shrugged her shoulders, and said: "Possibly". The patients, almost without pausing went on: "Because we have tried every kind of make-up on the market and have even stopped using it, but the itching and burning and late in the day pain continues.", thus answering their own question.

"It must be an infection, because the eyes are red and there is a 'discharge' that I know you don't see, but it is there.". They then went on to describe the discharge for seven minutes. The ophthalmologist said that it was an infection, and to take antibiotic drops four times a day, and to return someday. The antibiotic drops would relieve the burning temporarily, like tears, or allergy drops, or their friends contact lens solution, or the ear drops that they inadvertently placed in their eye once while smoking MJ. The ear drops did help that infection.

5

Case #1

The discomfort began to be greater than the itchiness and redness. In the AM or when one of them had to get up to go to the bathroom at night it seemed like their eyelids were stuck to their eyeballs. This was especially true in the AM and they had to use their fingers to gently pry open their eyes and the discomfort would persist for several minutes. During the day the complaint was that a foreign body would fly into the eye, only to fall out and then another one would lodge itself in the eye again. Ophthalmologists looked, and saw nothing, and would assume a thoughtful pose afterward as they talked of "paradox" and spoke of "conundrum". Once the eye really hurt, and the ophthalmologists' thought there was negative fluorescein staining, but said little, except to use artificial tears. Finally intense pain forced the patients into the ophthalmologists office where she noted a corneal abrasion. The patients said that something must have flown into their eye. A patch and antibiotic drops were used and the abrasion healed, but then the same symptoms happened again. The ophthalmologist thought of recurrent erosion, but ruled it out because he could not see the fingerprint lines of Cogan's Dystrophy. Several more episodes of early morning abrasions occurred.

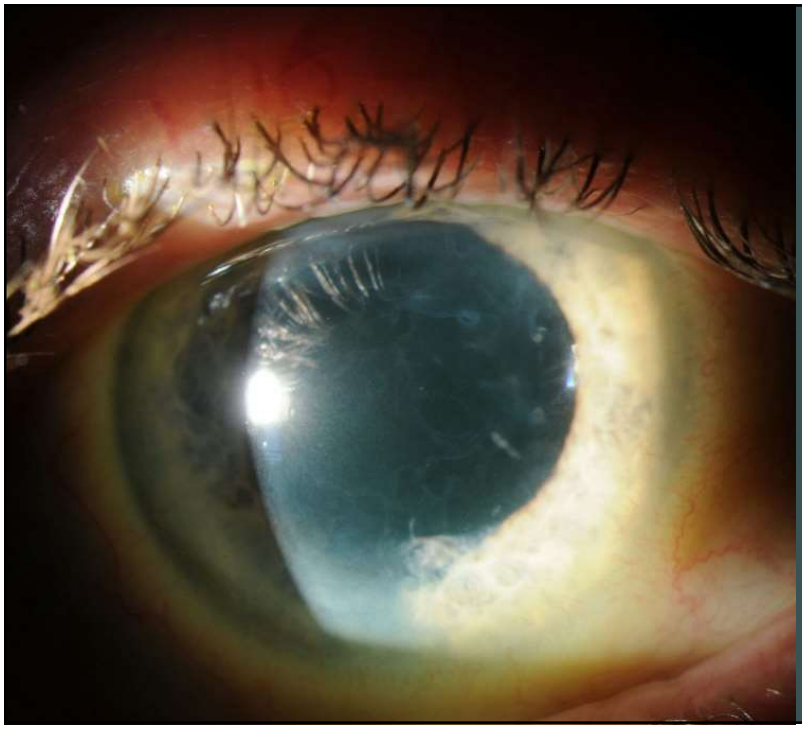
6

Case #1

The ophthalmologist listened to the patients speculations of: "it must be something I ate", or "I must have scratched my eye in my sleep with my fingernail", or "a bug must have gotten under my eyelid in my sleep". The ophthalmologist would answer with something like: "could be possible". A week of antibiotic/antibiotic-steroid drops or ointments would be prescribed for the conundrum/paradox. However the situation only worsened.

Finally the patient consulted an "Optometrist" by phone who after hearing of some of the story, interrupted and said that it sounded like the patient started with dry eyes and had progressed to a recurrent erosion. Examination of the patient disclosed signs of dry eyes, in line with the patients symptoms. There was no neurological defect, nor iritis nor elevated IOP. Fluorescein staining showed very rapid TFBUT and also negative staining, indicating that the corneal epithelium was elevated like a mild blister. The diagnosis was recurrent erosion.

7



Slit lamp of Corneal Disorder

8

Question #1.1

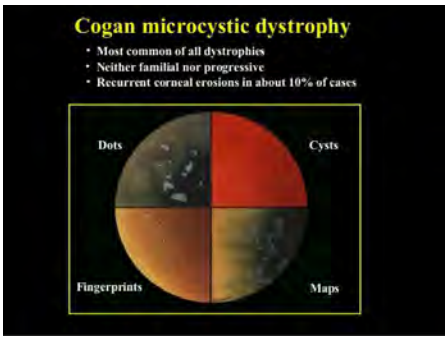
1. Treatment of recurrent erosion RCE consists of all but:
   a. Artificial tear drops and especially ointments.
   b. 5% NaCl drops and ointments
   c. A therapeutic bandage contact lens with or without amniotic membrane
   d. Corneal debridement/superficial keratectomy
   e. Corneal stromal puncture-stromal reinforcement by mechanical 25G needle
   f. YAG laser Bowman's Membrane stromal puncture
   e. Long term use of fish oil/flaxseed oil to improve the oil layer of the tear film, and so treat the underlying dry eye, which has resulted in corneal dry spots and nighttime palpebral conjunctival adherence to the cornea, and early am corneal epithelial trauma.
   f. A two hour dietary, social and psychological history so as to acquire "data" and "completely understand" this paradoxical conundrum, which has defeated the finest minds of ophthalmologists who mostly have obtained a grade of "A" in college level Calculus, Physics and Chemistry.

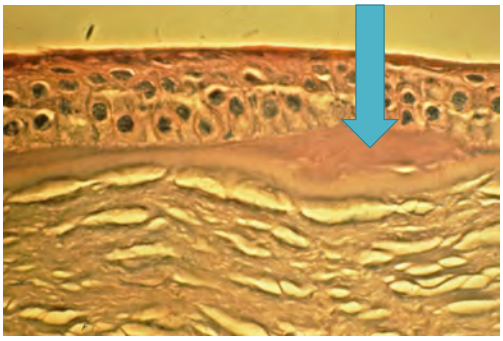
9

Question #1.2

2. The following is a True statement:
   a. Desmosomes anchor the corneal epithelium to the basement membrane.
   b. Wholly/Holy-Desmosomes anchor the corneal epithelium to the basement membrane.
   c. Hemidesmosomes anchor the corneal epithelium to the basement membrane
   d. Who needs anything to anchor epithelial cells. Nature gave you a basement membrane.

10





Cogan's Corneal Dystrophy

11

Question #1.3

3. Which is False:

a. Recurrent erosion is a blistering disease of the cornea epithelium.

b. Like open angle glaucoma, patients hardly know they have a problem with recurrent erosion, because there are no symptoms.

c. Cogan's Corneal Dystrophy has a higher incidence of recurrent erosions and in women.

d. One can see recurrent erosions in patients who do not appear to have preexisting Cogan's Dystrophy.

12

Question #1.4

4. Which is False:

a. Oral tetracyclines have a beneficial effect on corneal healing. Oral erythromycin may be of value for similar reasons.

b. Topical corticosteroids are sometimes used to decrease the secondary inflammation that accompanies this condition.

c. Topical pilocarpine is used for its miotic effect to decrease the photophobia that accompanies this condition. Mydriatic/cycloplegics are contraindicated.

d. Pressure patching can be used for the corneal abrasions of recurrent erosion.

e. Punctal plugs, cyclosporin and lifitegrast can be used to treat the underlying dry eye component.

13

Question #1.5

5. Which statement is True regarding bandage SCL and RCEs?

a. The eye looks redder and feels more painful the next day with placement of a SCL and the Doc thinks that the eye has gotten infected.

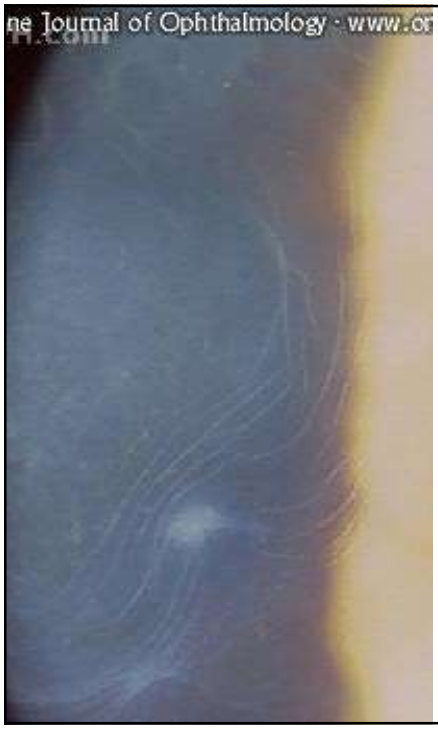
b. The eye looks worse with the CL and the Doc thinks that the bandage CL needs daily cleaning. Taking the CL out traumatizes the eye and patient, mostly by disrupting the epithelial healing.

c. The SCL mechanically irritated the eye, but the doctor isn't sure that the eye isn't infected, or the eye simply continues to hurt from the recurrent erosion itself.

d. There is no problem with a bandage SCL. That's why the company calls it a "bandage SCL". In fact, it makes concomitant use of topical AB/corticosteroid or just AB.

e. Bowman's membrane and the anterior corneal stroma in the area of the recurrent erosion begin to haze up a little, underneath the CL even though it is sterile corneal scarring. The doctor knows this but it is frightening.

14



ICD 10 for EBMD

H18.59–Other hereditary corneal dystrophy

CPT 4 Codes:

92285
External ocular photography

92025
Corneal topography

92071
Bandage contact lens

68761
Punctal occlusion

65778
Amniotic membrane placement

15

Case #2

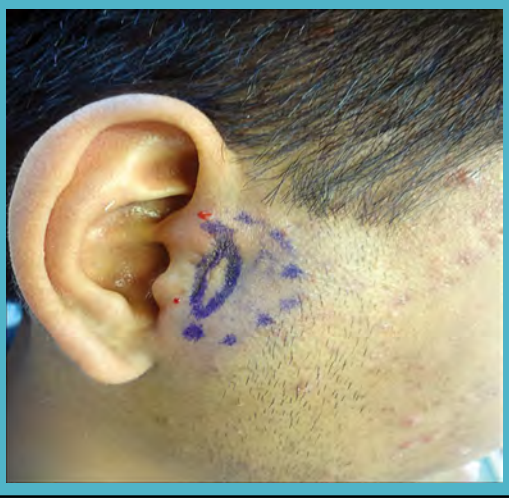
A 4 year old with two day onset of a right red eye presents for examination. You note good acuities (20/20--OU), no lid or peri-ocular vesicles, no cuts, bruises around the peri-ocular region. There is negative pre-auricular lymphadenopathy and lower lid palpebral papillary response with mild discharge in the lower cul-de sac.

16

I can't get my eye open in the morning!!
It doesn't hurt but there is "stuff" coming out in the morning.

17

What is your diagnosis, Ddx, Treatment?



Preauricular nodes drain the conjunctivae, skin of the cheek, eyelids, and temporal region of the scalp and rarely are palpable in healthy children. The oculoglandular syndrome consists of severe conjunctivitis, corneal ulceration, eyelid edema, and ipsilateral preauricular lymphadenopathy. Chlamydia trachomatis and adenovirus can cause this syndrome.

18

Differential Diagnosis

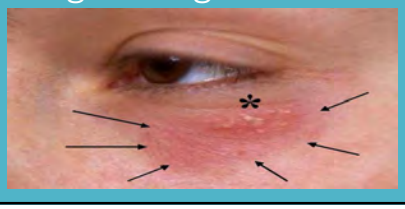
Bacterial Conjunctivitis (#1)

Check for Otitis –Conjunctivitis syndrome

Lids not involved or vesicles- so probably not gonorrhea or herpes simplex.

Redness of bulbar conjunctiva no apparent in circumlimbal area---not anterior uveitis.

No copious amounts of discharge –no gonorrhea



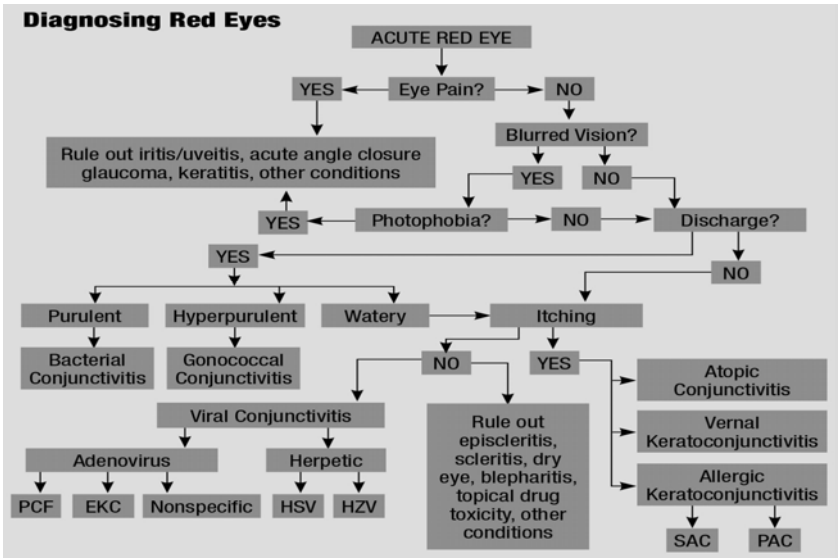
19

Treatment

Topical Antibiotic : Bacterial conjunctivitis is most often treated with ophthalmic antibiotic eyedrops or ointments such as Bleph (sulfacetamide sodium), Moxeza (moxifloxacin), Zymar (gatifloxacin), Romycin (erythromycin), Polytrim (polymyxin/trimethoprim), Ak-Tracin, Bacticin (bacitracin), AK-Poly-Bac, Ocumycin, Polycin-B, Polytracin .

Oral antibiotics if associated Otis inflammation, possible H. Flu. Consider gram negative.

20



21

TABLE 3. E/M CODING CHANGES PROPOSED FOR 2021		
Current E/M System		2021 E/M Changes
CPT code	Description	
99201	New patient, level 1	99201
99202	New patient, level 2	
99203	New patient, level 3	NEW SINGLE CODE
99204	New patient, level 4	
99205	New patient, level 5	99205
99211	Established patient, level 1	99211
99212	Established patient, level 2	
99213	Established patient, level 3	NEW SINGLE CODE
99214	Established patient, level 4	
99215	Established patient, level 5	99215

CPT 4 for Acute Bacterial Conjunctivitis

22

Example

Acute conjunctivitis, right eye

ICD-9-CM:

372.00 – Acute conjunctivitis, unspecified

ICD-10-CM:

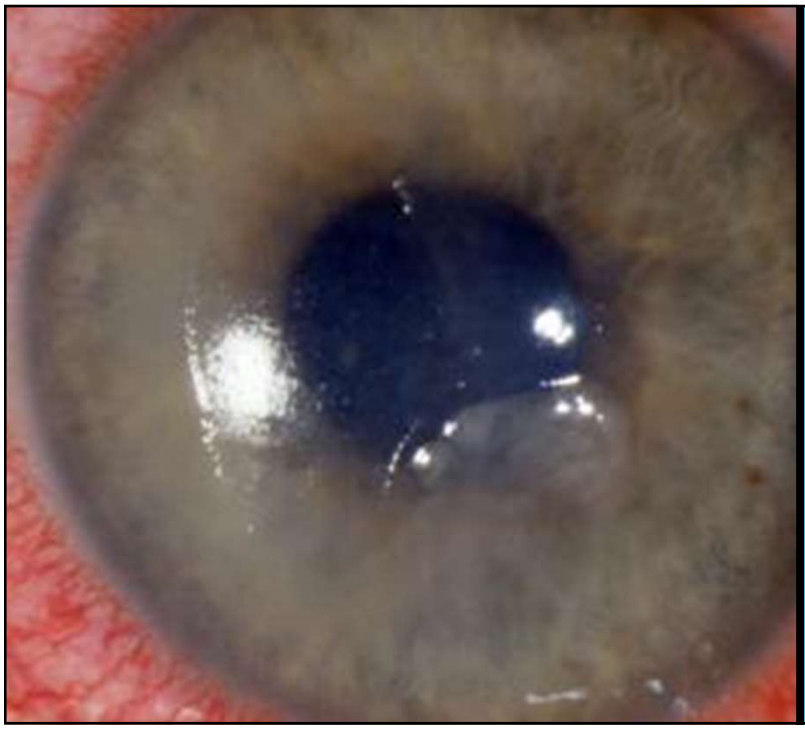
H10.31 – Unspecified acute conjunctivitis, right eye

Coding for Bacterial Conjunctivitis

23

Case #3

24



CORNEAL ABRASION

Clue: they come in holding their eye lid or have blepharospasm.

Hint: Pain goes away by adding topical anesthetic– not iritis or scleritis

25

Corneal Abrasion

Corneal abrasion is probably the most common anterior eye injury and perhaps one of the most neglected by eye care practitioners.

A traumatic corneal abrasion is the classic corneal abrasion in which mechanical trauma to the eye results in a defect in the epithelial surface.

Fingernails, animal paws, pieces of paper or cardboard, makeup applicators, hand tools, and branches or leaves are some of the more common etiologies.

26

Corneal Abrasions: Symptoms

Foreign body sensation or worse

Pain: mild to severe (worsens with blink, better with eyes closed)

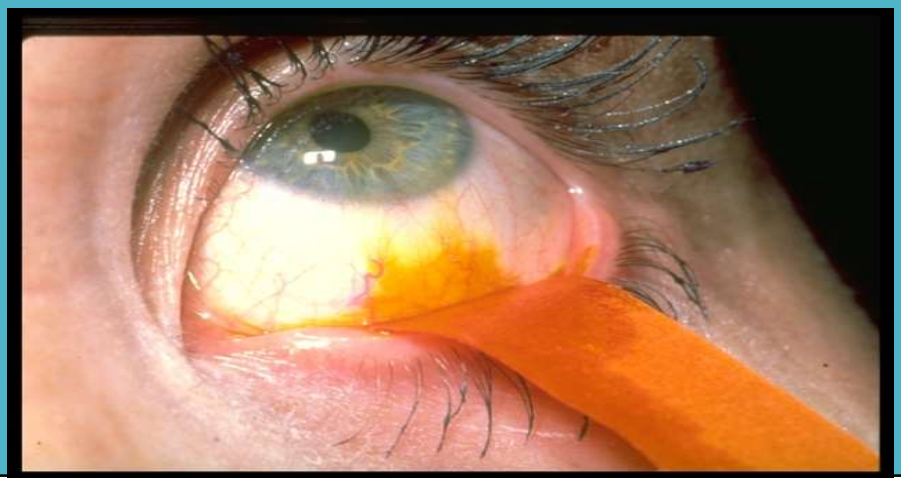
Tearing

Photophobia

Lack of definite Hx with mild FB sensation can be tip off for infectious Dx (HSK)

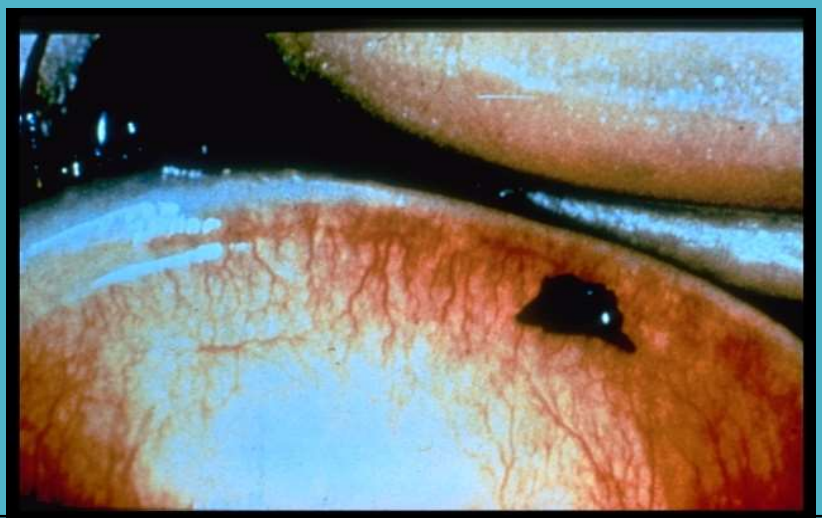
27

1. Use Anesthesia first
2. Fluorescein staining



28

Foreign body suspect or vertical NaFl staining (Always check under lids)



29

Corneal Abrasion: Treatment

Topical antibiotic:

(Vigamox (Moxeza), Zymar (Zymaxid), Ocuflox, Ciloxan, Erythromycin ointment, Poytrim)

Not gentamycin, sulfonamides

Fusidic acid viscous solution (fucithalmic)

Short acting cycloplegics: (photophobia / traumatic iritis/cells in the AC)

- DO NOT give out topical anesthetic drop to patient!! Topical NSAID may supplant for occlusion
- Occlude the eye or have the patient keep their eyes closed as much as possible for 24 hours.

30

Corneal Abrasion: Contact lens wearers

- Topical antibiotic to cover gram-negative organisms (Fluroquinolones)
- Do not patch
- Follow-up with Optometrist in 24 hours
- Monitor for infiltration near abrasion, may indicate infection.

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Corneal Abrasion: Follow-up

- Follow-up in 24 hours and repeat staining test (dimensions of abrasion should be smaller).

Consider referral if:

Not healing in 24 hours or getting worse

Related to CTL wear

White corneal infiltrate develops

32

ICD-10 / CPT-4 Codes for Corneal Abrasion

- S05.00XA Corneal abrasion w/o FB present
- CPT: The practice submitted CPT code 99213/4–57 for the exam, with modifier –57 indicating that this office visit was used to determine the need for surgery. Total: $150-200
- F/U: S05.01XD Injury of conjunctiva and corneal abrasion without foreign body, right eye, subsequent encounter

33

Update on Cataract Work Up and Use of Multifocal IOLs

Presented by John Maher, MD and David Sendrowski, OD

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“Acquired” CATARACTS

David P Sendrowski, OD, FAAO
John Maher, MD, FACS

Financial Disclosure Information

Lecture Bureau for:

Alcon Pharm.
Allergan Pharm.
VSP
Ista Pharm. (now B&L)

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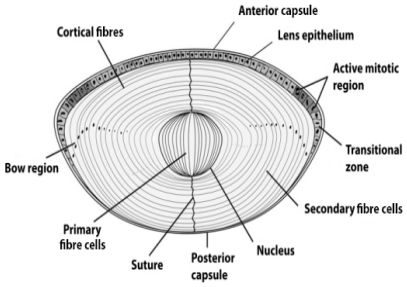
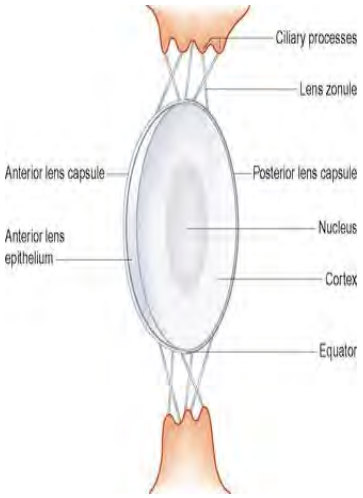
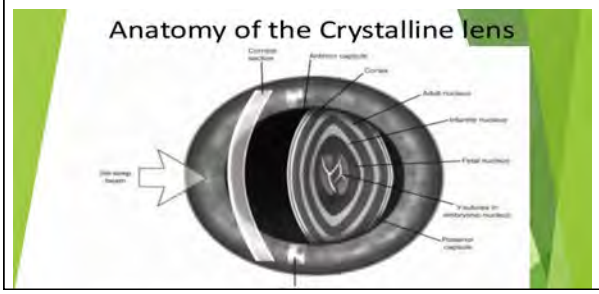
No animals were harmed during the development of this lecture!

Lens Anatomy







ACQUIRED (age related) CATARACTS

Indications for referral for surgical removal of cataracts

Patient's status and visual function

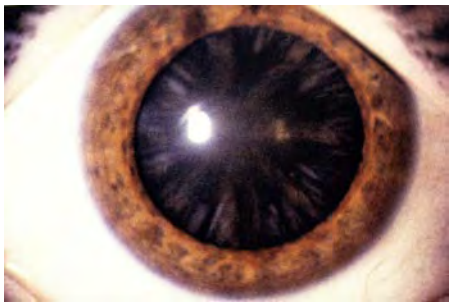
Diminished visual function (Should be Pt/OD decision)

#1 Gradual loss of Vision (months to years) NS/ CC not PSC

Loss of independence (hate to drive at night)

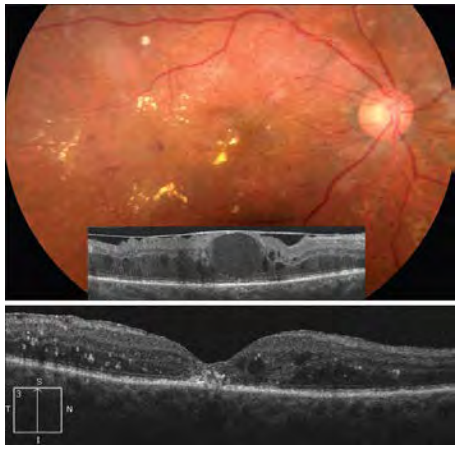
Inability to perform ADLs (activities of daily living)

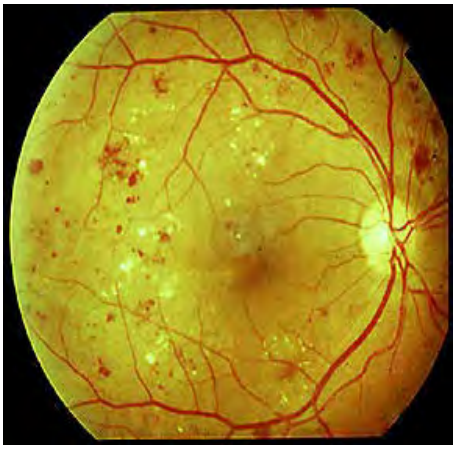
High visual demand



Ocular health

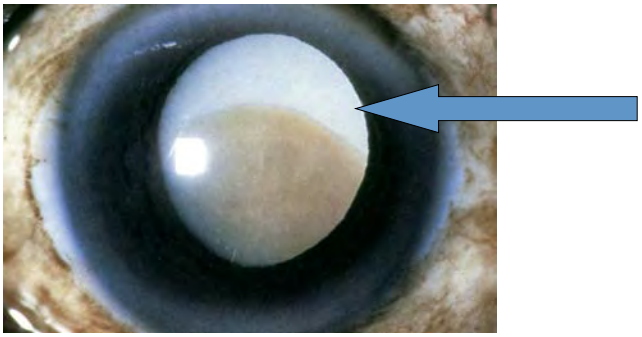
Inability to view retinal, optic nerve head or macular structures when needed for management (i.e., diabetes, glaucoma, ARMD, etc.)





Medical indications

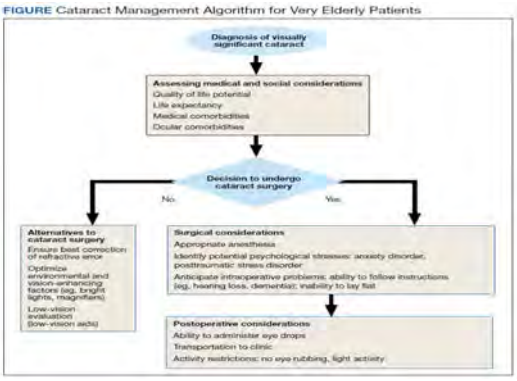
Phacolytic glaucoma
Phacomorphic glaucoma
Phacoanaphylaxis glaucoma
Dislocated lens
Amblyopia 2° to congenital cataract in newborn (Big one !!)

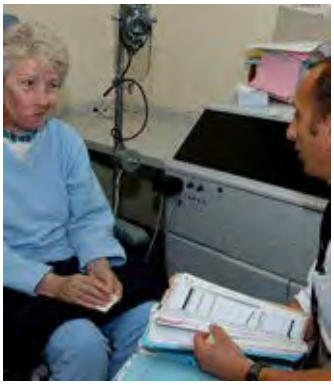


Goals

Patients should be motivated to have surgery (elective)
Patient should have good education as to overall ocular health other than the cataract
Patient should be given all viable options (Rx or surgery)

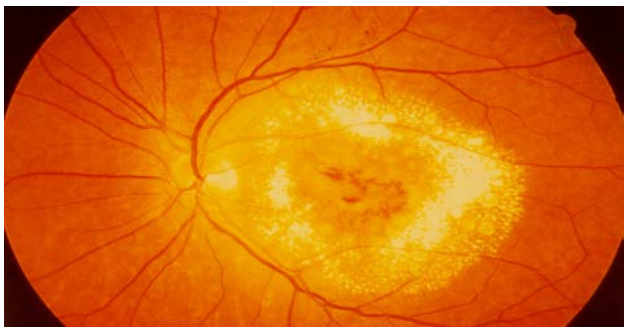
Patient should be given time to generate questions and discuss with family members, friends the decision to operate
Patient should be given risk/benefit ratio of having procedure performed





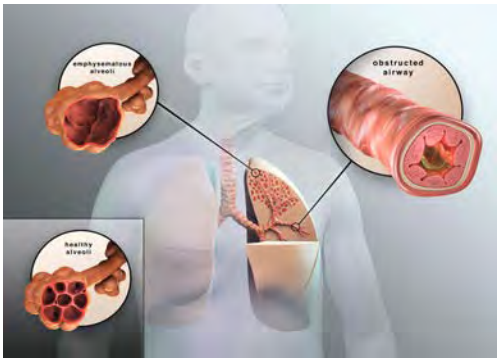
Contraindications to Referral

- Procedure would not improve visual function or improve usage of low vision device by having surgery
- Amaurotic eye
- Longstanding detached macula/retina
- Long standing end stage nAMD



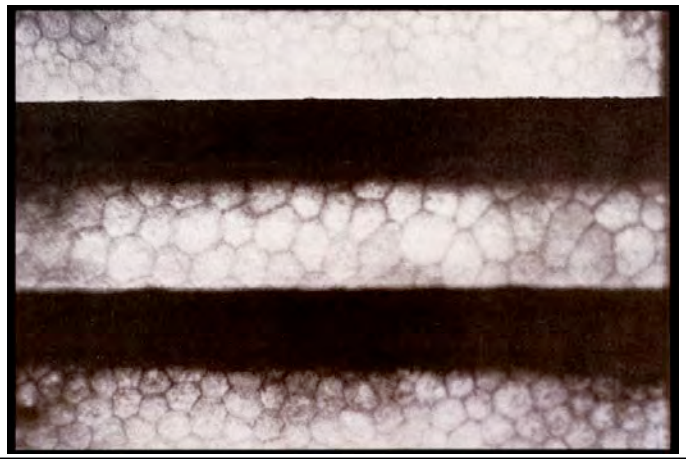
Systemic health

- Cardiovascular, neurologic, problems which need to be handled first
- Debilitating illness
- Any systemic disease which may increase risk factor of having surgery



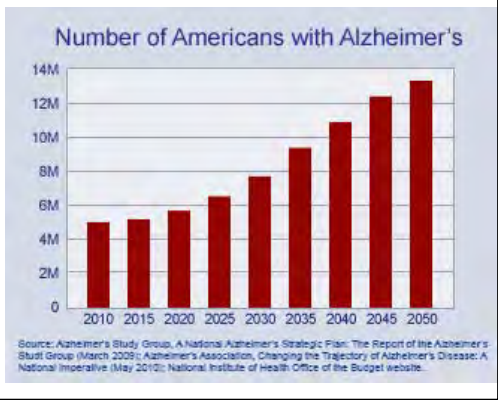
Ocular health

- Corneal endothelial disease
- Successfully corrected patient with spectacles/contact lenses



Mental status

- Improving visual function would not improve patient's life functioning (i.e., end stage Alzheimer's patient)
- Mentally handicapped patient (same situation as above)



Pre-Operative Ocular Evaluation

Examination procedures

Patient complaint/history

Visual dysfunction = cataract problem (#1 goal)

visual needs (***** VERY IMPORTANT)**

Cataract surgery significantly reduces falls in elderly

Palagyi A, et al. J Cataract Refract Surg.December 15, 2017

ocular history

medical history

family history

Best Corrected Visual acuity (W/PH)

distance/near

Pupils

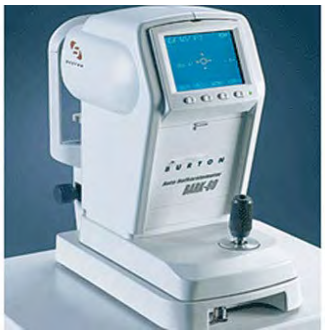
excellent neurological test

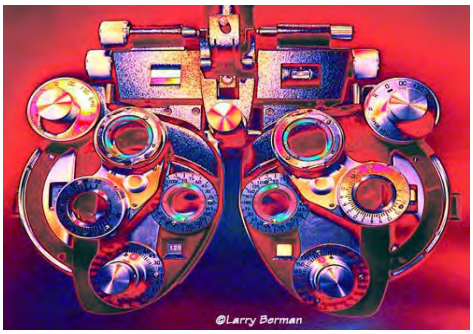
Keratometry

- data necessary for A-scan ultrasonography
- can estimate post-surgical cyl. (and cost to correct)
- very important for multifocal implants

Refraction

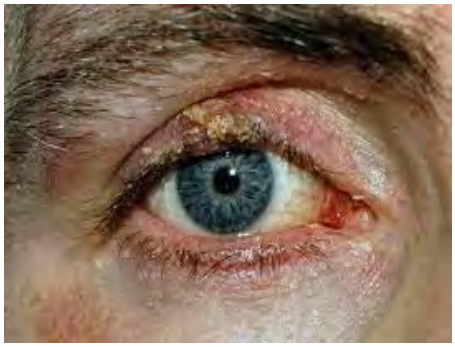
- vital to avoiding unnecessary procedures
- may need to PH best corrected refraction



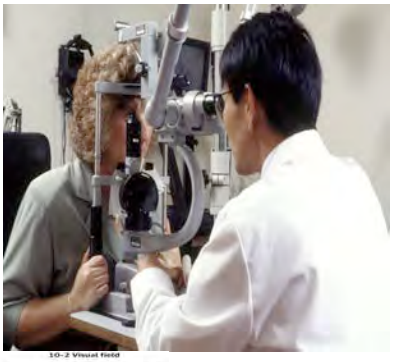


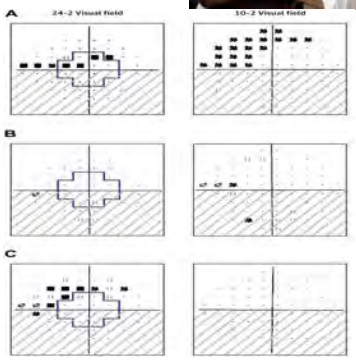
Biomicroscopy

- lid disease needs to be ruled out
- corneal health and endothelial function
- A/C estimation and clarity
- type of cataract - visual dysfunction
- anterior vitreous evaluation (clear?)

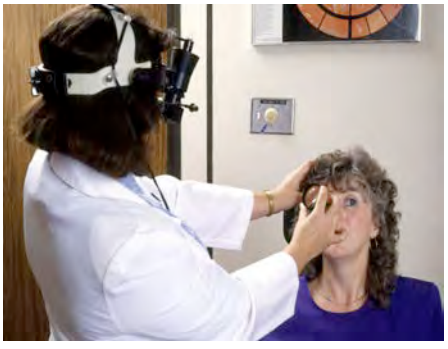


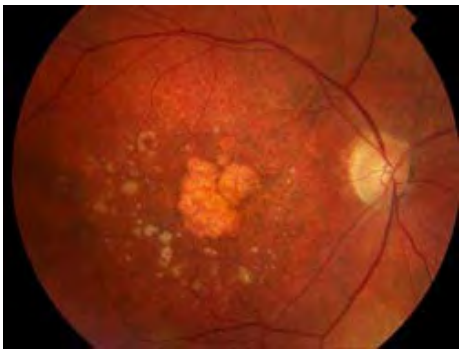
Tonometry
R/O pre-existing glaucoma
Visual fields
- screening indicated
- cataracts cause generalized depression
- but may cause any type of field defect

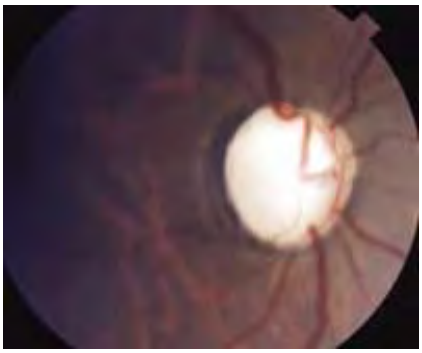


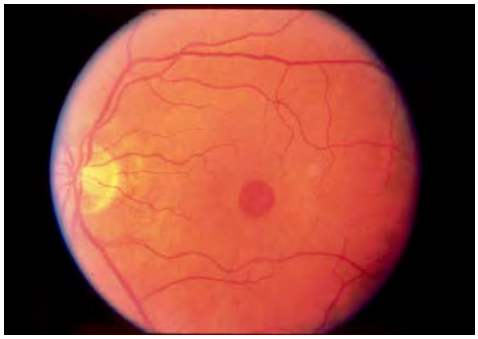


Dilated Fundus Exam (DFE)
- R/O peripheral retinal anomalies which may increase post-operative RD risk
- R/O macular disease
- allow potential acuity assessment
- check vitreous for anomalous adhesions









TYPES OF ACQUIRED CATARACTS

PREVALENCE AND TYPE OF AGE-RELATED CATARACTS IN PATIENTS AGED 75 YEARS AND OLDER

Type	Percent
Nuclear	65.5
Cortical	27.7
Posterior subcapsular	19.7

Modified from Sperduto and Hiller.[3]

Pathophysiology of Cataracts

Multiple mechanisms contribute to the progressive loss of transparency of the lens
Progressive oxidative damage to the lens with aging takes place, leading to senile cataract development.

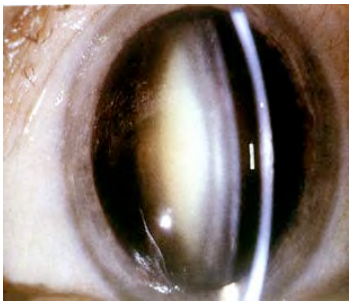
Another mechanism involved is the conversion of soluble low-molecular weight cytoplasmic lens proteins to soluble high molecular weight aggregates, insoluble phases, and insoluble membrane-protein matrices

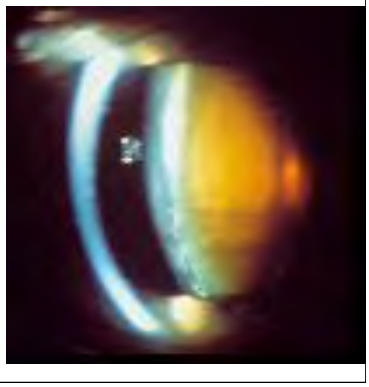
As the lens ages, its weight and thickness increases while its accommodative power decreases

Nuclear Sclerotic

Symptoms

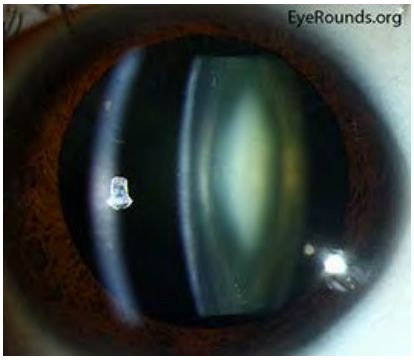
- slowly progressive visual loss or blurring over months to years
- **glare (#1) from oncoming headlights while driving at night**
- image blur, and distortion also possible visual complaints
- reduced color perception, esp (reds/greens)
- retina may be indistinct with direct ophthalmoscopy
- patients Rx shifts toward myopia
- patient sees better up close without their reading glasses ("second sight")





Signs

- slit-lamp: yellow or brown discoloration of the central part of the lens
- distance VA ↓; near VA ↑ (PH ↑ DVA)
- myopic shift in Rx
- macular area normal
- visual field; generalized depression



Treatment

If VA is decreased where Rx cannot improve it, and activities of daily living (ADLs) are affected consider surgery

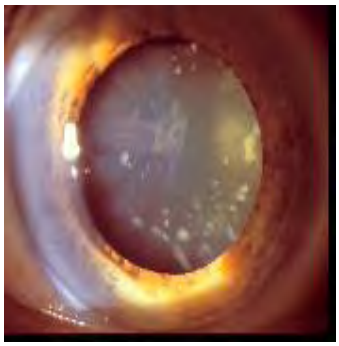
Consider referral for cataract surgery.

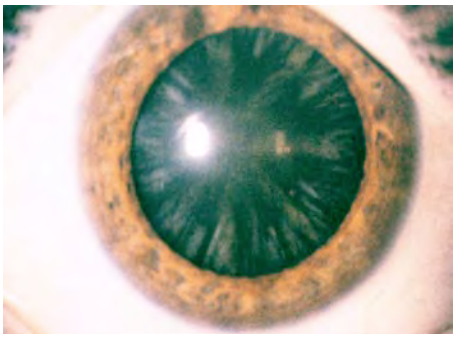
Cortical Cataracts

Symptoms

often **asymptomatic** until changes develop and affect central visual axis

may have some glare w/headlights while driving at night





SIGNS:

slit lamp: radial or spoke-like opacities in the lens periphery. They expand to involve the anterior and posterior part of the lens

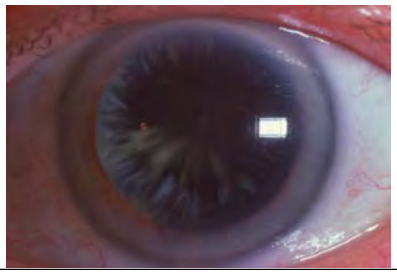
VA distance - good until central involvement

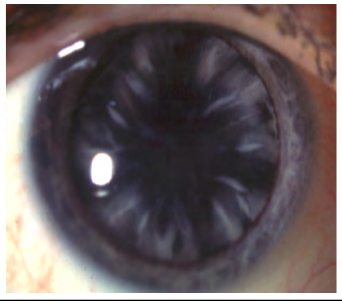
VA near - good until central involvement

Visual fields: variable loss (usually none)

Macula/optic nerve are normal

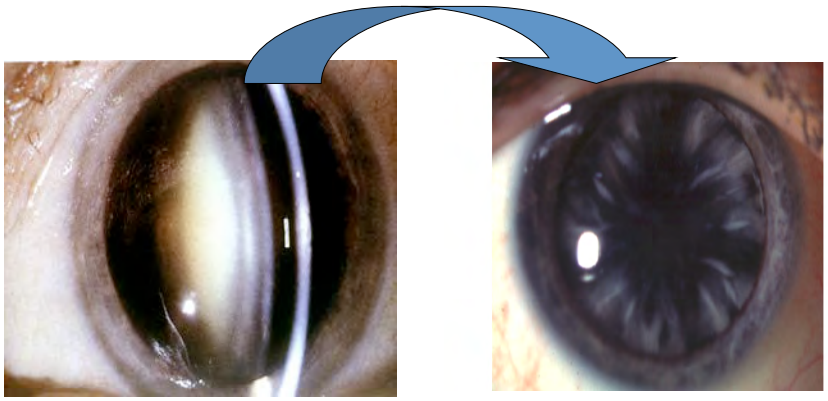
May be concurrent with nuclear sclerotic cataracts (Very common)





Treatment

same as with nuclear sclerotic



Posterior Subcapsular Cataracts (PSC)

Symptoms

rapid loss of VA (weeks to months)

decreased VA at distance and near

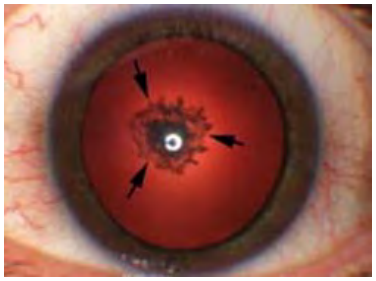
a lot of glare with headlights while driving at night

very hard to recognize familiar faces or signs

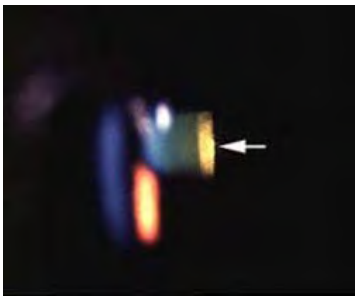
difficulty with reading is very common

cataract may be associated with: ocular inflammation (uveitis), prolonged steroid use, diabetes, trauma, radiation exposure

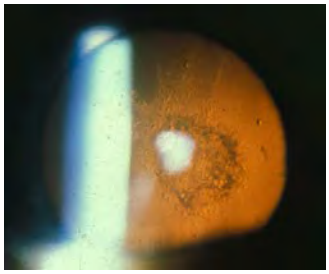
classically occurs in **younger patients** (<50)

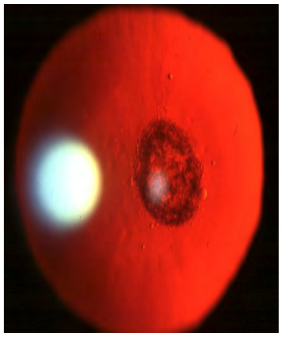


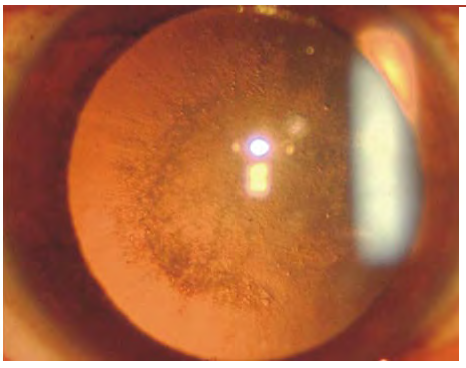
Blocks light on retro

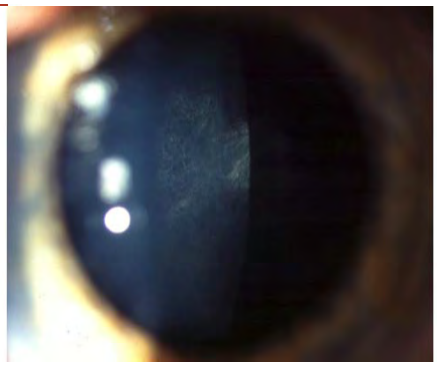


Ground Glass on direct

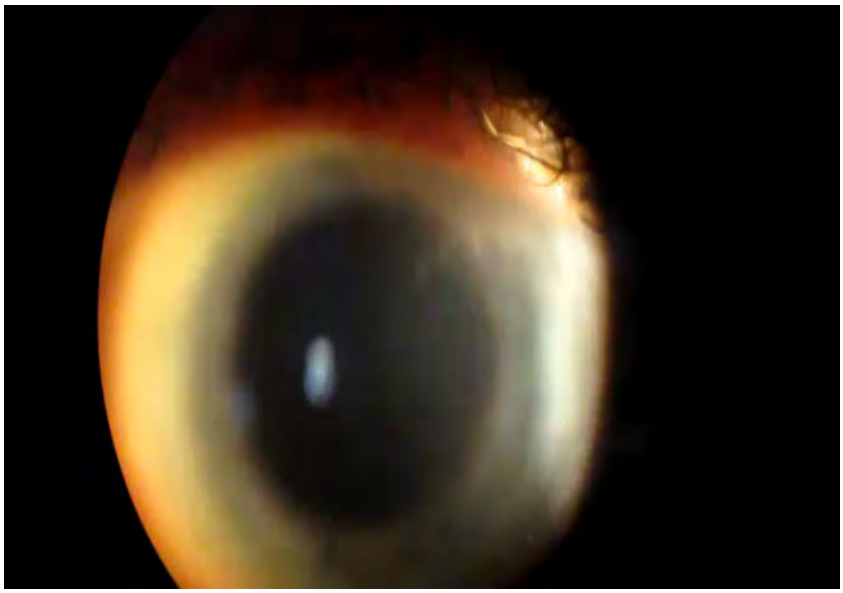








Patient's BCVA: 20/400 (PH: HM)
Never go by appearance of lens.



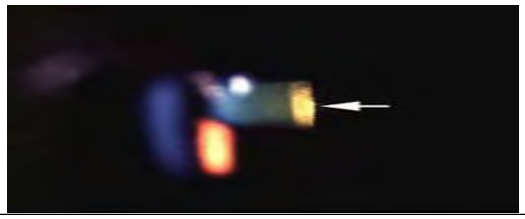
Signs

Slit lamp: opacity appears near the posterior aspect of the lens. May or may not be along the visual axis. Forms a plaque

Best seen w/direct-retro illumination off the retina where it appears dark against the red fundus reflex

Visual fields: variable

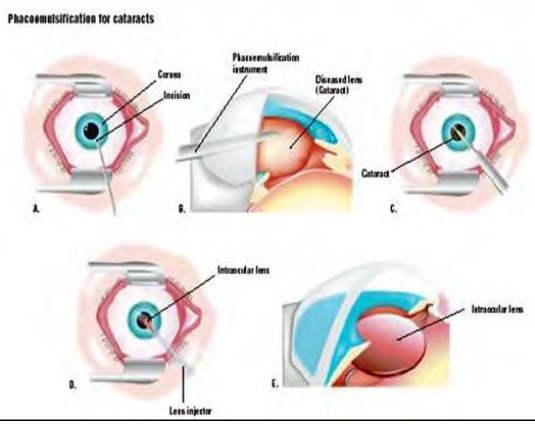
Macula and optic nerve head are normal

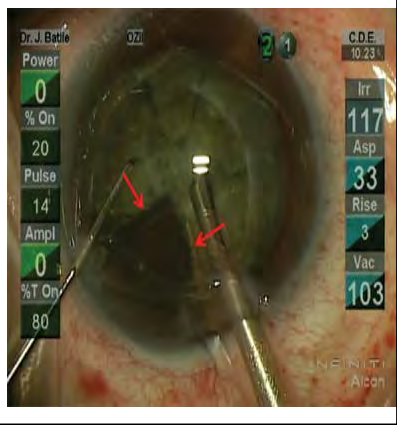


Treatment

if on-axis: visually devastating requiring referral for cataract removal

if off-axis: need to monitor patient q 6 months with education to watch VA q 2-3 weeks to look for changes

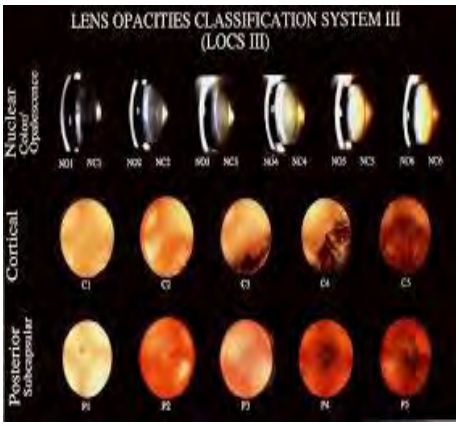


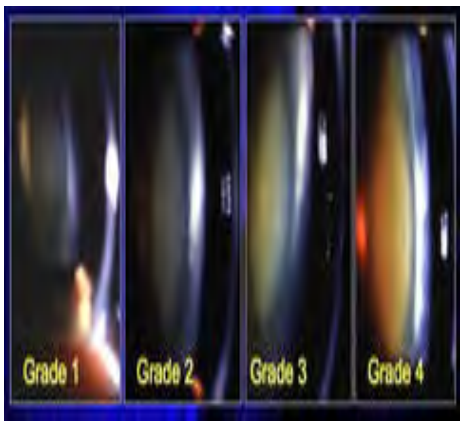


Standardized clinical grading and photographic systems (comparing a patient's cataract with standard photographs

A. Lens Opacities Classification System (LOCS) III Clinical and Photographic Grading system
B. Wisconsin Clinical and Photographic Cataract Grading system
C. Wilmer Clinical and Photographic Cataract Grading system
D. Oxford Clinical Cataract Grading system
E. Age-Related Eye Disease Study (AREDS) Cataract Grading System
F. Other systems such as the Japanese CCRG Cataract Grading system and the World Health Organization Cataract Grading System

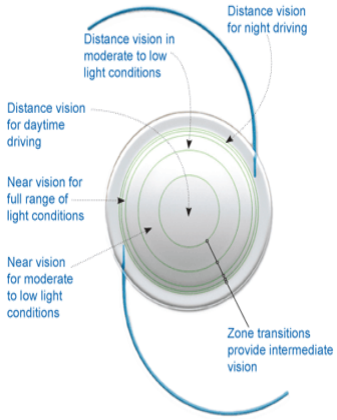
Grading of Cataracts LOCS III

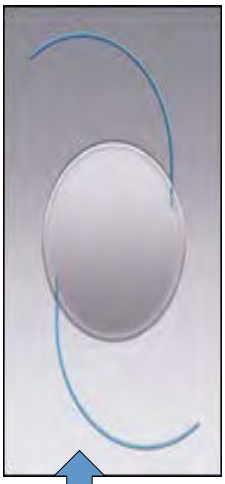




LOCS III grading was shown to be highly reproducible for nuclear cataract

Odd Cataract Treatments – They don't work!! They Delay Surgery





Multi-Focal IOL: apodized diffractive optics

Monofocal IOL

Newest MF IOL PanOptics on the market 2019

The First And Only Trifocal Lens In The U.S.

This design is quite clever because the second order of the intermediate range (+1.75 with FineVision, for example) doubles and coincides with the reading addi-tion (+3.50), thus harnessing light that would otherwise be lost and adding to the focal point at near

PURPOSE

A retrospective comparison of two prospective studies with four lens groups:

- Binocular Crystalens AO (N=26, Bausch + Lomb)
- Binocular AcrySof ReSTOR +3.0 D (N=25, Alcon)
- Binocular Tecnis +4.0 D Multifocal (MF) IOL (N=22, J&J Vision)
- Contralateral IC-8 IOL (N=105, AcuFocus) and a colorless aspheric monofocal IOL

ACCOMMODATING LIGHT SPLITTING SMALL APERTURE

Accomodation vs. Pseudoaccomodation

Accomodation: Change in lens shape and position mediated primarily by ciliary muscle contraction

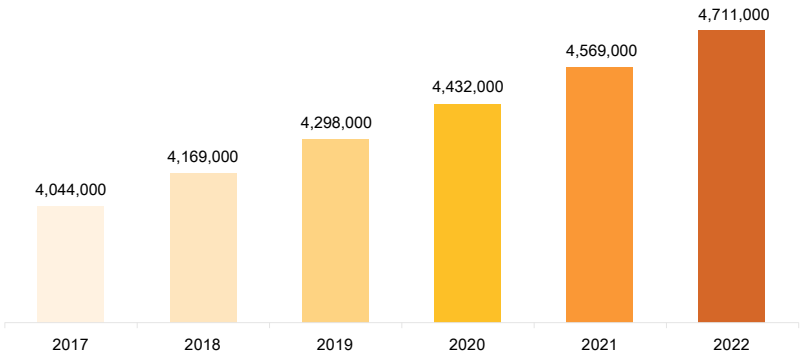
Pseudoaccomodation:

- Static
  - Pupil size
  - Against the Rule Cylindrical error
  - Irregularity and Multifocality of the Cornea
- Dynamic
  - Anterior Movement of the Implant by Anterior Vitreous Displacement

More Patients Need You

Between 2006 and 2030, the US population of adults aged 65+ will nearly double from 37 million to 71.5 million people.[1]

Forecast of US Cataract Surgical Procedures[2]



1. Livable Communities Baby Boomer Facts and Figures. https://www.aarp.org/livable-communities/info-2014/livable-communities-facts-and-figures.html. 2. 2017 Ophthalmic Surgical Instrument Report: *A Global Analysis for 2016 to 2022*. Saint Louis, MO: Market Scope®, 2017.

Be Their Guide[1]

Across their real-world journey, patients are seeking information that you can provide.

At Diagnosis

Understanding Cataracts

1.9 MILLION GOOGLE SEARCHES ANNUALLY

to understand their diagnosis

Approaching Surgery

Decision Making

1.2 MILLION GOOGLE SEARCHES ANNUALLY

to help make vision care decisions

After Surgery

Returning for Continued Care

THE PATIENT-OPTOMETRIST RELATIONSHIP IS LIFELONG

1. Google Patient Journey. Alcon data on file, 2015.

Education Is an Opportunity

People considering cataract surgery want to know their options. When they understand the benefits, they're more likely to choose an IOL that accounts for presbyopia or astigmatism.

Only **1 in 4** people are **knowledgeable** about cataract surgery[1]

90% say they want to know about **all of the lens options** available to them[1]

39% of people are willing to **upgrade to an ATIOL** once they understand the benefits[1]

1. 2018 Cataract Patient Trade-off Research.

Medical Eye Care Needs Continue to Rise[1]

Demand for **eye care services** has been projected to increase

23% from 2013-2025

Supply of **ophthalmologists** has been projected to decrease

11% from 2013-2025

1. US Department of Health and Human Services, Health Resources and Services Administration, Bureau of Health Workforce, National Center for Health Workforce Analysis. National and regional projections of supply and demand for surgical specialty practitioners: 2013-2025. https://bhw.hrsa.gov/sites/default/files/bhw/health-workforce-analysis/research/projections/ surgical-specialty-report.pdf. Published December 2016. Accessed July 25, 2018.

Be With Your Patients Each Step of the Way

The cataract patient journey often starts with optometrists.

At Diagnosis

- Educate about cataracts and cataract surgery
- Position cataract surgery as a once-in-a-lifetime opportunity
- Introduce the cost conversation, so patients can plan ahead financially
- Discuss cataract progression and set expectations for surgery

Approaching Surgery

- Reiterate that IOL choice is a once-in-a-lifetime opportunity to enhance vision
- Ask, "How do you want to use your eyes after surgery?"
- Discuss lens eligibility and manage post-op expectations
- Explain roles of OD and MD in journey to come
- Communicate with the surgeon you refer

After Surgery

- Follow up with post-op recovery and checkups
- Celebrate their new vision
- Communicate outcomes and any complications to their surgeon

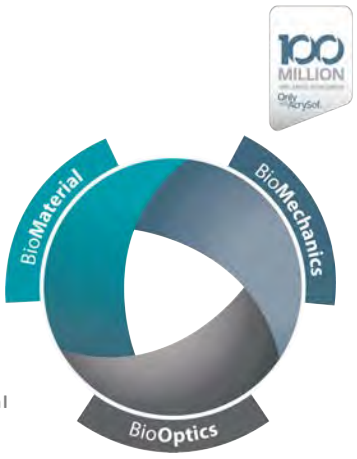
Building on a Platform of IOL Excellence

AcrySof ® IQ IOLs

Have been **implanted over 100 million times**, more than any other brand[1]

Offer a full range of products to **meet each individual's needs, including astigmatism and presbyopia treatment**

Have a natural chromophore that **emulates the light transmission of a healthy, natural lens** by filtering both UV and high-energy blue light[2]



1. Alcon data on file. 2. AcrySof IQ [product information]. Fort Worth, TX: Alcon Laboratories, Inc; 2010.

Getting to Know the Acrysof® IQ PanOptix® Lens

Enables less reliance on glasses [1]

Provides excellent near, intermediate, and distance vision

Available in toric for astigmatism

1. AcrySof® IQ PanOptix® Directions for Use.

1ST

The **AcrySof® IQ PanOptix®** IOL is the first and only trifocal available in the US.

TECHNOLOGY LANDSCAPE

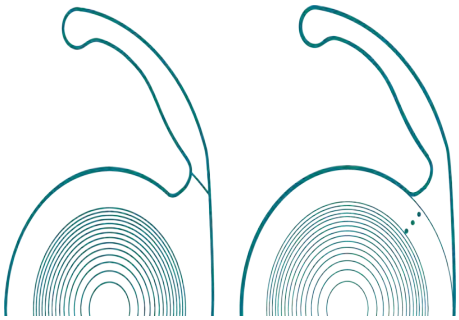
For well over a decade now, surgeons have been able to offer presbyopia-correcting intraocular lenses (IOLs).

Until now, multifocality meant bifocality: Light energy directed to two of the three primary focal points.

THE FIRST AND ONLY TRIFOCAL IOL IN THE U.S.

AcrySof® IQ PanOptix® and AcrySof® IQ PanOptix® Toric IOLs are innovative trifocal lenses that offer you the thrill of delivering a level of refractive performance that breaks free from tradition.

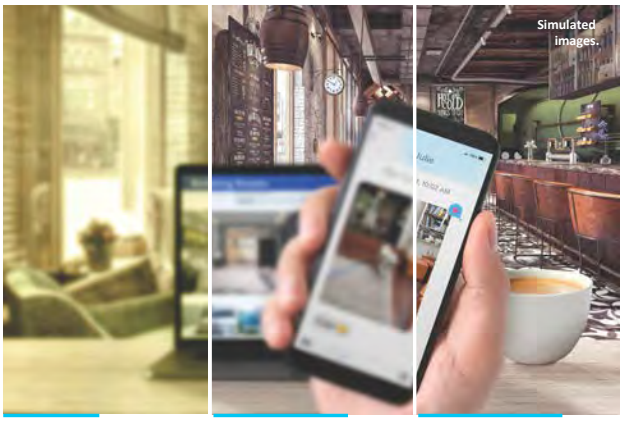
- 20/20 near, intermediate and distance vision is now possible*,†,1
- Proprietary **ENLIGHTEN**® Optical Technology
- 99.2% of patients would have had the same lens implanted again**,2
- Available in toric for astigmatism correction



*Based on mean value of binocular defocus curve at near, intermediate and distance at 6 months (n=127).
†Snellen VA was converted from logMAR VA. A Snellen notation of 20/20-2 or better indicates a logMAR VA of 0.04 or better, which means 3 or more of the 5 ETDRS chart letters in the line were identified correctly.
**Response to the following question on IOLSAT questionnaire (Ver. 1.0, Dec. 20, 2018) at 6 months post-op: "Given your vision today, if you had to do it all over, would you have the same lenses implanted again?"

Advanced Lens, Exciting Possibilities

With **AcrySof® IQ PanOptix®** IOLs, your patients can seize life with clear, complete vision.

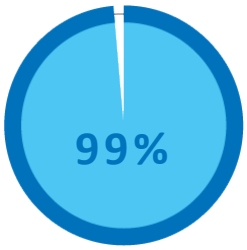


Cataracts | Monofocal Lens | PanOptix® Lens

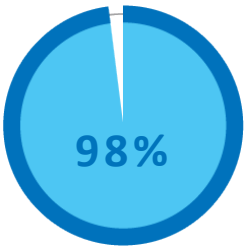
Results That Make a Point

AcrySof® IQ PanOptix® IOLs

In a clinical study, 129 patients were asked about their experience with the **PanOptix®** Lens:



99% of people with the **PanOptix®** Lens would **choose the same lens** again.[1]

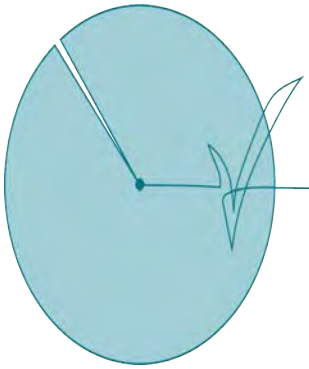


98% of people with the **PanOptix®** Lens would **recommend it** to family and friends.[1]

1. AcrySof® IQ PanOptix® Directions for Use.

UNDENIABLE PATIENT SATISFACTION

2



Data collected 6 months post-op:

99.2%

of patients would have had the same lens implanted again.‡,§,2

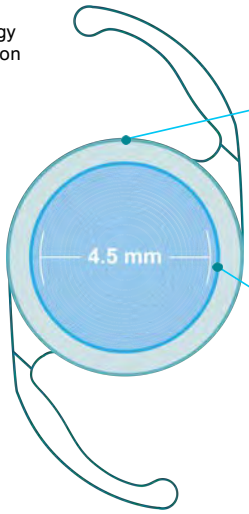
‡ n=127

§Response to the following question on IOLSAT questionnaire (Ver. 1.0, Dec. 20, 2018) at 6 months post-op: "Given your vision today, if you had to do it all over, would you have the same lenses implanted again?"

What Makes the PanOptix® Lens Different?

Enhanced Technology

Our proprietary, non-apodized **ENLIGHTEN®** Optical Technology optimizes light energy distribution to reduce pupil dependency in different lighting conditions.



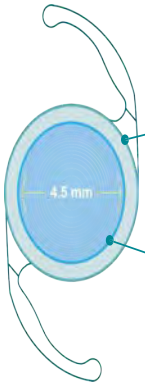
88% total light utilization at a 3 mm pupil size[1]
(Light allocation: 50% distance, 25% intermediate, 25% near)

Reduces dependence on pupil size[1,2] with a 4.5 mm diffractive zone

1. Alcon data on file. 2. Alcon data on file.

OPTIMIZED LIGHTENERGY

Proprietary, non-apodized design engineered to optimize light utilization



The unique diffractive structure allows the lens to transmit **88% of light** to the retina at a 3 mm pupil size for exceptionally high light utilization.[3]

Featuring a 4.5 mm diffractive zone to reduce dependence on pupil size **in different lighting conditions**.[3,4]

THE ENLIGHTEN® OPTICAL DESIGN STORY: STEP 1

BIFOCAL IOLS

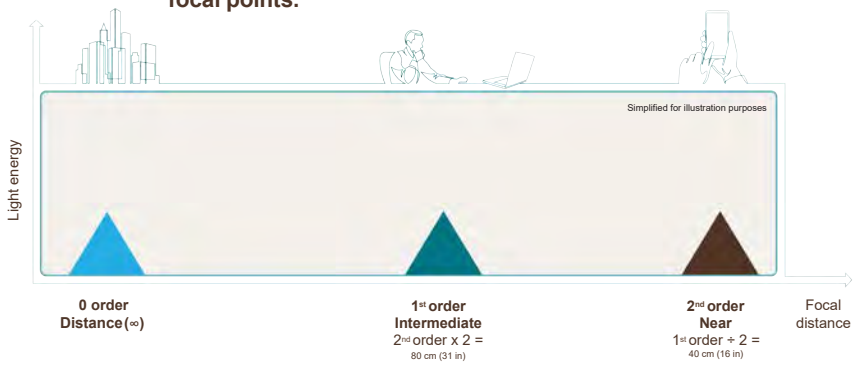
DESIGN The first multifocal IOLs offer distance vision and one additional focal point.

RESULT Bifocal IOLs provide two of the three primary focal points.

THE ENLIGHTEN® OPTICAL DESIGN STORY: STEP 2

TRADITIONAL TRIFOCALITY

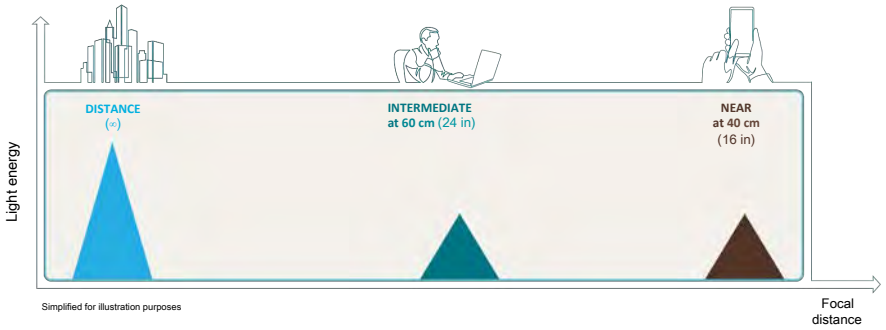
DESIGN Based on the rules of diffractive optics, trifocality requires sequential, equally spaced focal points.



RESULT Traditional trifocality has an 80 cm focal point, which is not a comfortable intermediate distance for most patients.[4,5]

The PanOptix® Lens Breaks Free from Traditional Trifocality

The **PanOptix®** Lens is designed to optimize intermediate vision, without compromising exceptional near and distance vision.[1]



1. AcrySof® IQ PanOptix® Directions for Use.

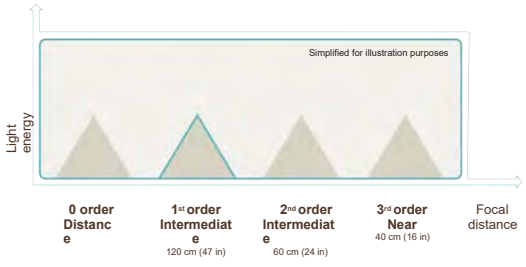
THE ENLIGHTEN® OPTICAL DESIGN STORY: STEP 3

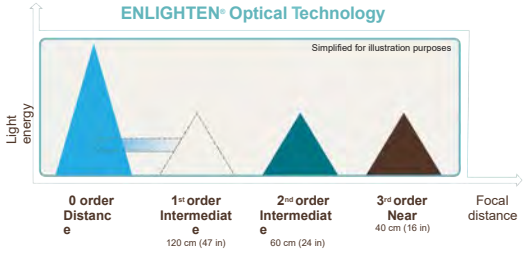
PANOPTIX® ADVANCED TRIFOCAL IOL

DESIGN

To create ENLIGHTEN® Optical Technology, we first created an additional focal point at 120 cm.

Then, we redirected the new 1st order intermediate focal point's light energy to distance.





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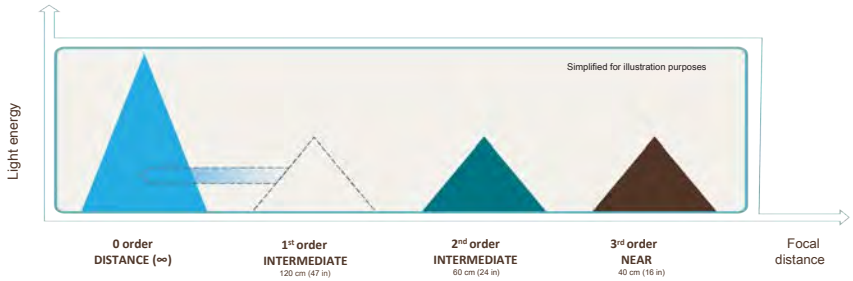


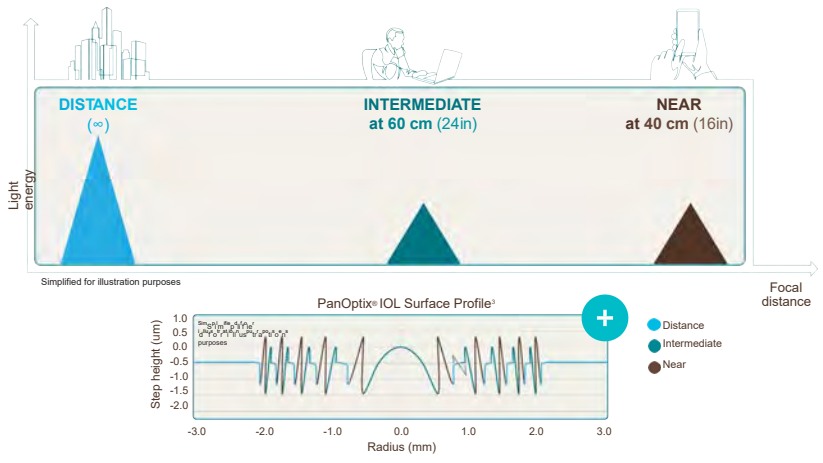
With an additional focal point at 120 cm, the **PanOptix®** Lens functions by redirecting the new 1st order intermediate focal point's light energy to distance.

1. AcrySof® IQ PanOptix® Directions for Use.

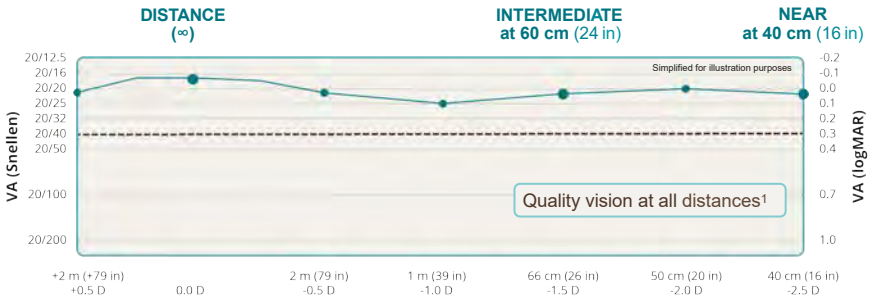
THE **ENLIGHTEN®** OPTICAL DESIGN STORY: STEP 4

REIMAGINE MULTIFOCAL PERFORMANCE

RESULT ENLIGHTEN® **Optical Technology optimizes intermediate without compromising near and distance vision.**



20/20 NEAR, INTERMEDIATE AND DISTANCE VISION IS NOW POSSIBLE*,†,1



*Based on mean value of binocular defocus curve at near, intermediate and distance at 6 months (n=127).
†Snellen VA was converted from logMAR VA. A Snellen notation of 20/20-2 or better indicates a logMAR VA of 0.04 or better, which means 3 or more of the 5 ETDRS chart letters in the line were identified correctly.

REIMAGINE MULTIFOCAL PERFORMANCE

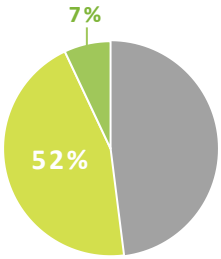
Break free from tradition and unleash the power of the **PanOptix® IOL**.

- **20/20 near, intermediate and distance vision is now possible*,†,1**
- **Proprietary ENLIGHTEN® Optical Technology**
- **99.2% of patients would have had the same lens implanted again‡,6**

*Based on mean value of binocular defocus curve at near, intermediate and distance at 6 months (n=127).
†Snellen VA was converted from logMAR VA. A Snellen notation of 20/20-2 or better indicates a logMAR VA of 0.04 or better, which means 3 or more of the 5 ETDRS chart letters in the line were identified correctly.
‡Response to the following question on IOLSAT questionnaire (Ver. 1.0, Dec. 20, 2018) at 6 months post-op: "Given your vision today, if you had to do it all over, would you have the same lenses implanted again?"

Available in toric on the platform you can rely >

Many Patients Would Seize the Opportunity for Better Vision



52% of cataract patients **with astigmatism** are within the **treatable range of a toric IOL**.

Only 7% of patients receive one.[3]

39% of people are willing to **upgrade to an ATIOL** once they understand the benefits.[4]

53% of people with **astigmatism** are willing to **upgrade to an ATIOL** lens.[4]

1. East Valley Ophthalmology website. Distribution of corneal astigmatism in normal adult population. Keratometry database. http://www.doctor-hill.com/iol-main/astigmatism_chart.htm. Accessed May 12, 2017. 2. AcrySof® IQ Toric [product information]. Fort Worth, TX: Alcon Laboratories, Inc; 2009. 3. Market Scope. Cataract: Q1-2017 cataract quarterly update; Alcon data on file 2017. 4. 2018 Cataract Patient Trade-off Research.

Your Role: Choosing Ideal Patients

Clinical Considerations

Patients within the parameters for the **PanOptix**® Lens:

- Have not undergone refractive surgery
- Do not have glaucoma or retinal pathology
- Do not have irregular astigmatism
- Do not have unmanaged dry eye
- Have a healthy cornea

Lifestyle Considerations

If you understand the patient—their lifestyle, personality, and habits—you'll be able to make a more informed lens recommendation.

What you should ask:

- What do you do for fun? For work?
- What types of activities do you enjoy?
- What do you do to stay active?
- What do you want to get out of cataract surgery?
- What bothers you in your vision?

Your Role: Leading the Conversation

As you discuss their procedure, decisions, and benefits:

- Use plain, patient-friendly language
- Use visual tools to improve recall and comprehension
- Limit the amount of information provided—and repeat it
- Use open-ended questioning techniques to learn more about the patient

Guiding Your PanOptimists

Connect with PanOptimists throughout their decision process and move them towards better vision.

At Diagnosis

- Send your patients to CataractSurgery.com

Approaching Surgery

- Brochure
- Placemat
- Poster
- Focus Magazine

After Surgery

- Share patients' stories* on your practice's social media using #PanOptimist

Order resources at MyAlcon.com/CataractResources

*Remember to obtain all the necessary consents and respect patient privacy when using social media.

Guiding Your PanOptimists

Educational Brochure

Guiding Your PanOptimists

Consultation Day Checklist

Surgery Day Checklist

Additional resources for your patients are available at CataractSurgery.com

You Are the Bridge to Better Vision

In your patients' eyes, you are their:

- **Expert** on technologies and equipment
- **Partner** as someone invested in their well-being
- **Confidante** through open communication
- **Resource** for information about their upcoming cataract surgery

Discussion Points

1 What role do you want to play in your cataract patient's journey?

2 How will you talk to your patients about cataract surgery?

3 What resources do you plan to leverage thatyou didn't previously?

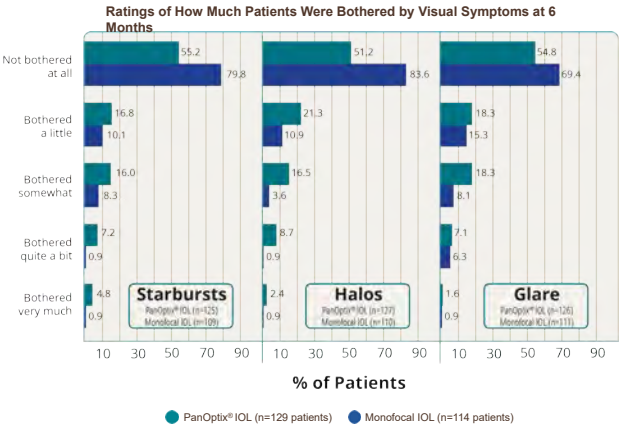
Figure 1. There are three distinct types of photopsias or distortions of a point source of light.

PATIENT-REPORTED VISUAL DISTURBANCES[6]

Results from a **patient-prompted** and **validated** QUVID questionnaire at 6 months when asked: "In the past 7 days, how much were you bothered with starbursts, halos and glare?"

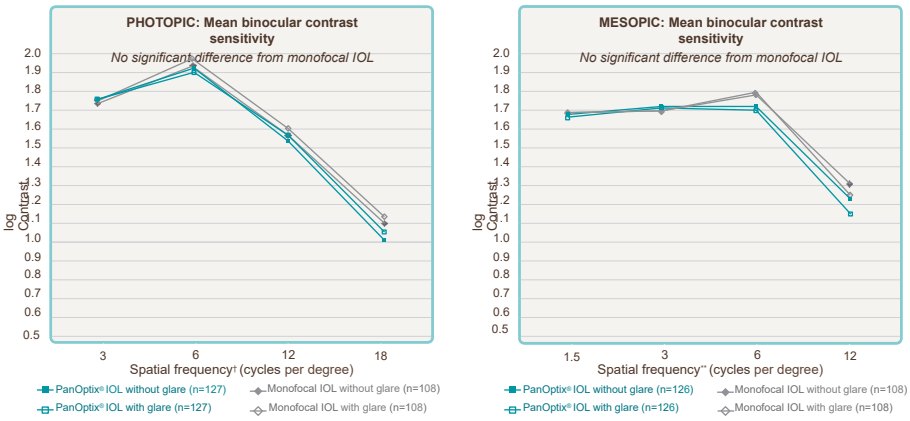
Most bothersome visual disturbances. Percent of patients bothered very much by:

- **4.8%** by Starbursts (n=125)
- **2.4%** by Halos (n=127)
- **1.6%** by Glare (n=126)



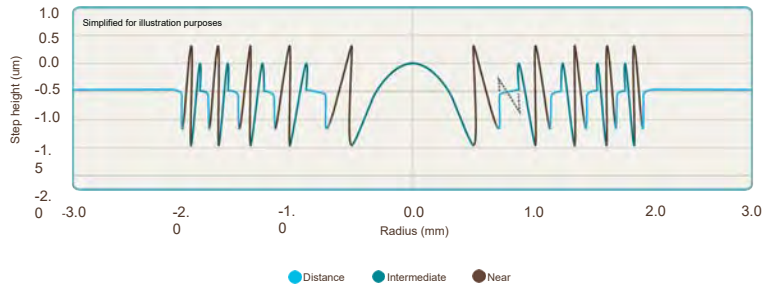
CONTRAST SENSITIVITY

The **PanOptix® IOL** delivers excellent contrast sensitivity compared to a monofocal IOL at 6 months — in both photopic and mesopic conditions.*,1



*Contrast above 0.3 is clinically meaningful.
†At 85 cd/m2 in photopic conditions.
††At 3 cd/m2 in mesopic conditions.

PanOptix® IOL Surface Profile[3]



PRECISE BIOMETRY PRACTICES

Critical factors for helping to achieve accurate outcomes when implanting PCIOLs include precise biometry measurements and the use of modern formulas, such as:

- Barrett Universal II
- Hill-RBF
- Holladay II
- Olsen C

Optic Powers	+6.0 through +30.0 in 0.5 increments, T0, T3-T6
Available in BLF and UV-only.	
Optical A-Constant	119.1

Formula	Parameters for ELP Prediction	Uses	Optimal Axial Length[5]
Barrett Universal II	AL, K, ACD, WTW, LT	Lens Factor	Short, Normal, Long
Hill-RBF	AL, K, ACD	A-Constant	Short, Normal, Long
Hoffer Q	AL, K	ACD	Short, Normal
Haigis	AL, ACD	a0, a1, and a2	Short, Normal, Long
Holladay I	AL, K	Surgeon Factor	Short, Normal, Long
Holladay II	AL, ACD, WTW, LT, age, pre-op refraction	ACD	Short, Normal, Long
Olsen	Uses pre-op ACD and lens thickness to provide a C-Constant for effective lens position	C-Constant	Short, Normal, Long
SRK/T	AL, K	A-Constant	Normal, Long

PATIENT SELECTION

After your first 5 bilateral patients, you can also reference the Patient Lifestyle Questionnaire and Trifocal Expectations Worksheet to help you identify potential appropriate candidates.

Understand your patient's post-surgery vision goals:

- Hobbies
- Activities
- Current lifestyle

Patient Lifestyle Questionnaire

Trifocal Expectations Sheet

ENHANCING THE PATIENT EXPERIENCE

PATIENT SATISFACTION

Patients whose providers listen to them, elicit goals and concerns, and explain all the options are **3-5 times more satisfied** with their providers.[6]

PATIENT OUTCOMES

Effectively communicating with patients has a **beneficial effect on medical outcomes**, including[6,7]:

- Lower rates of anxiety, pain and psychological distress
- Higher rates of compliance and symptom resolution

? **What communication techniques can be easily applied to help improve patient satisfaction and outcomes?**

PATIENT EXPECTATIONS

It's important to help your patients understand what to expect before and after surgery with the PanOptix® IOL. You can utilize the Trifocal Expectations Worksheet to facilitate patient discussions.

What you should let your patients know:

- You should not evaluate your vision until you've had surgery in both eyes
- You may see some glare and halos around lights following surgery
- You can expect to see well and read comfortably in different lighting conditions
- Your range of vision should be excellent and, with time, will adjust

Trifocal Expectations Sheet

REFERENCES

1. AcrySof® IQ PanOptix® Directions for Use.
2. Alcon Data on File.
3. Alcon Data on File.
4. Carson D, et al. Optical bench performance of 3 trifocal intraocular lenses. *J Cataract Refract Surg*. 2016;42:1361-1367.
5. Kohnen T, et al. Visual performance of a quadrifocal (trifocal) intraocular lens following removal of the crystalline lens. *Am J Ophthalmol*. 2017;184:52-62.
6. Alcon Data on File.

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1. AcrySof ® IQ PanOptix® Directions for Use.
2. Alcon Data on File.
3. Alcon Data on File.
4. Alcon Data on File.
5. IOL Power Calculation Formulas. http://www.doctor-hill.com/iol-main/formulas.htm. Accessed December 12, 2017.
6. Alston C, Paget L, Halvorson, G, et al. Communicating with Patients on Health Care Evidence. Discussion Paper. Institute of Medicine of the National Academies. September 2012.
7. Weiss BD. Health literacy and patient safety: Help patients understand–Manual for Clinicians. http://med.fsu.edu/userFiles/file/ahec_health_clinicians_manual.pdf. AMA Foundation; 2007. Accessed November 9, 2017.
8. Fortin AH. The Beginning of the Interview: Smith's Patient-Centered Interviewing. Third Edition. 2012.

email: johnfmahermd@me.com

Table 2. The MIGS Family of Procedures[2–11]

Site of Bypass (Type of Procedure)	Device	Maker	Approved in the United States and Canada	Approved in Europe	Stand-alone	Approach	Filtration
Schlemm canal (internal MIGS)	Trabectome[1]	NeoMedix Corporation	Yes	Yes	Yes	Interno	Interno
	iStent[3]	Glaukos Corporation	Yes	Yes	Yes (Europe) No (United States)	Interno	Interno
	Hydrus[4]	Ivantis Inc	Yes	Yes	Yes (Europe) No (United States)	Interno	Interno
	Kahook Dual Blade[7]	New World Medical, Inc	Yes	Yes	Yes	Interno	Interno
	iTrack for GATT[5]	Ellex	Yes	Some countries	Yes	Interno	Interno
	iTrack for ab interno canaloplasty[8]	Ellex	Yes	Some countries	Yes	Interno	Interno
	VISCO360[9]	Sight Sciences	Yes	Yes	Yes	Interno	Interno
Suprachoroidal space (internal MIGS)	CyPass*[1]	Alcon	Yes	Yes	No	Interno	Interno
	iStent Supra[10]	Glaukos Corporation	No	Yes	Yes (Europe)	Interno	Interno
	Gold shunt[6]	SOLX, Inc	Yes (United States) No (Canada)	Yes	Yes	Externo	Interno
Subconjunctival space (external MIGS)	EX-PRESS[11]	Alcon	Yes	Yes	Yes	Externo	Externo
	XEN Gel Stent[12]	Allergan	Yes	Yes	Yes	Interno	Externo
	MicroShunt[13]	Santen Inc	No	Yes	Yes	Externo	Externo

Abbreviations: GATT, gonioscopy-assisted transluminal trabeculotomy; MIGS, minimally invasive glaucoma surgery.

* Off market August 29, 2018

SOUTHERN CALIFORNIA COLLEGE OF OPTOMETRY

CONTINUING EDUCATION COURSE SCHEDULE

2021 COURSE SCHEDULE

DATE	LOCATION	COURSE TOPIC	CE UNITS
July 10 & 11	**SCCO	MBKU** *Live Webinar*	**Ocular Disease Part II** *COPE Approval Pending*	16
September 19	**SCCO	MBKU** *Live Webinar*	**Joint SCCO I USC I VA Symposium** *COPE Approval Pending*	8
December 12	**SCCO	MBKU** *Live Webinar*	**Contemporary Topics in Optometry** *COPE Approval Pending*	8

GENERAL INFORMATION

MBKU CAMPUS LOCATIONS

SCCO I FULLERTON CAMPUS
2575 Yorba Linda Blvd. Fullerton, CA 92831

LEARN MORE & REGISTER *ketchum.edu/ce*

CONTACT US

email: ce@ketchum.edu

Marshall B. KETCHUM UNIVERSITY
Southern California College of Optometry

Neurotrophic keratitis is a degenerative disease that warrants immediate attention[1]

oxervate®
(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

OXERVATE is the first FDA-approved pharmacologic treatment that targets the root pathogenesis of neurotrophic keratitis (NK)[2]

Cenegermin-bkbj, the active ingredient in FDA-approved OXERVATE, is structurally identical to the human nerve growth factor (NGF) protein made in ocular tissues.[3]

Endogenous NGF is a protein involved in the differentiation and maintenance of neurons and is believed to support corneal integrity through three mechanisms (in preclinical models): corneal innervation, tear secretion, and epithelial cell growth.[3-5]

In clinical studies, with a single 8-week course of therapy:

- Up to **72%** of patients with NK achieved complete corneal healing*†[2]
- **80%** of patients who achieved complete corneal healing remained completely healed at 1 year (REPARO trial)[6]

OXERVATE is a recombinant human nerve growth factor indicated for the treatment of neurotrophic keratitis.

Important Safety Information

WARNINGS AND PRECAUTIONS

Patients should remove contact lenses before applying OXERVATE and wait 15 minutes after instillation of the dose before reinsertion.

ADVERSE REACTIONS

The most common adverse reaction in clinical trials that occurred more frequently with OXERVATE was eye pain (16% of patients). Other adverse reactions included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and increase in tears (1%-10% of patients).

Please see additional Important Safety Information on accompanying page and full Prescribing Information, including patient information, at OXERVATE.com/prescribing-information.

You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Dompé at 1-833-366-7387 or Usmedinfo@dompe.com.

TREAT NK TODAY
OXERVATE.com/HCP

*Study NGF0212 (REPARO): 52 patients per group; European patients with NK in one eye; 72% of patients completely healed; key findings were after 8 weeks of treatment; 6 times daily; vehicle response rate 33.3%.[2] Study NGF0214: 24 patients per group; US patients with NK in one or both eyes; 65.2% completely healed; vehicle response rate 16.7%[2,7]

†Complete corneal healing was defined as the absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of OXERVATE treatment.[2]

References: 1. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579. **2.** OXERVATE (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) [US package insert]. Boston, MA: Dompé U.S. Inc.; 2019. **3.** Voelker R. New drug treats rare, debilitating neurotrophic keratitis. *JAMA*. 2018;320:1309. **4.** Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017;232:717-724. **5.** Muzi S, Colafrancesco V, Sornelli F, et al. Nerve growth factor in the developing and adult lacrimal glands of rat with and without inherited retinitis pigmentosa. *Cornea*. 2010;29:1163-1168. **6.** Data on file. Dompé U.S. Inc.; 2021. NGF0212. **7.** Pflugfelder SC, Massaro-Giordano M, Perez VL, Hamrah P, Deng SX, Espandar L, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy. *Ophthalmology*. 2020;127:14-26.

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US-OXE-1900180.02 02/21

oxervate™
(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

Brief Summary of Safety

Consult the full Prescribing Information for complete product information.

INDICATIONS AND USAGE

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

ADVERSE REACTIONS

Clinical Studies Experience Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Animal Data

In embryofetal development studies, daily subcutaneous administration of cenegermin-bkbj to pregnant rats and rabbits throughout the period of organogenesis produced a slight increase in post-implantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the MRHOD). A no observed adverse effect level (NOAEL) was not established for post-implantation loss in either species. In rats, hydrocephaly and ureter anomalies were each observed in one fetus at 267 mcg/kg/day (1709 times the MRHOD). In rabbits, cardiovascular malformations, including ventricular and atrial septal defects, enlarged heart and aortic arch dilation were each observed in one fetus at 83 mcg/kg/day (534 times the MRHOD). No fetal malformations were observed in rats and rabbits at doses of 133 mcg/kg/day and 42 mcg/kg/day, respectively. In a pre- and postnatal development study, daily subcutaneous administration of cenegermin-bkbj to pregnant rats during the period of organogenesis and lactation did not affect parturition and was not associated with adverse toxicity in offspring at doses up to 267 mcg/kg/day. In parental rats and rabbits, an immunogenic response to cenegermin-bkbj was observed. Given that cenegermin-bkbj is a heterologous protein in animals, this response may not be relevant to humans.

Lactation

There are no data on the presence of OXERVATE in human milk, the effects on breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older [*see Clinical Studies (14)*].

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis and Mutagenesis Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD). In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

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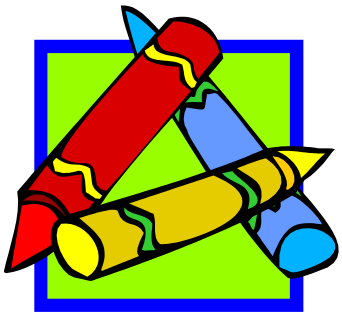
Amblyopia Treatment Study

RECRUITMENT UNDERWAY FOR NIH-SPONSORED STUDY

Amblyopia is the most common cause of monocular visual impairment in children. The choice of a sequential approach versus a simultaneous approach to "optical treatment (glasses) plus patching treatment" remains unresolved, with some existing data supporting one approach and some data supporting the other. There is a reasonable rationale for either approach. This unresolved controversy results in a dichotomy of current clinical practice, with some care providers favoring one approach and others favoring the opposite approach. In addition, the influence of adherence to patching on treatment response is not well understood.

The Pediatric Eye Disease Investigator Group (PEDIG) is conducting a clinical trial to evaluate if treating amblyopia with glasses and patching at the same time improves vision as well as treating amblyopia first with glasses and then with patching, if needed. This study will also use occlusion dose monitors (ODMs) to record adherence with prescribed patching treatment, to study dose-response. The study is supported through funding from the National Eye Institute of the U.S. National Institutes of Health and is being coordinated by the Jaeb Center for Health Research in Tampa, Florida.



Study Specifics

- 544 children are expected to be enrolled
- Children must be between 3 to < 13 years old
- Visual acuity in the amblyopic eye must be between 20/40 and 20/200
- Random assignment to either:
  - **Sequential treatment**: full-time glasses first, with subsequent patching for 2 hours per day/7 days per week if there is no further improvement in amblyopic eye visual acuity with glasses alone and there is residual amblyopia, OR
  - **Simultaneous treatment:** full-time glasses and part-time patching for 2 hours per day/7 days per week
- Occlusion dose monitors (ODMs) will be used to record actual patch wear time during prescribed patching
- Follow-up visits every 8 weeks for 56 weeks
- No previous treatment for amblyopia is allowed, including glasses or contact lenses.

How Can You Help?

- Your assistance is needed in referring children who may qualify.
- Referrals can be sent to the investigator listed below, or for more information, visit the PEDIG website at http://pedig.net/ or call the PEDIG Coordinating Center toll free at 1-888-797-3344

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NATIONAL INSTITUTES OF HEALTH

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Pediatric Eye Disease Investigator Group