Eye complications in cystinosis & Status of eye treatment

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Disclosures

- Dr LIANG Hong has received honoraria and/or consulting fees from:
  - Recordati Rare Diseases
  - AVROBIO
  - CHIESI SAS

PLAN

Eye complications in cystinosis

Physiopathology of ocular cystinosis

Cornea complications by Slit lamp/OCT/IVCM

Glaucoma, Retinopathy

Status of eye treatment

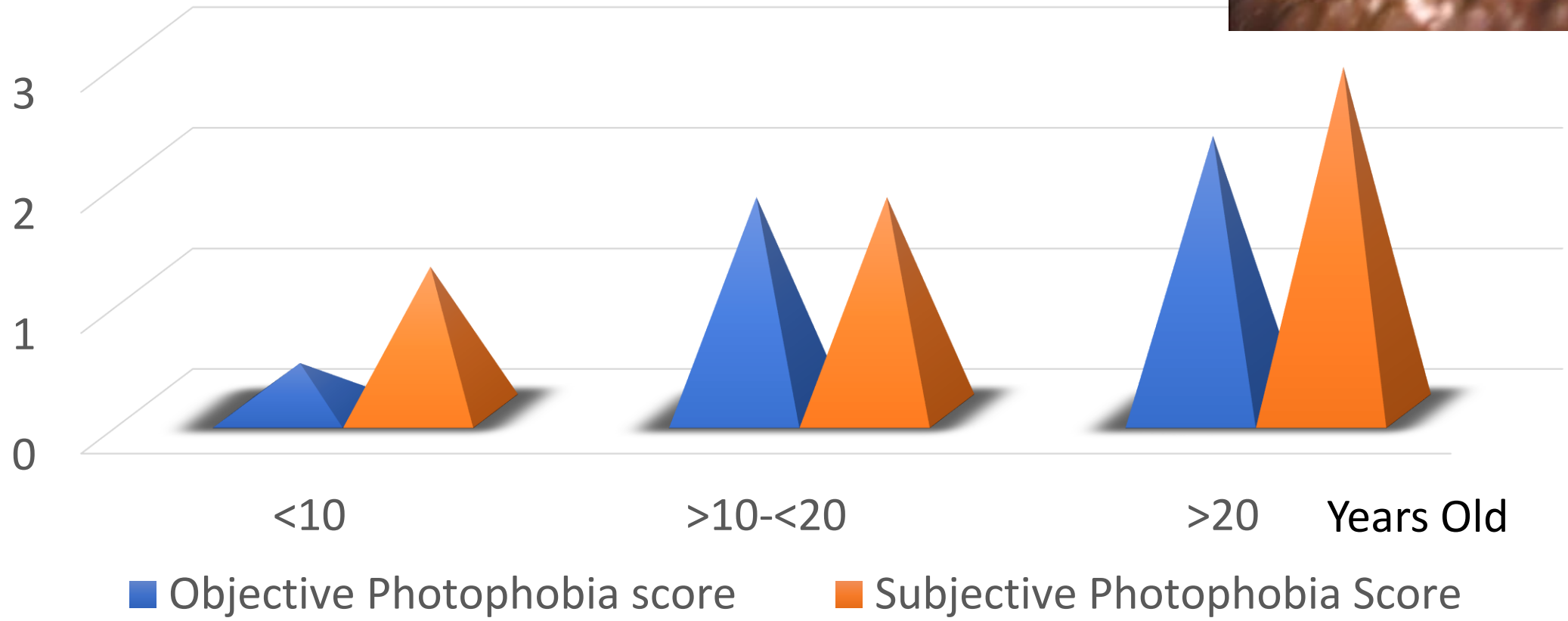
Chart for eye cystinosis: Cysteamine + other local treatments

Real life of cystadrops in treatment

Clinical practice experiences

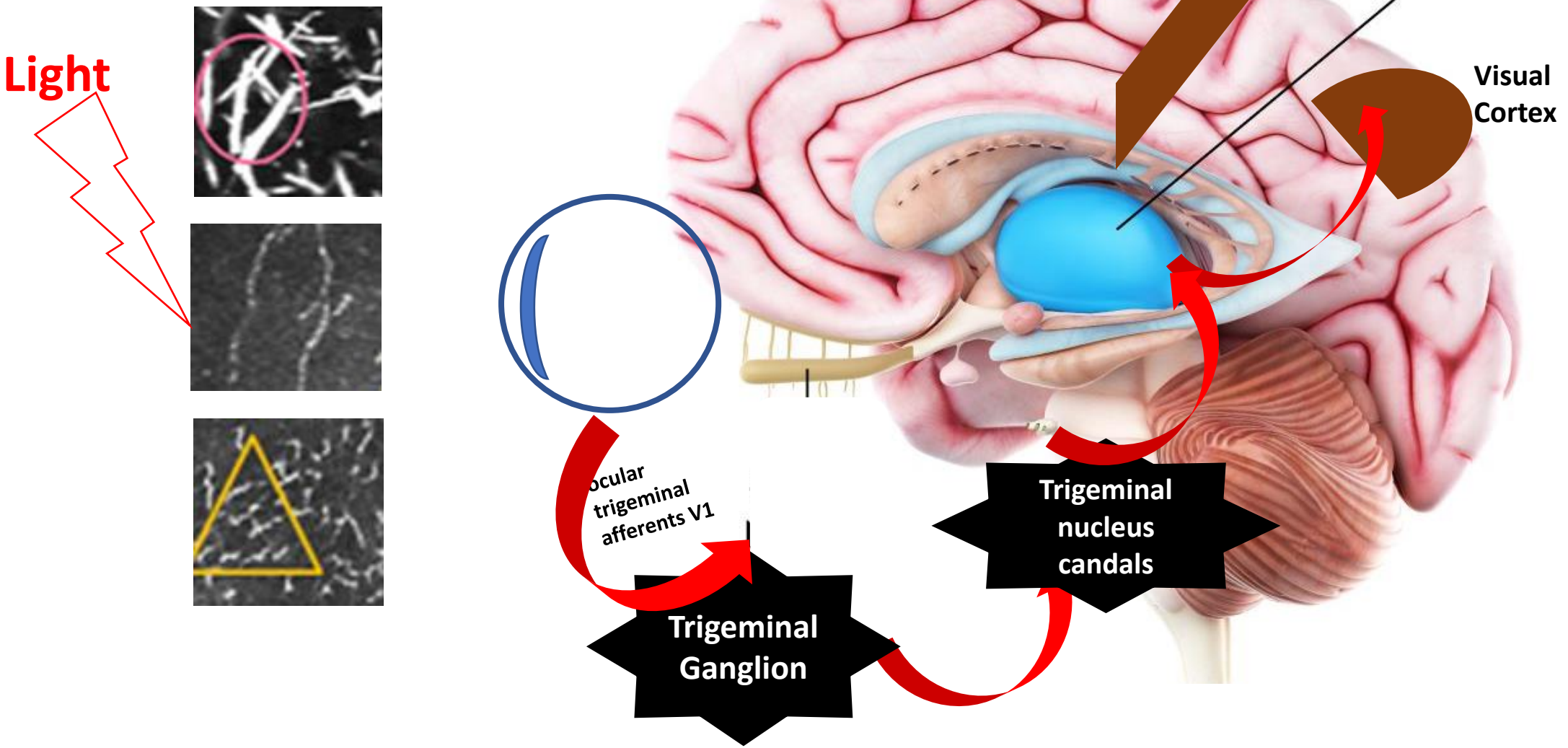
Physiopathology of ocular cystinosis

Symptoms: Photophobia



Dr LIANG H et al. Unpublished data

PHOTOPHOBIA MIGRAINE OCULAR PAIN



LIANG et al., IOVS 2015

Ocular Manifestations and Complications

Anterior segment

Conjunctiva

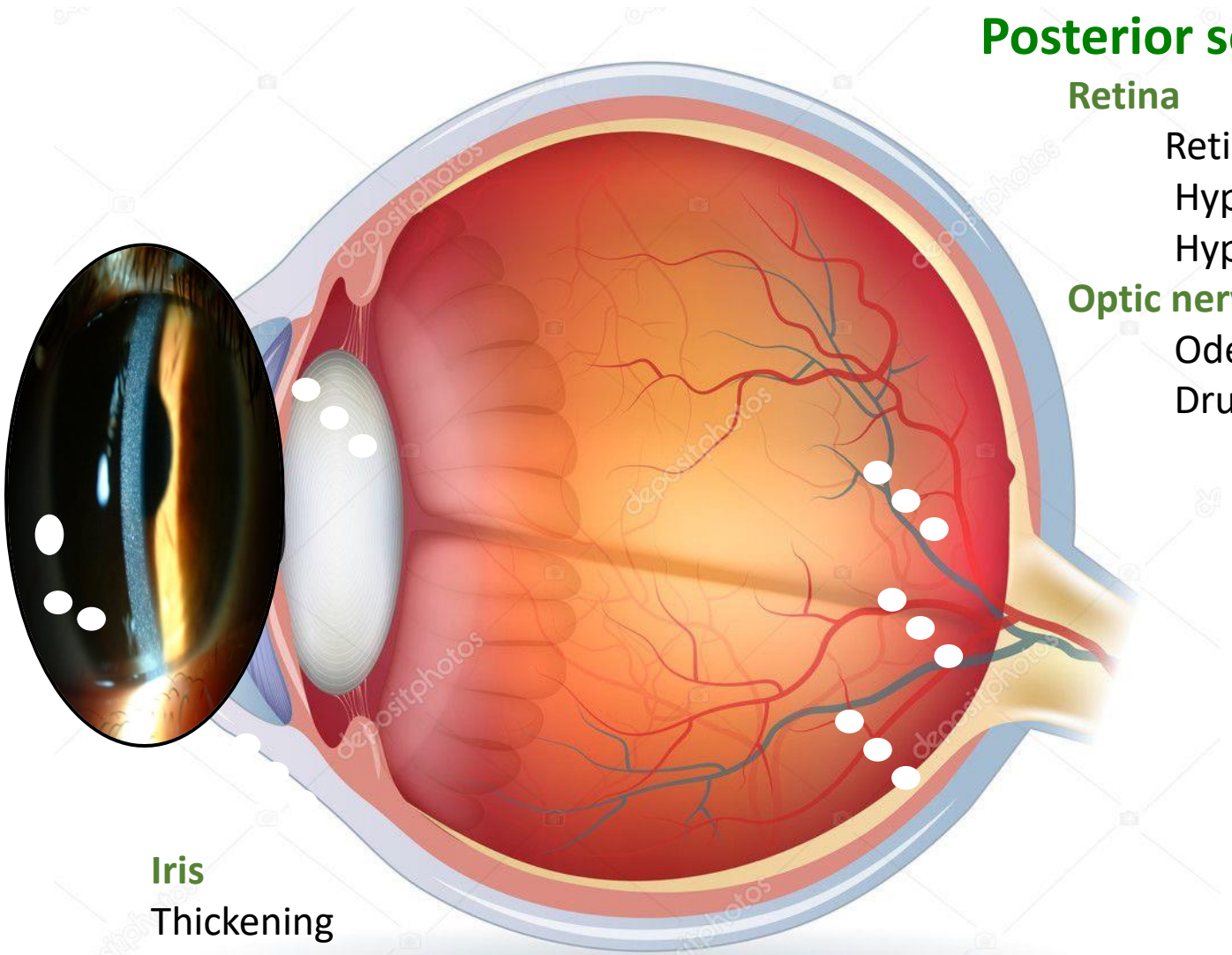
Meibomian gland dysfunction

Limbus

Limbal stem cell deficiency (LSCD)

Cornea

blepharospasm
Superficial punctate keratopathy
Band keratopathy
Peripheral neovascularization
Cornea ulcer
Opacitication



Iris

Thickening
Atrophy
Angle abnormalities (glaucoma)

Posterior segment

Retina

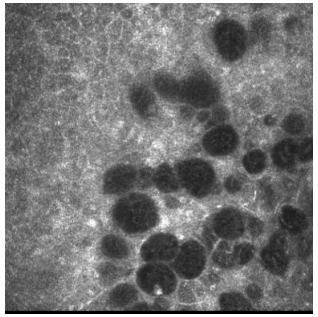
Retinal degeneration
Hyper/
Hypopigmentation

Optic nerve

Odema
Drusen

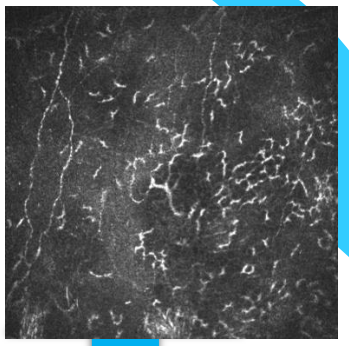
Tsilou E et al. *Surv Ophthalmol* 2007;52(1):97-105. Labbé A et al. Br J *Ophthalmol* 2009; 93(5):673-677

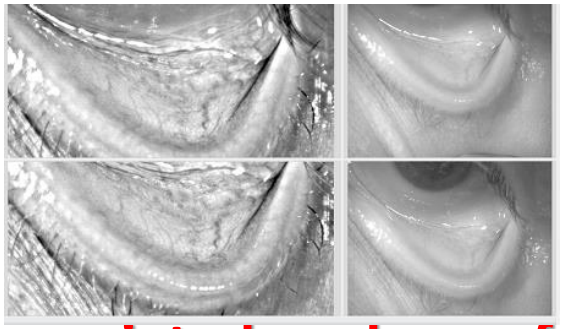
Vicious cycle of ocular cystinosis



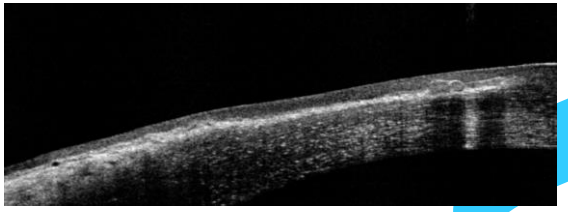
Apoptosis

Inflammation





Dry eye associated ocular surface diseas



Band Keratopathy

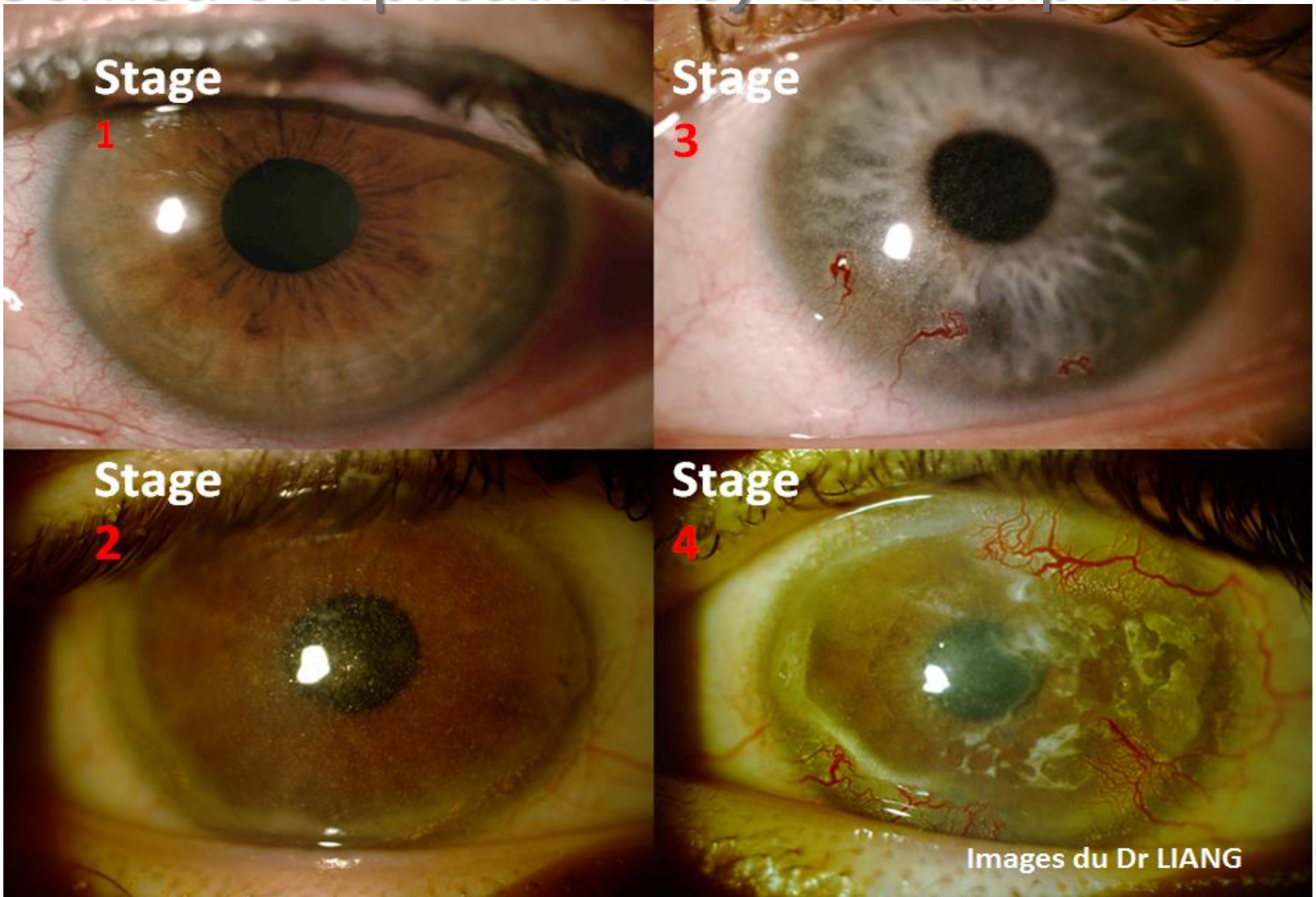
Cornea
Crystals

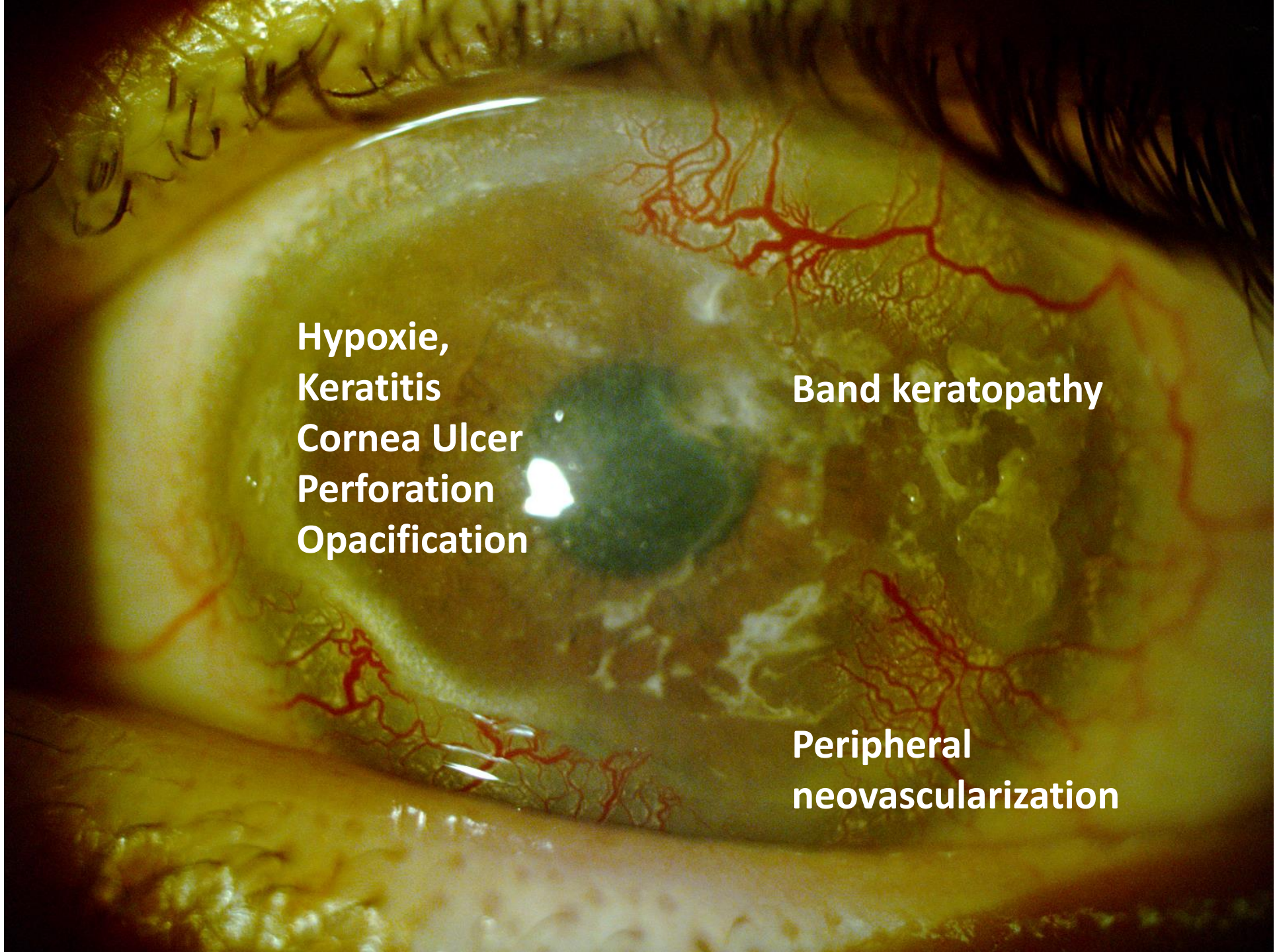
Cornea Neovascularisation

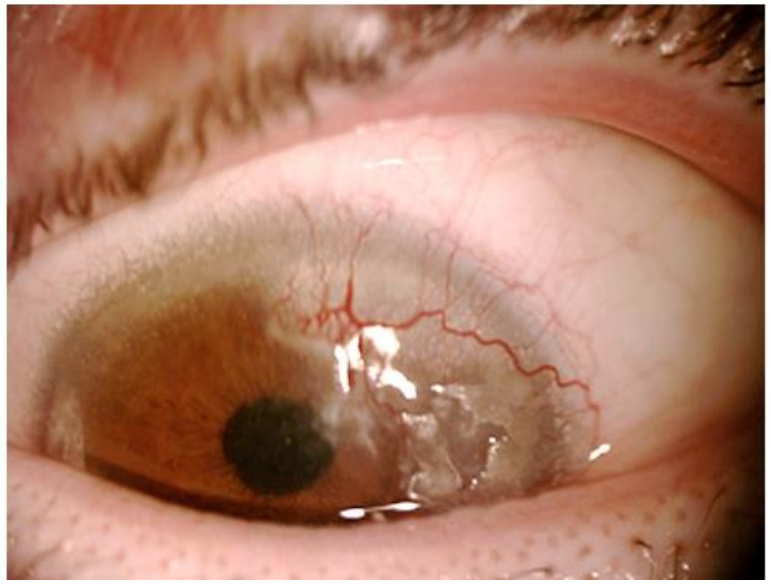
Limbal stem
cell deficiency (LSCD)

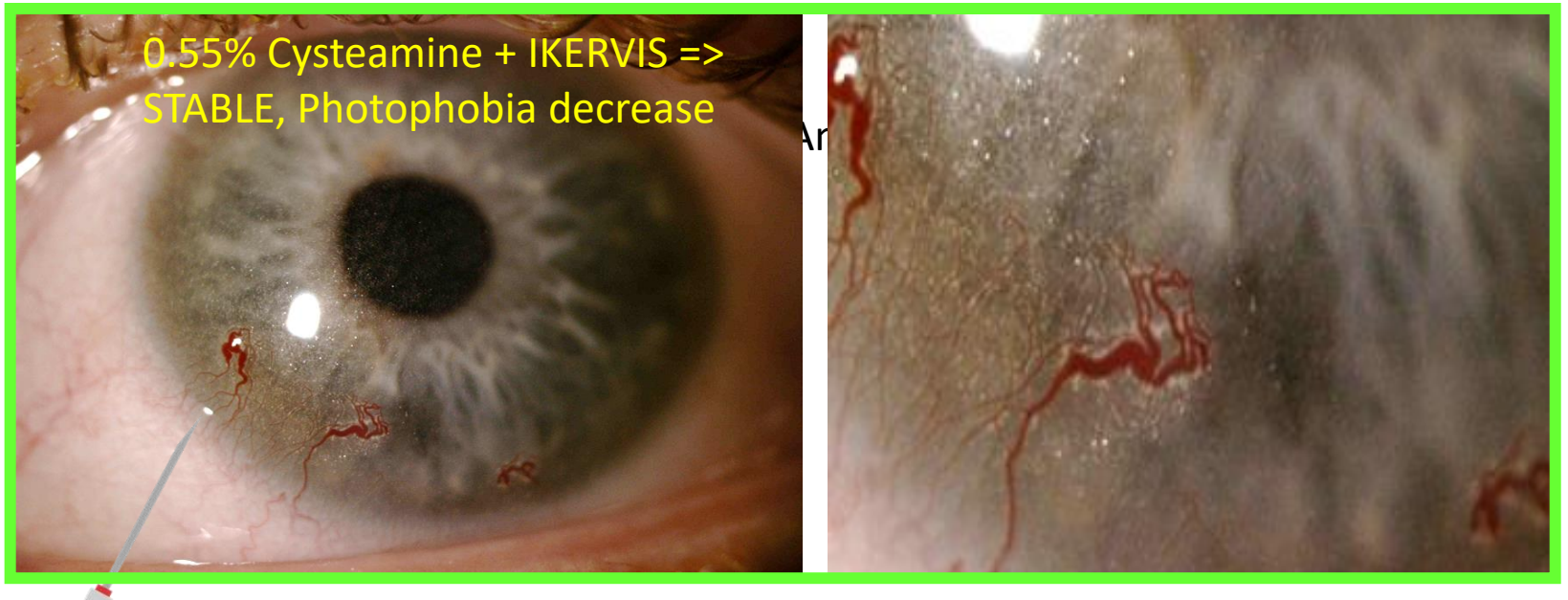
Cornea
Neurodegeneration,
even neurotrophic

Cornea complications by Slit Lamp View

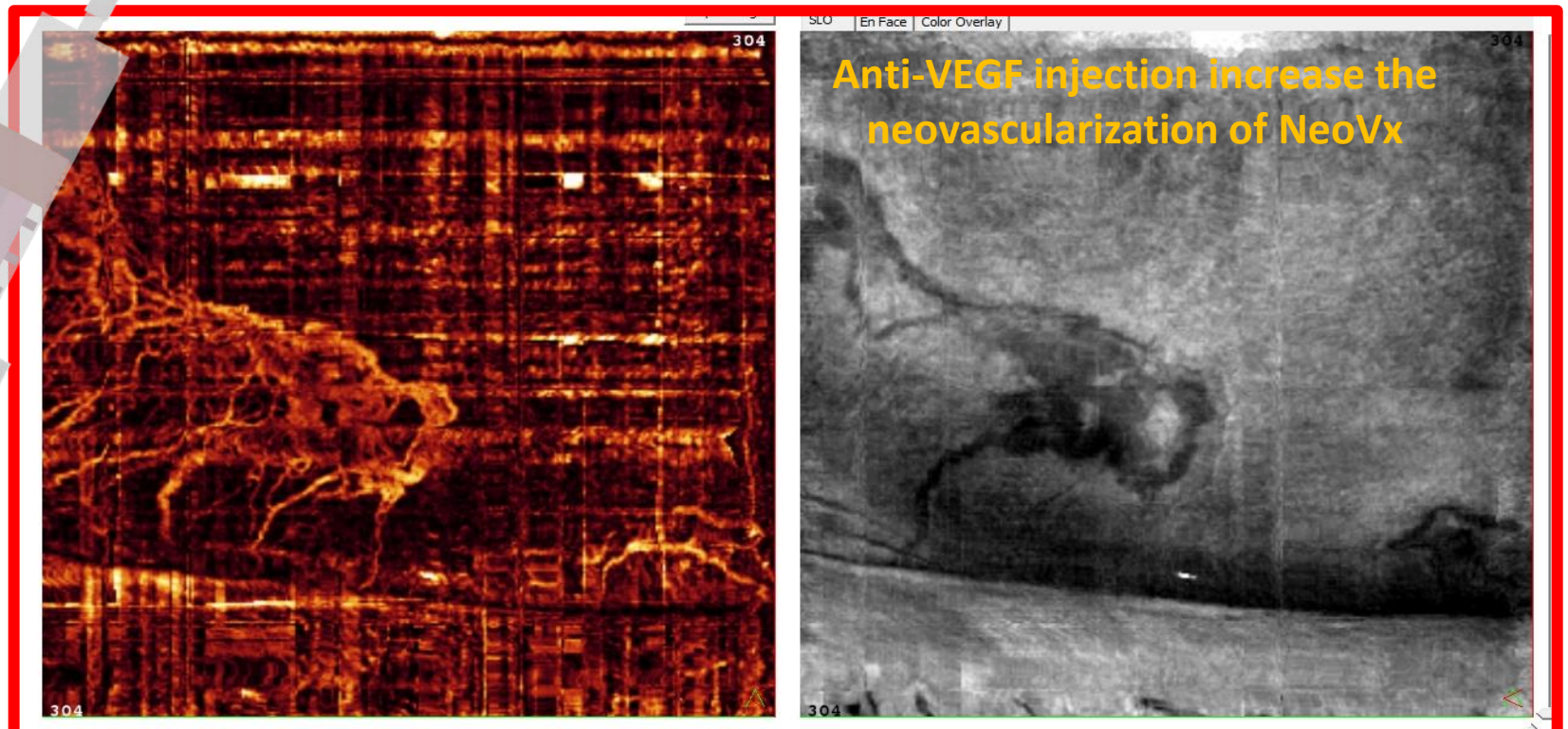


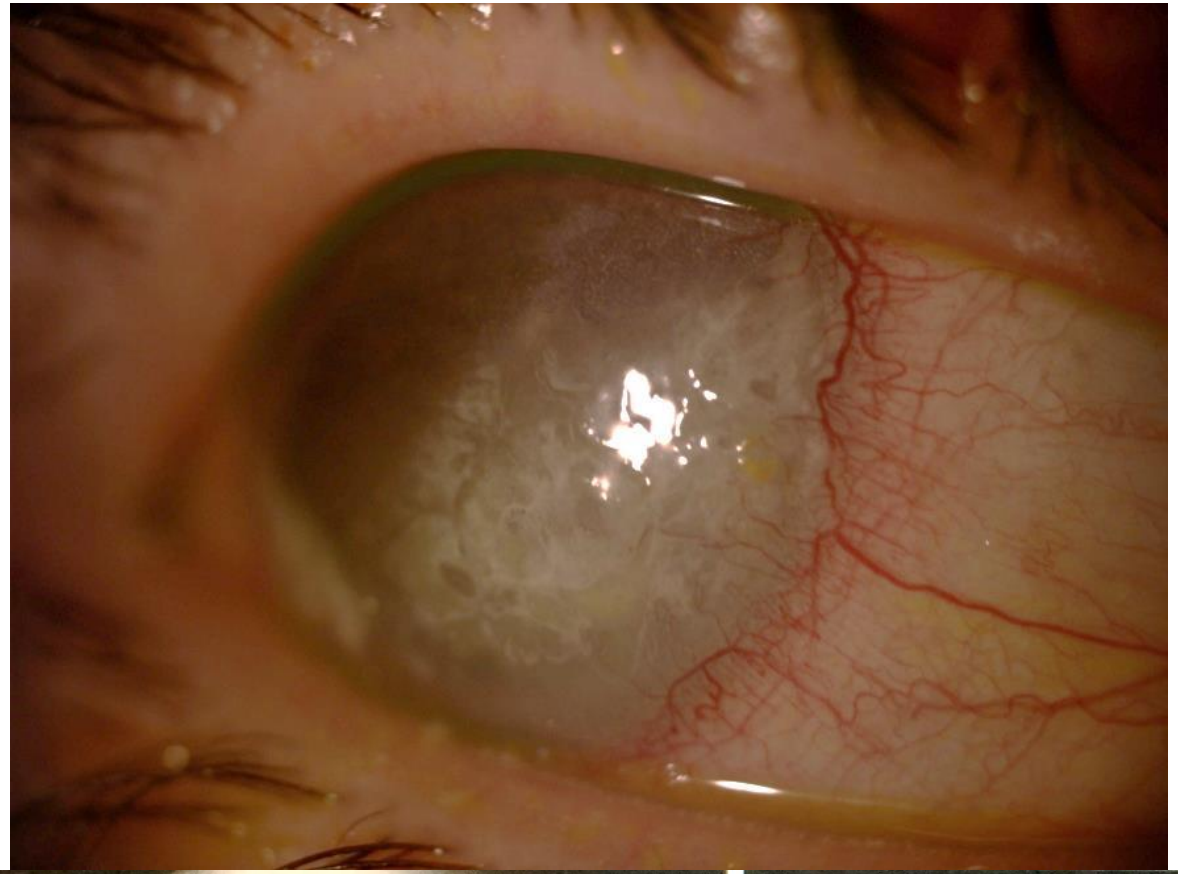

Hypoxie,
Keratitis
Cornea Ulcer
Perforation
Opacification
Band keratopathy
Peripheral
neovascularization

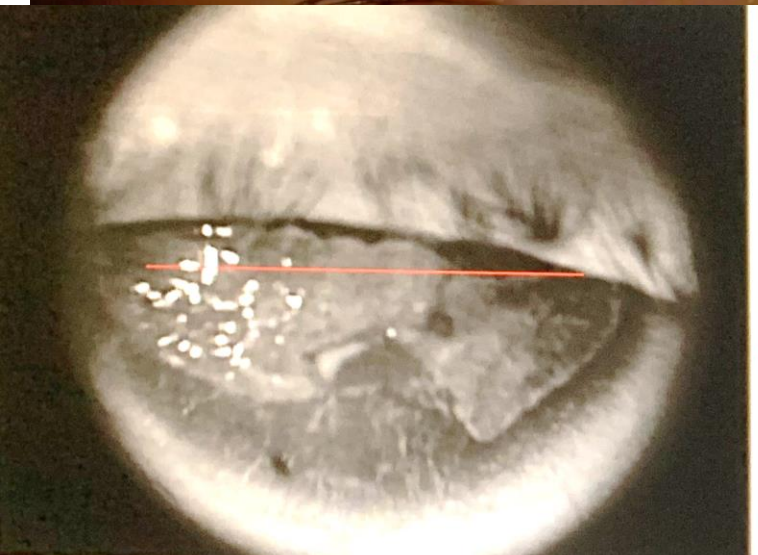




The Failure of anti VEGF injection







Images du Dr LIANG

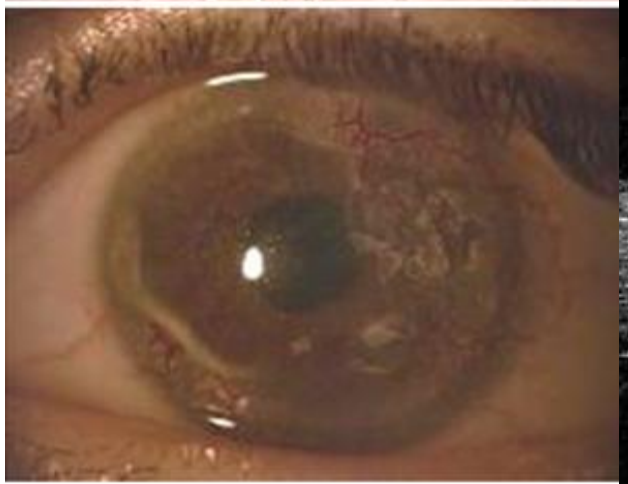
Cornea complications from OCT view

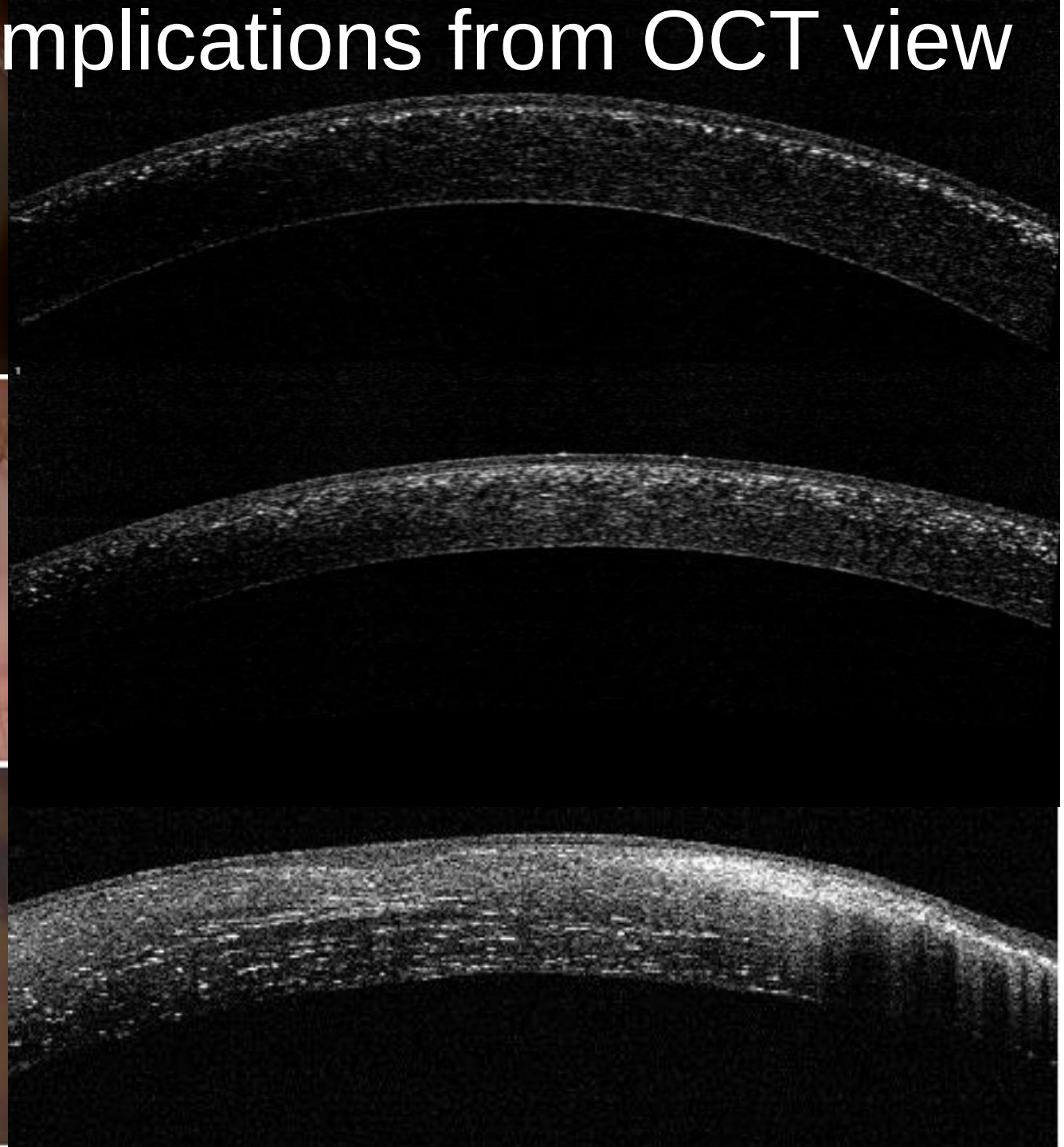
years old

<10

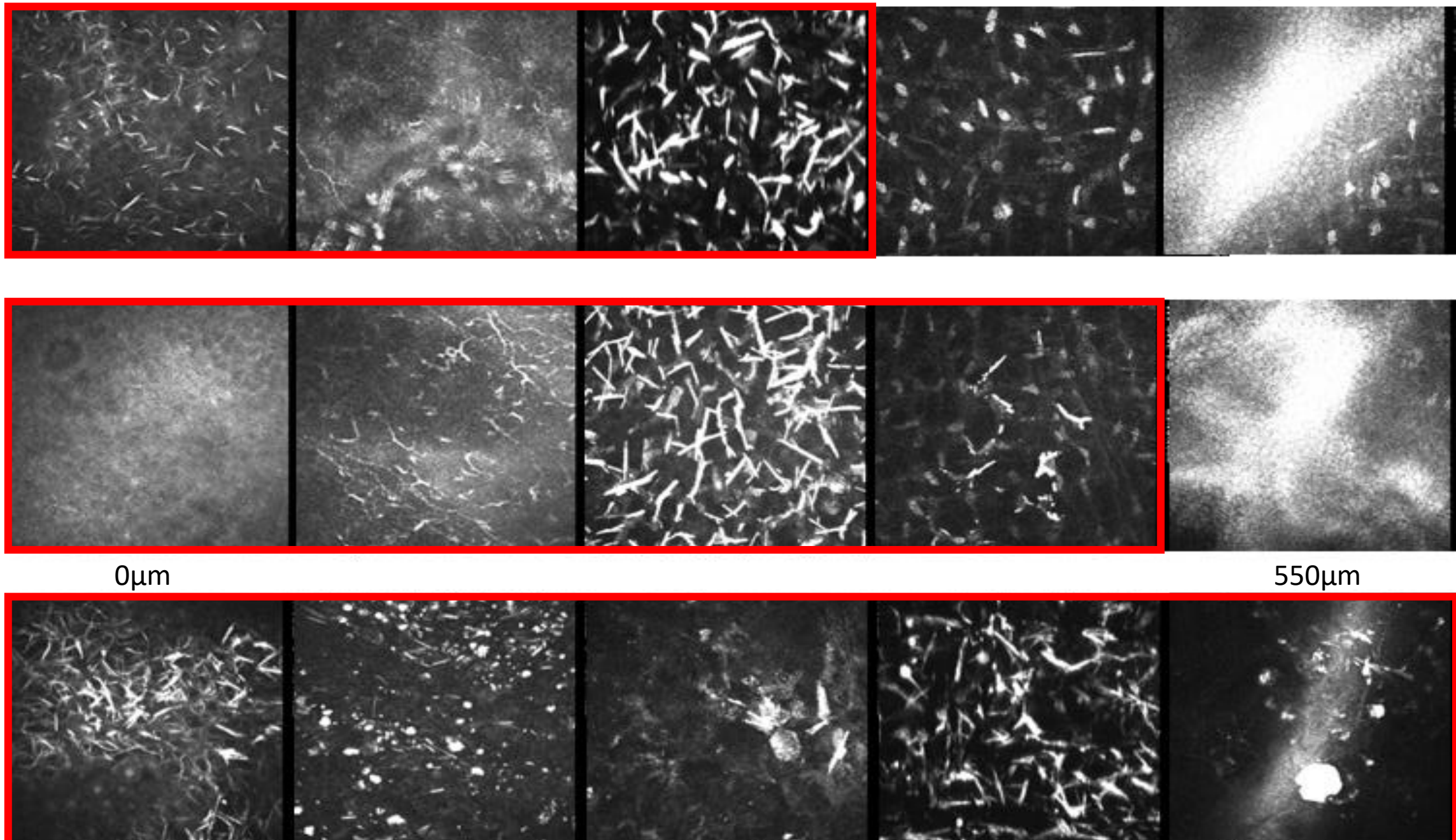
10-20

>30

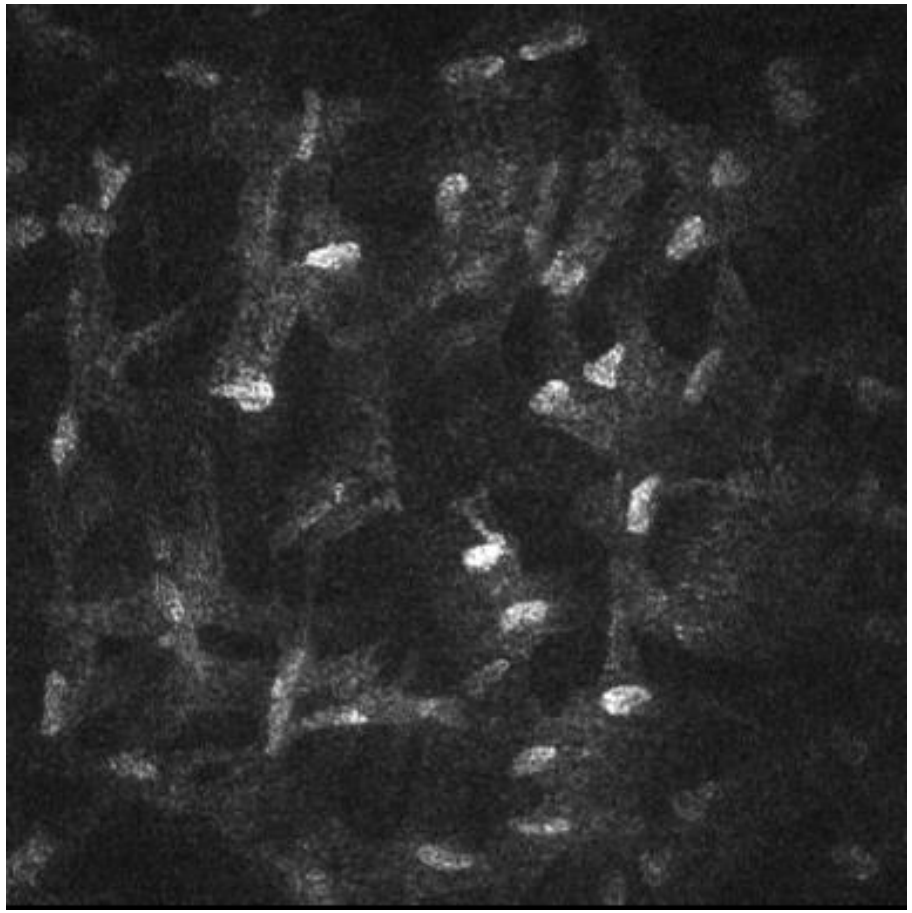




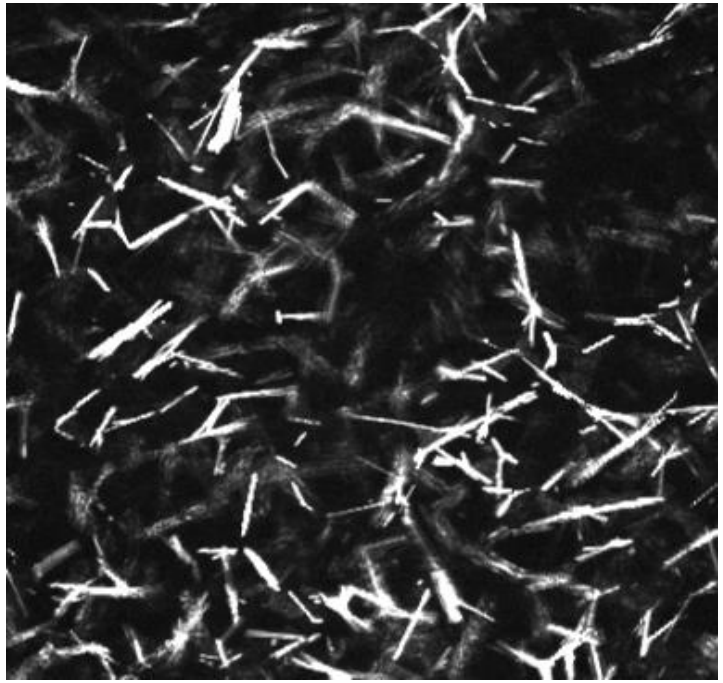
Complications from IN VIVO CONFOCAL MICROSCOPY (IVCM) view



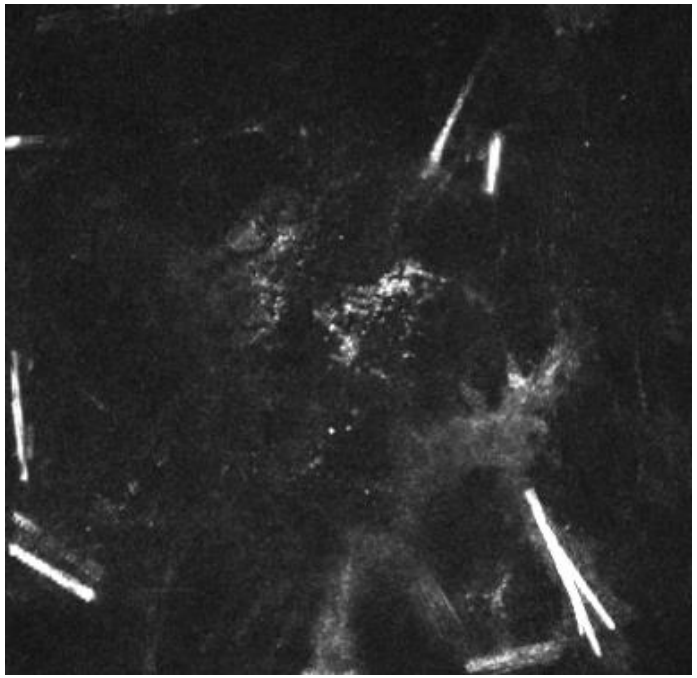
Normal cells



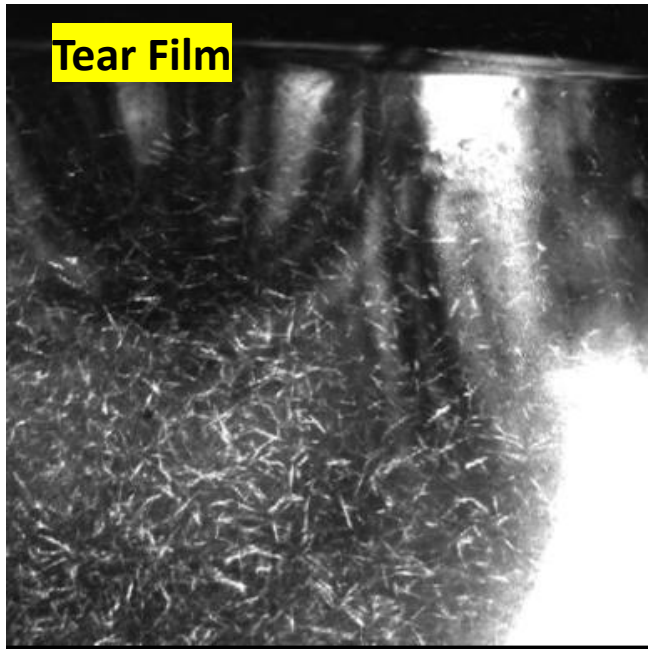
Infiltration of crystals+++

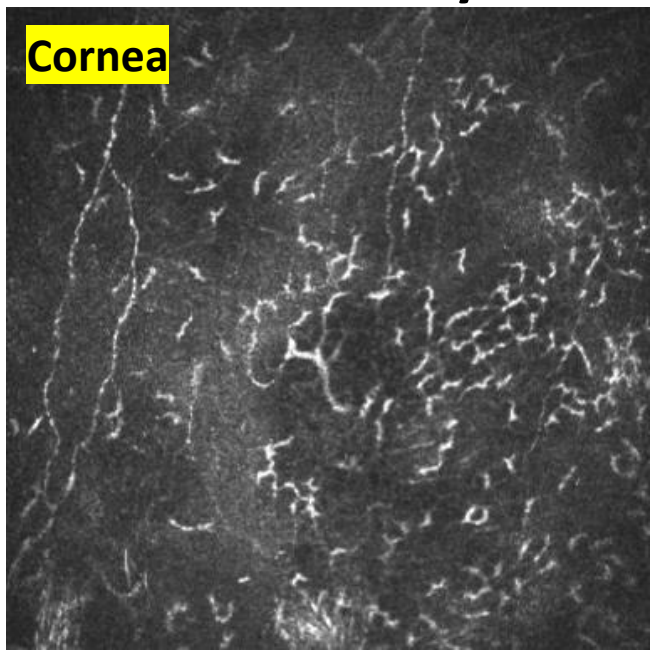


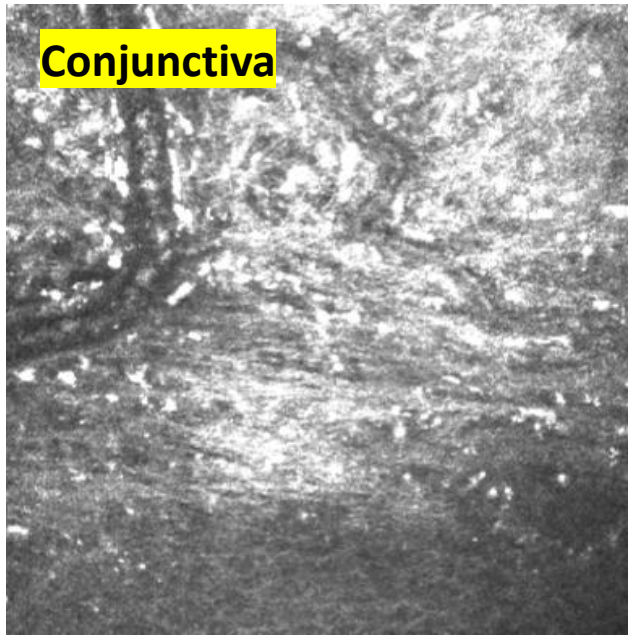
Disappearance of normal cells and crystals

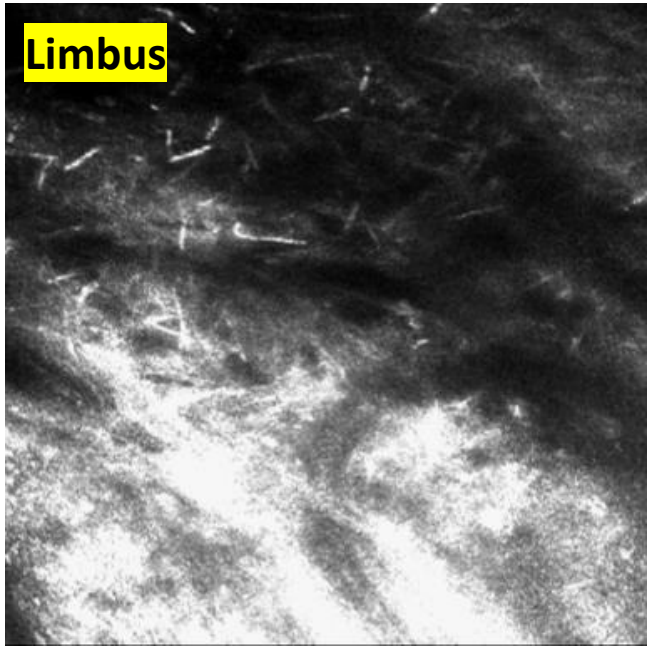


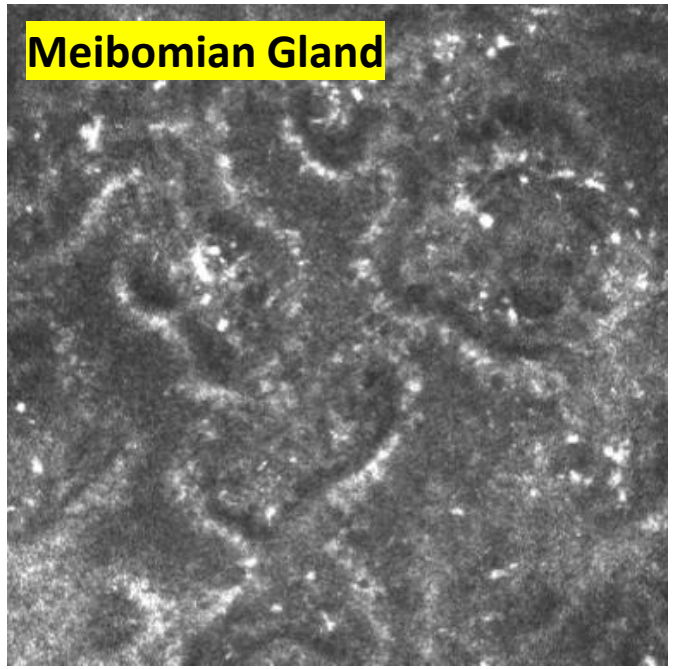
Crystals + Inflammatory Cells at all ocular surface



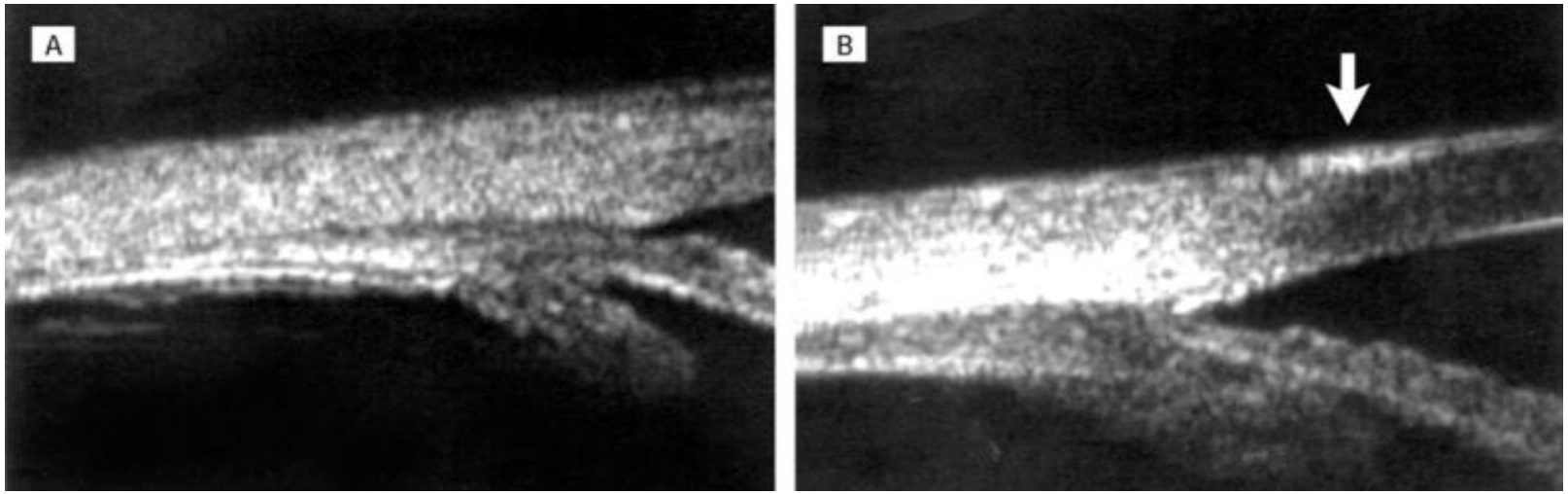




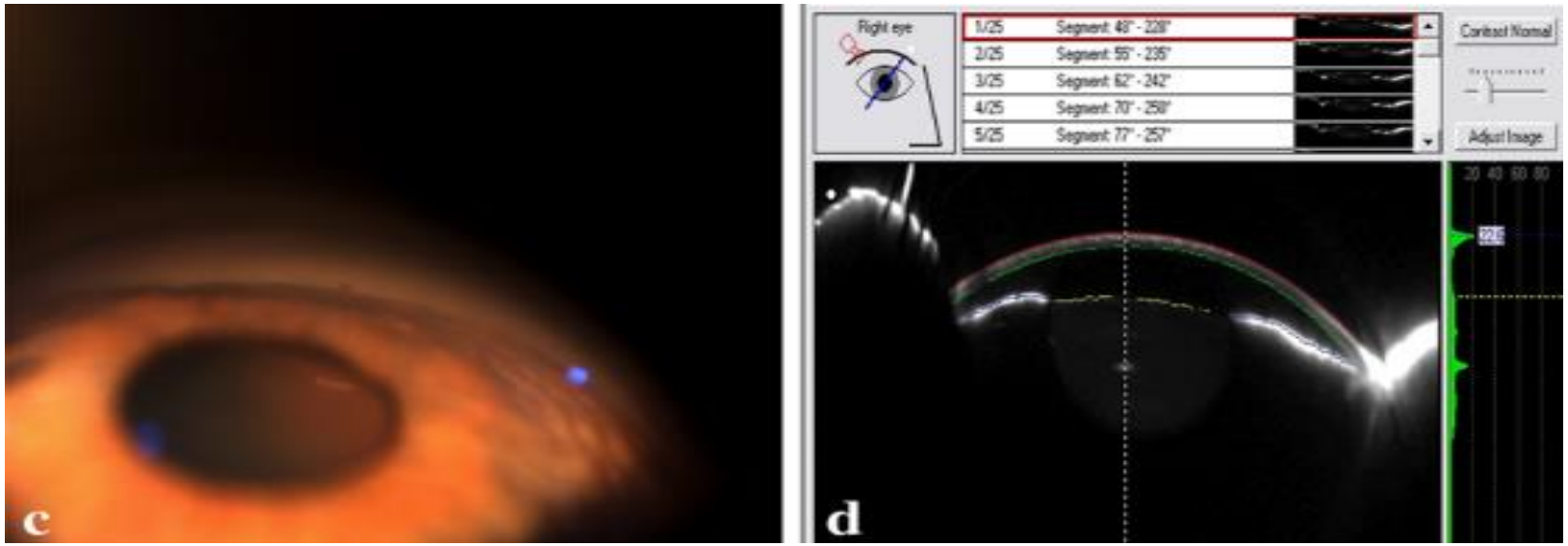




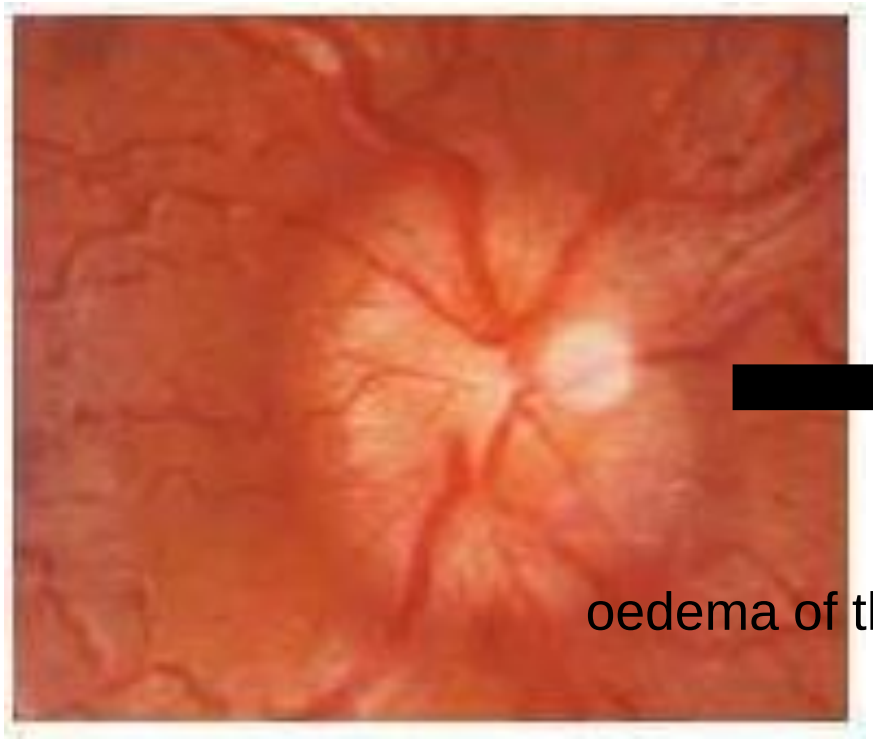
Gonioscopy/UBM/OCT visante (iridocorneal angle)→ glaucoma



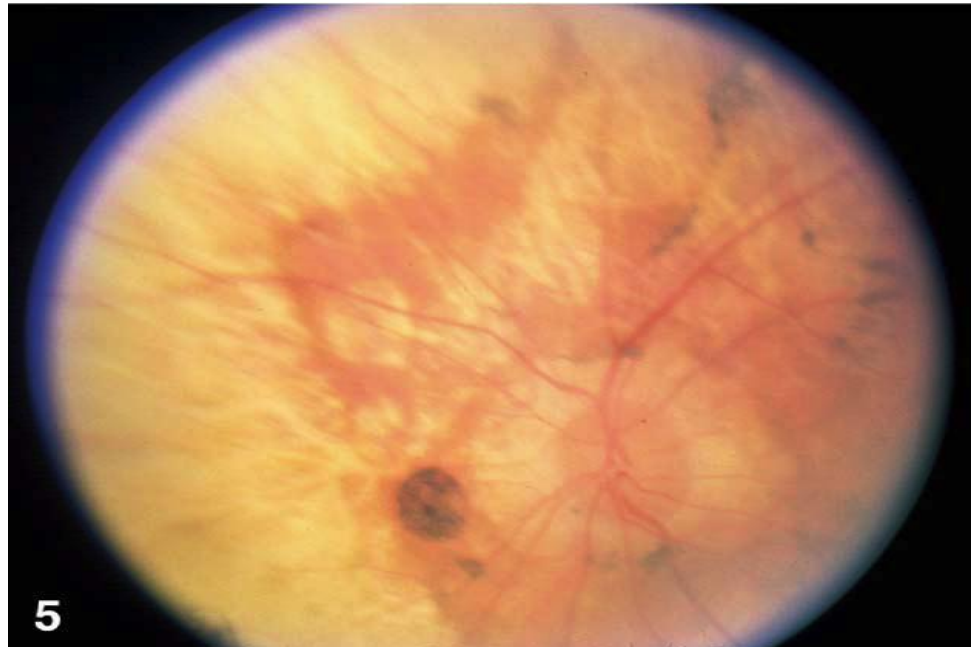
Mungan N_2000 Arch Ophthalmol.;118(10):1329-1333.



Sonmez K BMC Ophthalmology 2012



oedema of the optic nerve



Pigmentary changes resembling Retinitis pigmentosa

Tsilou E, et al. *Ophthalmology* 2006;113:1002–9

Ophthalmic Images

Intraretinal Crystals in Nephopathic Cystinosis and Fanconi Syndrome

Igor Kozak, MD, PhD; J. Fernando Arevalo, MD; Samir S. Shoughy, MD, FRCS

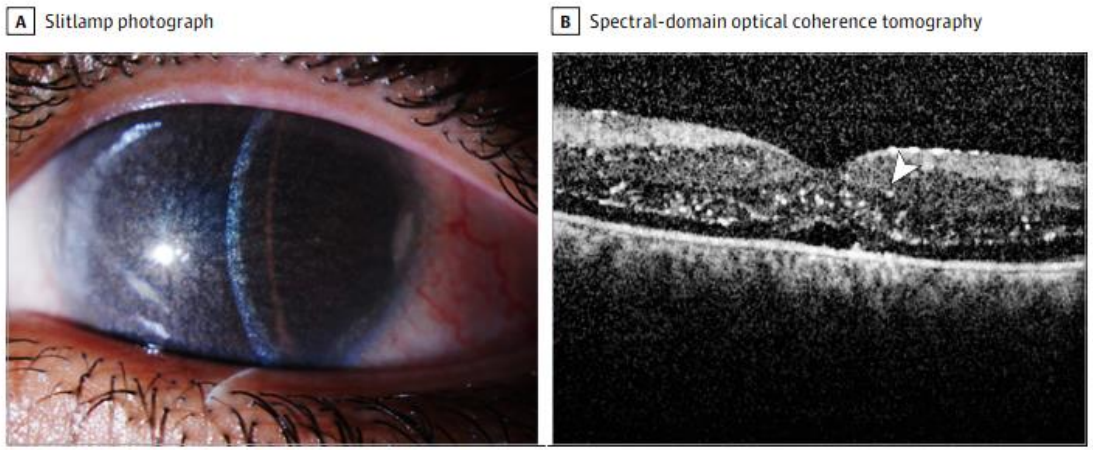


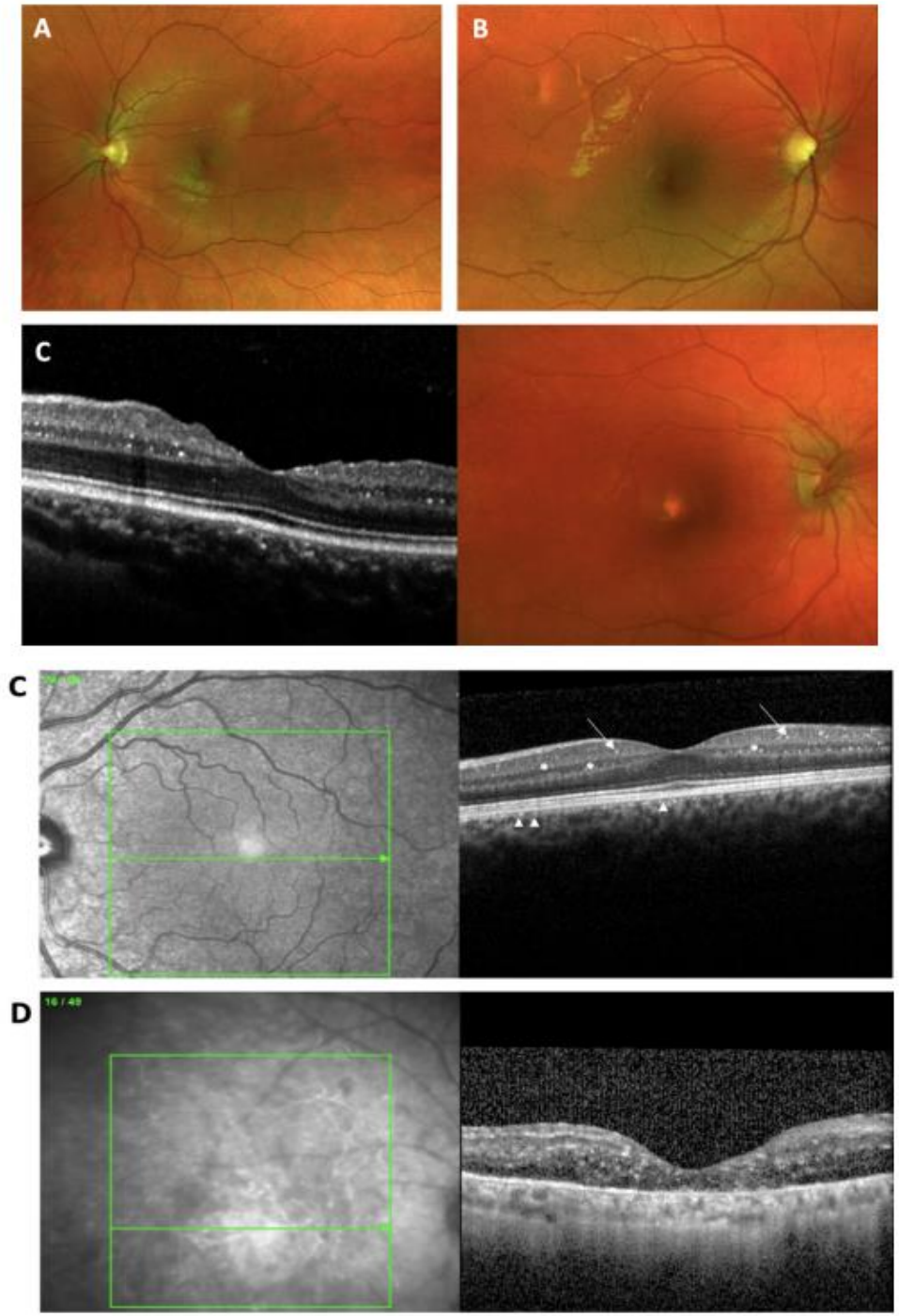
Figure. A, Slitlamp photograph shows corneal deposition of cystine crystals. B, Spectral-domain optical coherence tomography shows intraretinal deposition of cystine crystals (arrowhead).

Clinical science

Spectral domain optical coherence tomography-based retinochoroidal cystine crystal score: a window into infantile nephropathic cystinosis

Leonie Keidel [1], Katharina Hohenfellner,[2] Benedikt Schworm,[1] Siegfried Priglinger,[1] Nikolaus Luft,[1] Claudia Priglinger[1]

Br J Ophthalmol: first published

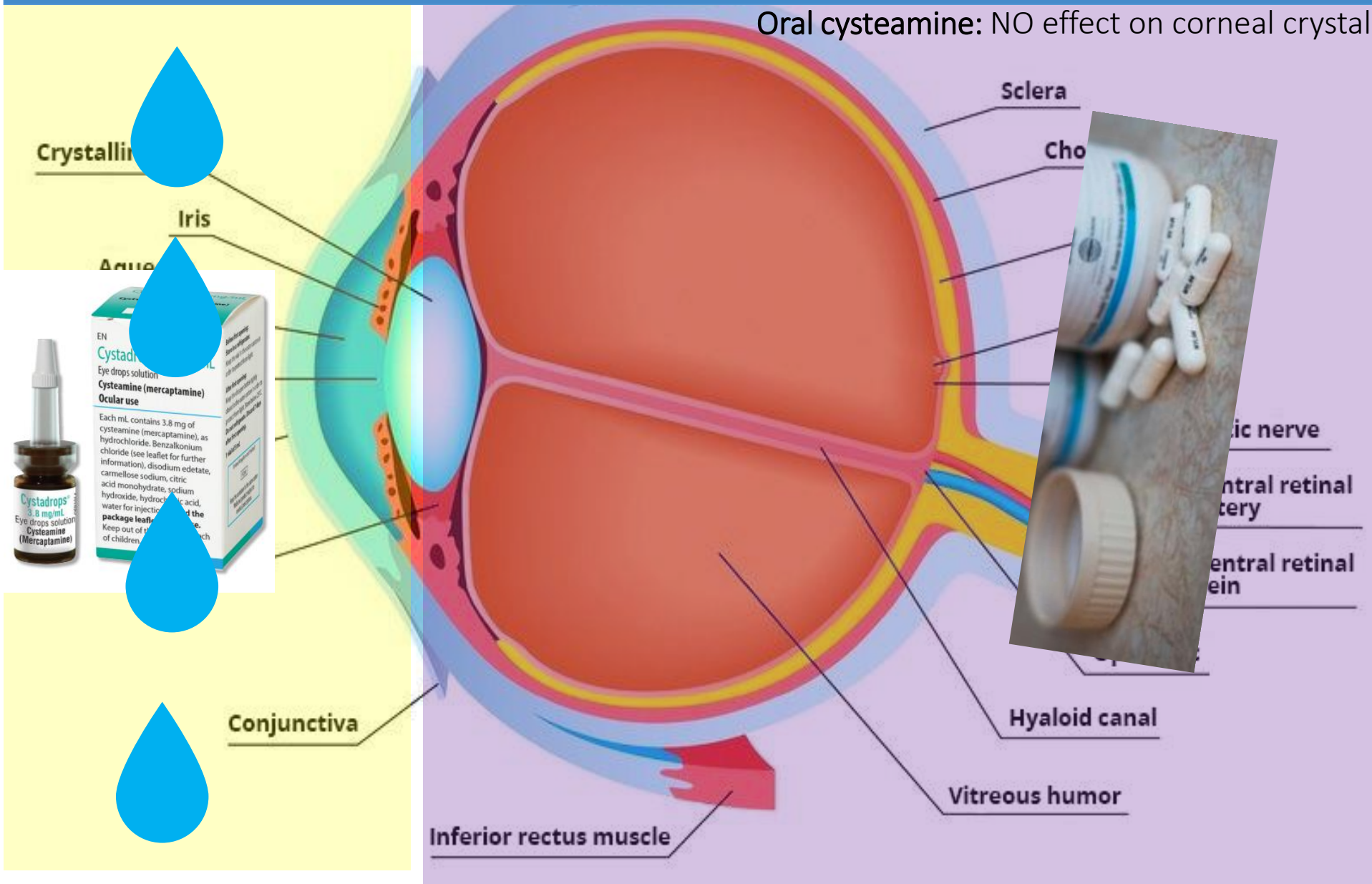


Status of Eye Treatment

Anterior Part

Posterior Part

Oral cysteamine: NO effect on corneal crystal accumulation



Recommendations for treatment of ocular cystiosis

‘Cystadrops®’ (vCH 0.55%)

viscous solution (0.55% cysteamine hydrochloride):

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Ophthalmic	Eye drops viscous solution containing 3.8 mg / mL of cysteamine (0.37% w/w) equivalent to 0.55% (w/w) cysteamine hydrochloride*	Benzalkonium chloride (as preservative) Carmellose sodium Citric acid monohydrate Disodium edetate Hydrochloric acid (for pH adjustment) Sodium hydroxide (for pH adjustment) Water for injection

*also known as mercaptamine hydrochloride

CYSTADROPS is supplied as a 5 mL sterile solution in a 10 mL amber glass vial closed by a bromobutyl stopper and sealed with an aluminium tear-off cap. A PVC dropper applicator with HDPE closure is packed separately and included in each carton box.

the only stable topical cysteamine treatment licensed in Europe

From **1 to 4 times** per day

< 1 week DON’T keep longer

=> Instablility

Ineffective

Infection

Anti-inflammatory agents

Artificial tear

Cyclosporine

Anti-odema: ODM5

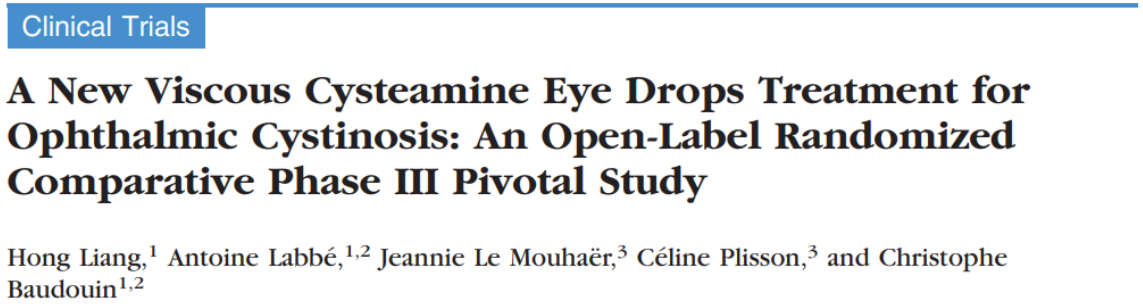
Surgery

EDTA + epithelium scrapping

Cornea graft

Clinical development in XV-XX Hospital for 'Cystadrops®'

	OCT-1	CHOC	Post ATU	PASS
Study design	Phase I/II trial	Open-label, randomised, comparative parallel group Phase III trial	Long-term effects of ocular treatments ATU	Post Authorisation Study
Number	8	32	130	>70
Duration	4 years	3 months	4 years	5 years
Objective	Safety	Superiority of viscous CH formulation (vCH) 0.55% *versus* CH 0.10%	Cystadrops Safety	Safety Study


Clinical Trials

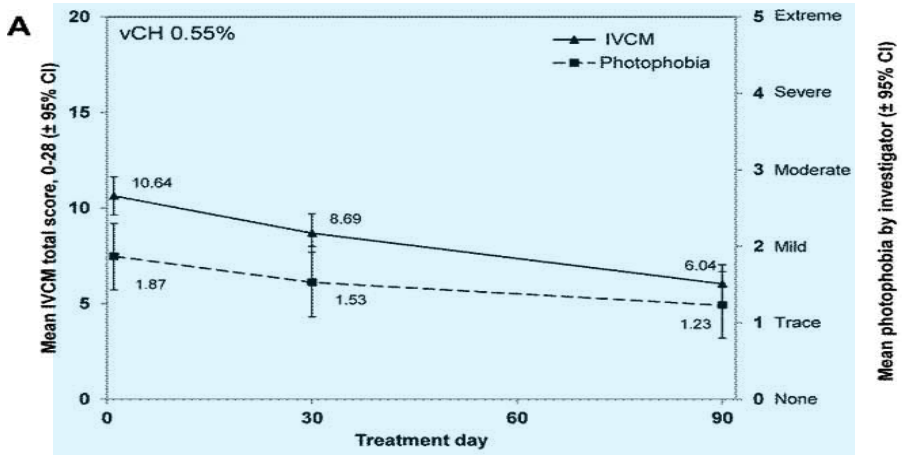
A New Viscous Cysteamine Eye Drops Treatment for Ophthalmic Cystinosis: An Open-Label Randomized Comparative Phase III Pivotal Study

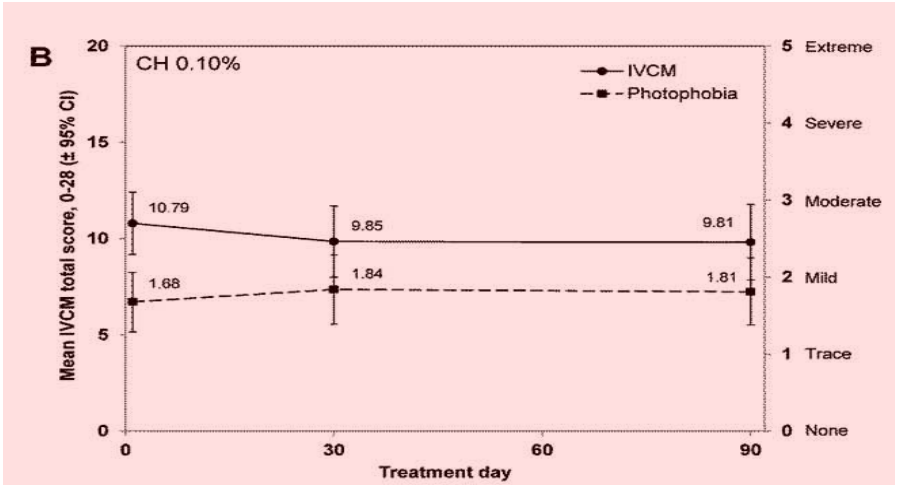
Hong Liang,[1] Antoine Labbé,[1,2] Jeannie Le Mouhaër,[3] Céline Plisson,[3] and Christophe Baudouin[1,2]

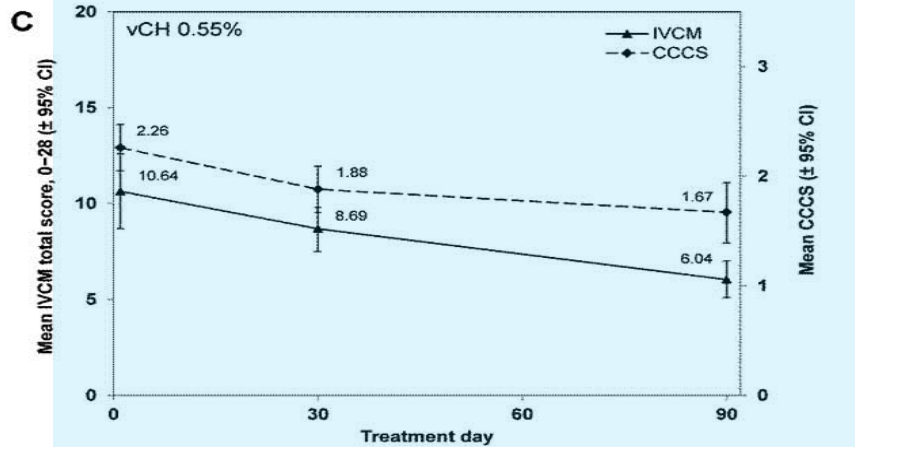

Clinical science

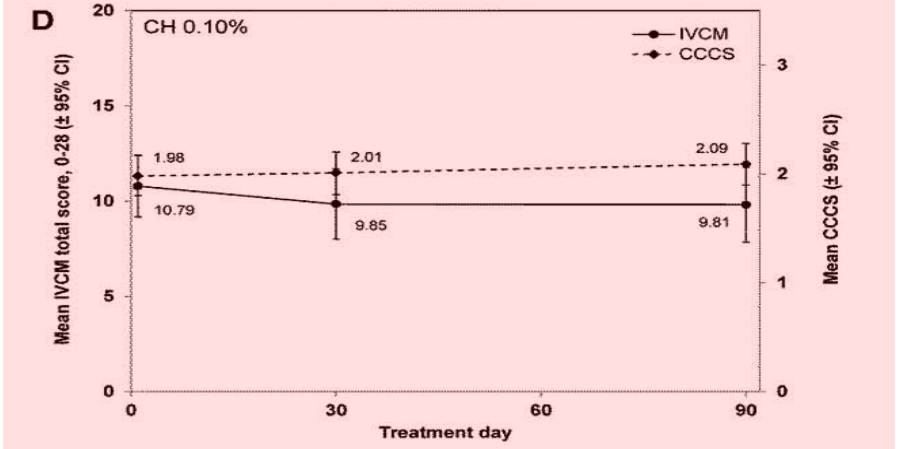
Long-term follow-up of cystinosis patients treated with 0.55% cysteamine hydrochloride

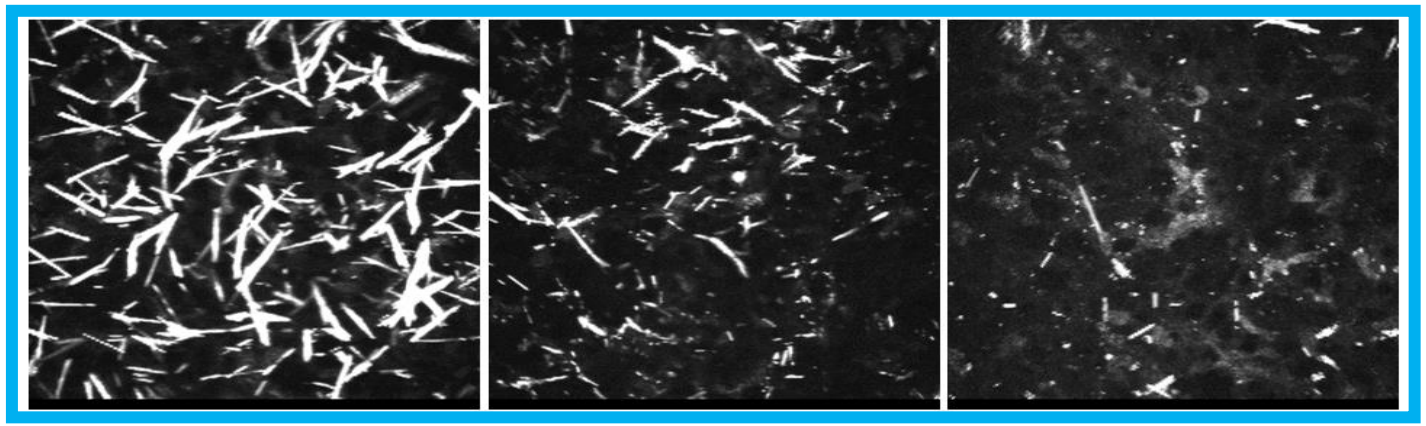
Hong Liang,[1] Antoine Labbé,[1,2,3] Christophe Baudouin,[1,2,3] Celine Plisson,[4] Vincenzo Giordano[4]











Liang H *et al.* *Invest Opthalmol Vis Sci* 2017;58:2275-83

Long-term effects of ocular treatments ATU
More real life

Clinical science

OPEN ACCESS

Long-term follow-up of cystinosis patients treated with 0.55% cysteamine hydrochloride

Hong Liang [1], Antoine Labbé,[1,2,3] Christophe Baudouin,[1,2,3] Celine Plisson,[4] Vincenzo Giordano[4]

2020 Jun 27;bjophthalmol-2020-316450.

⇒ATU cohort included **130 cystinosis patients** in France

⇒Treated by **0.55% Cysteamine in viscous solution**

⇒From 24/09/2013 to 16/06/2017

Visual Acuity

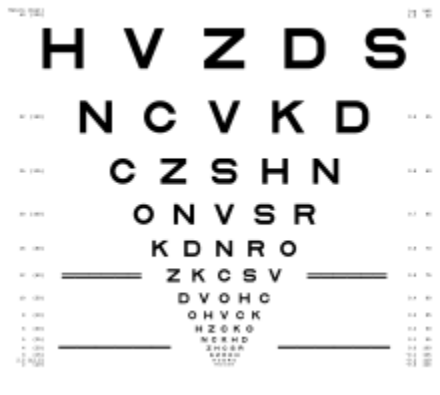
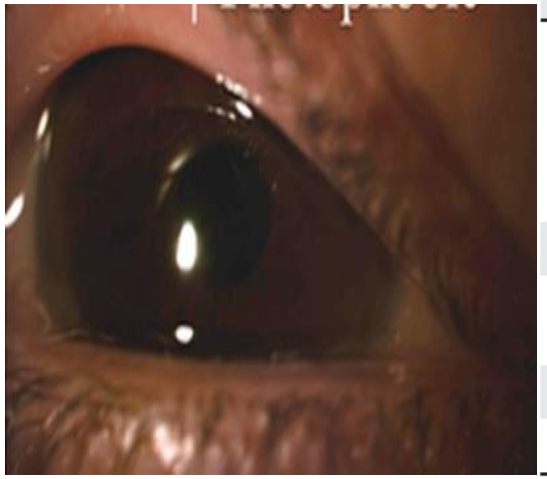


Table 3 Results of ophthalmic evaluations over the duration of treatment for patients with at least one follow-up visit (N=eyes)

	Duration of treatment								
	Start N=164	0–3 months N=30	3–9 months N=102	9–15 months N=64	15–21 months N=78	21–27 months N=58	27–33 months N=50	33–39 months N=34	39–45 months N=8
Visual acuity: Log scale									
N (missing)	148 (16)	26 (4)	94 (8)	64 (0)	78 (0)	58 (0)	50 (0)	34 (0)	8 (0)
Mean (± SD)	0.14 (±0.31)	0.01 (±0.19)	0.09 (±0.28)	0.11 (±0.34)	0.04 (±0.16)	0.05 (±0.19)	0.07 (±0.16)	0.06 (±0.14)	0.00 (±0.00)
Median (range)	0.00 (–0.15–2.00)	0.00 (–0.25–0.50)	0.00 (–0.25–1.00)	0.00 (–0.25–1.30)	0.00 (–0.20–0.70)	0.00 (–0.10–1.30)	0.00 (0.00–1.00)	0.00 (0.00–0.70)	0.00 (0.00–0.00)



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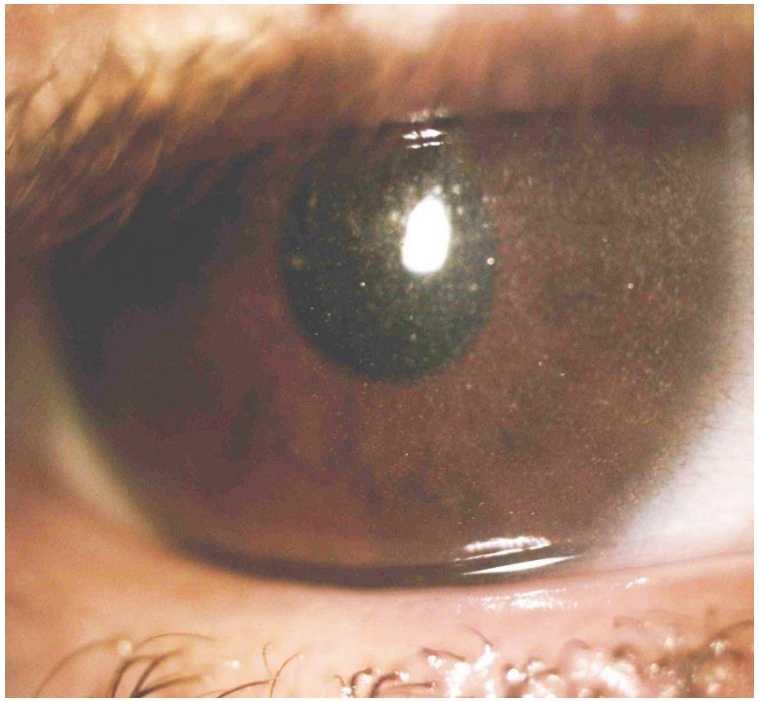
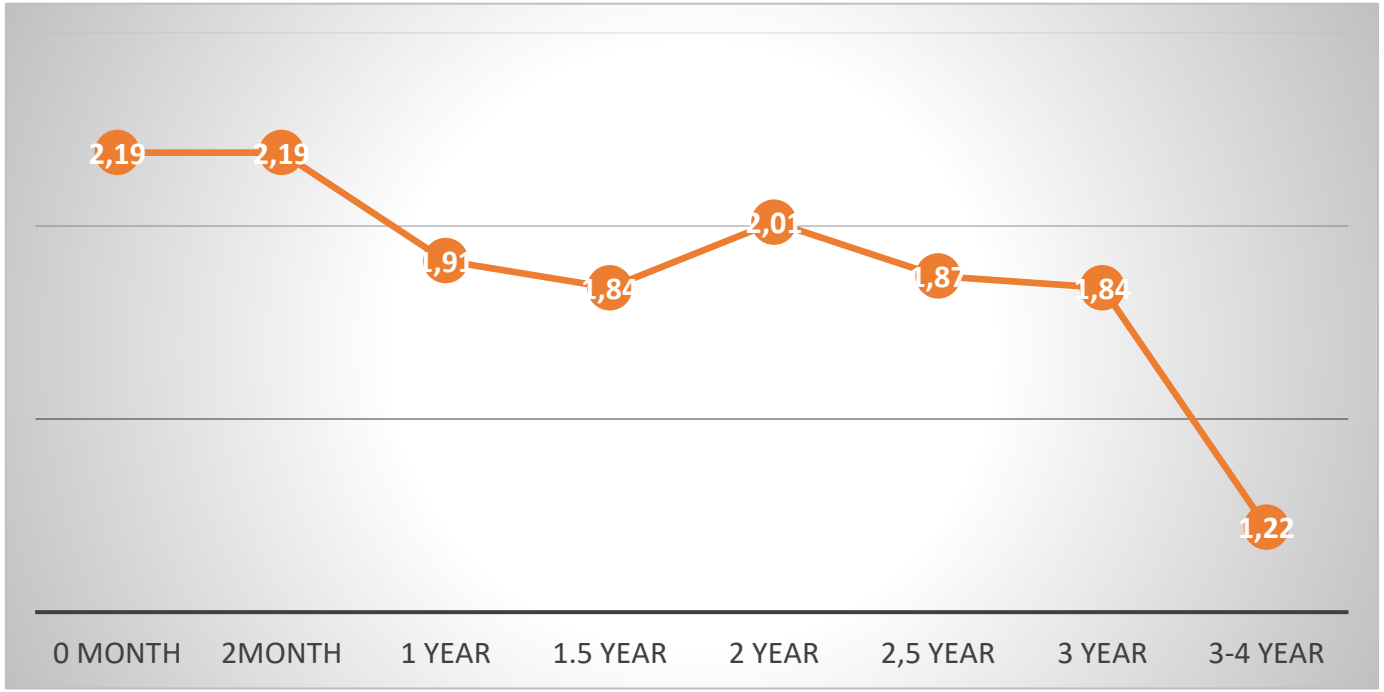
Photophobia									
N (missing)	160 (4)	28 (2)	96 (6)	61 (3)	74 (4)	51 (7)	48 (2)	34 (0)	8 (0)
Mean (SD)	2.19 (±1.34)	1.46 (±0.92)	1.77 (±1.22)	1.64 (±1.24)	1.70 (±1.33)	1.51 (±1.04)	2.17 (±1.33)	1.53 (±1.05)	1.75 (±0.89)
Median	2.00	1.00	2.00	2.00	2.00	1.00	2.00	1.00	1.50
Range	0–5	0–4	–0–5	0–4	0–5	0–5	0–5	0–3	1–3

Table 3 Results of ophthalmic evaluations over the duration of treatment for patients with at least one follow-up visit (N=eyes)

	Duration of treatment								
	Start N=164	0–3 months N=30	3–9 months N=102	9–15 months N=64	15–21 months N=78	21–27 months N=58	27–33 months N=50	33–39 months N=34	39–45 months N=8
Cystinosis Corneal Crystal Score (CCCS)									
N (missing)	120 (44)	29 (1)	88 (14)	55 (9)	70 (8)	51 (7)	48 (2)	34 (0)	8 (0)
Mean (SD)	2.19 (±0.64)	2.19 (±0.75)	1.99 (±0.77)	1.91 (±0.77)	1.84 (±0.89)	2.01 (±0.82)	1.87 (±0.76)	1.84 (±0.79)	1.22 (±0.67)
Median	2.00	2.25	2.00	2.00	2.00	2.00	2.00	2.00	1.13
Range	0.5–3.0	0.5–3.0	0.00–3.0	0.25–3.0	0.00–3.0	0.50–3.0	0.25–3.0	0.25–3.0	0.50–2.25





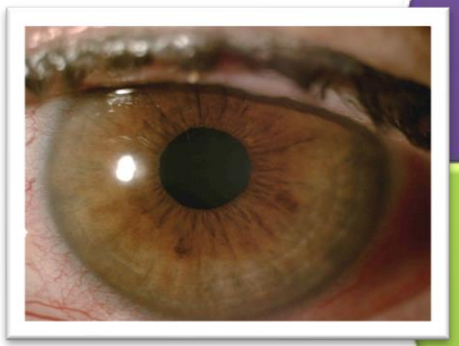
Side effects among 130 patients

Preferred term	Patients (%)	Corneal crystal	Inflammation	Cornea Nerves damages	Preservative (Benzalkonium)
Eye irritation (burning)	13 (10)		++	++	++
Eye pain (tingling, itchy)	7 (5.4)		+++	++	+
Blurry vision	4 (3.1)	+	++	+	
Ocular hyperaemia	3 (2.3)		++	++	+
Keratitis	1 (0.8)	+	+++	++	++
Ulcerative keratitis	1 (0.8)	+	+++	++	++
Eye deposit	2 (1.5)	+	++	++	
Increased lacrimation	1 (0.8)		++	++	
Itching of the eye	1 (0.8)		++	+++	+++
Dry eye	1 (0.8)		+++	++	+++
Glare	1 (0.8)		++	++	++
Ocular discomfort (cornea)	1 (0.8)		+++	+	++
Ocular discomfort	1 (0.8)	+	+++	+	++
Discomfort at instillation site	3 (2.3)	++	+++	++	+++

Clinical practice experiences

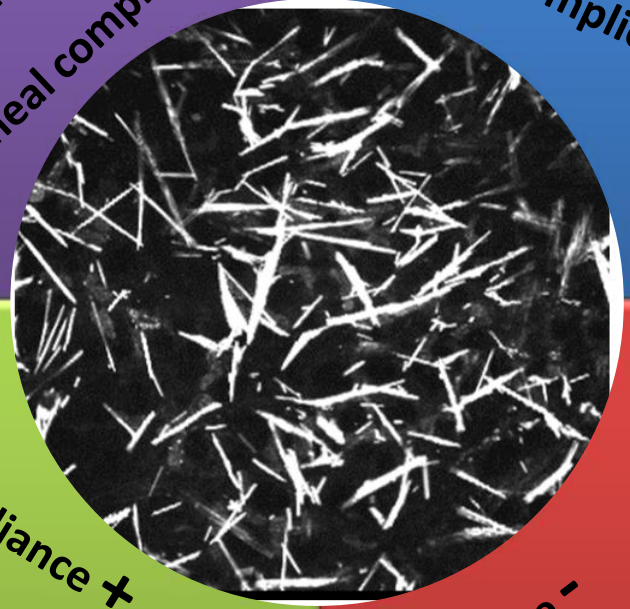
Close follow-up
Visit/6 month
Education

-Encouragement



Compliance -
Corneal complication -

Compliance +
Corneal complication +



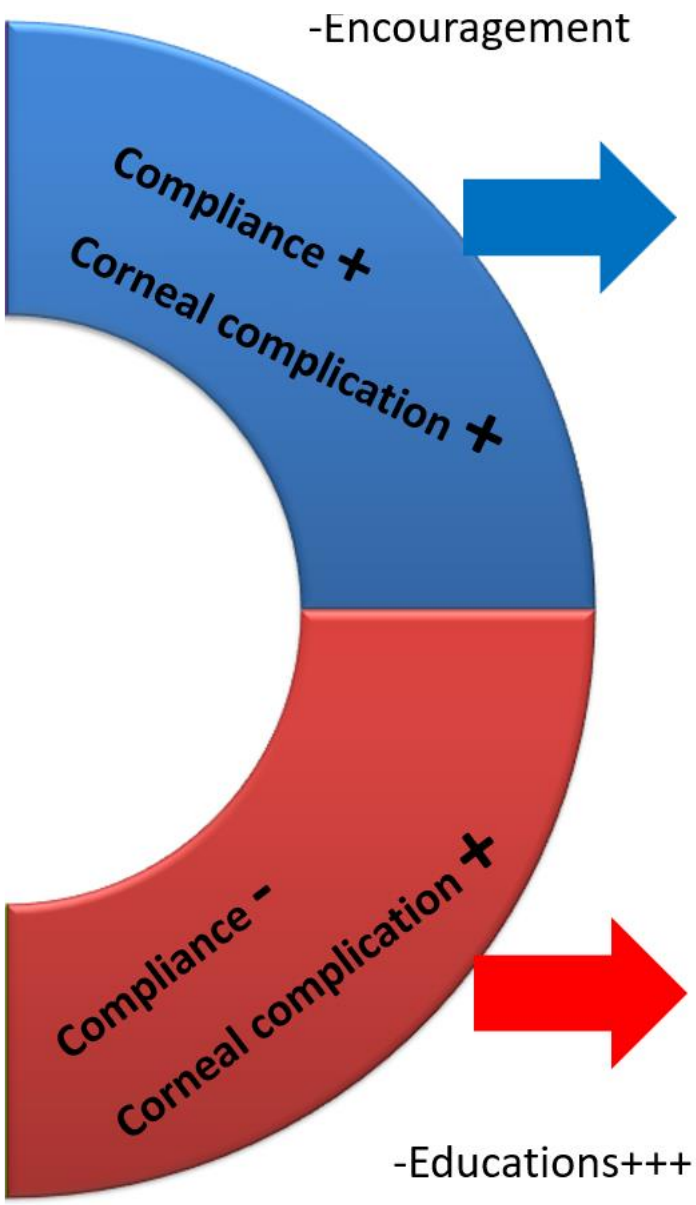
Compliance +
Corneal complication -

Compliance -
Corneal complication +

-Visit frequency++
-Complementary examinations (OCT, Visual Fields, etc)

Routine follow-up
Visit/Year

-Educations+++

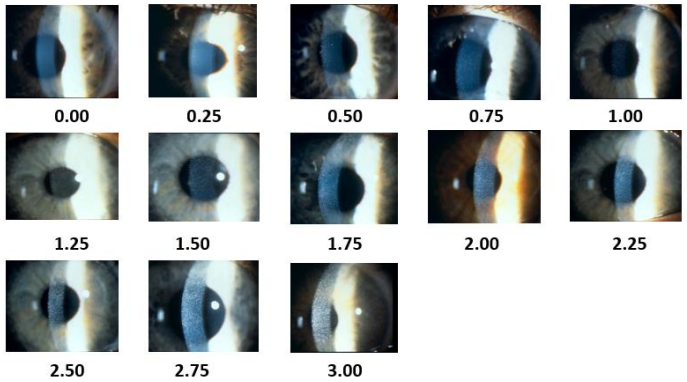


Difficulties and Challenges

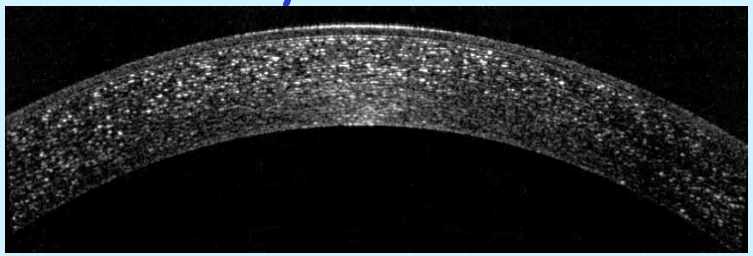
- Prescription of eyeglasses, Astigmatisme++
- Contact lens?
- Difficult to support eyedrops (cystadrops) + other eyedrops, too many eyedrops
- Severe cornea complications =>psychological problems and depression

Multimodal imaging system

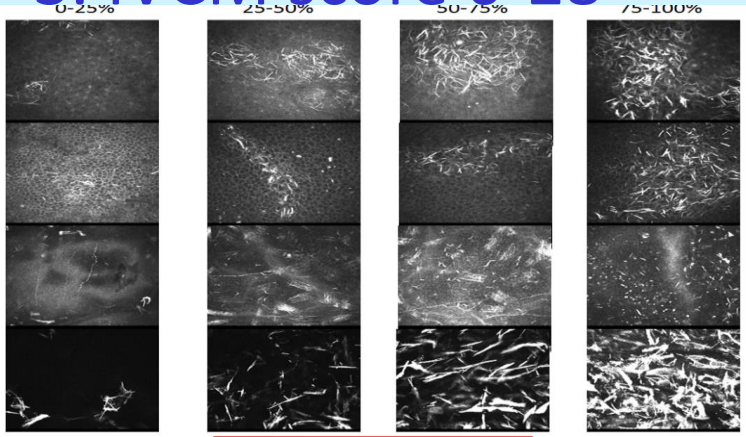
1. Gahl Score 0-3



2. OCT cystinosis 0-100%

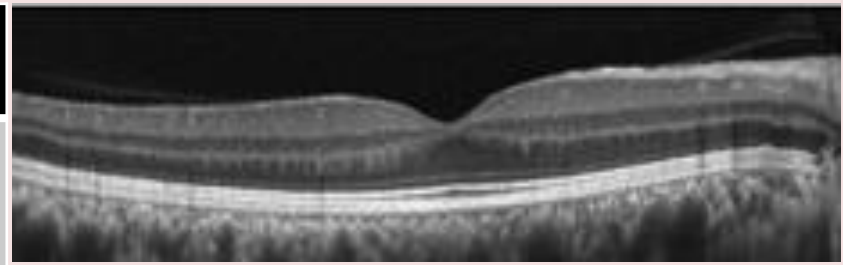


3. IVCM score 0-28

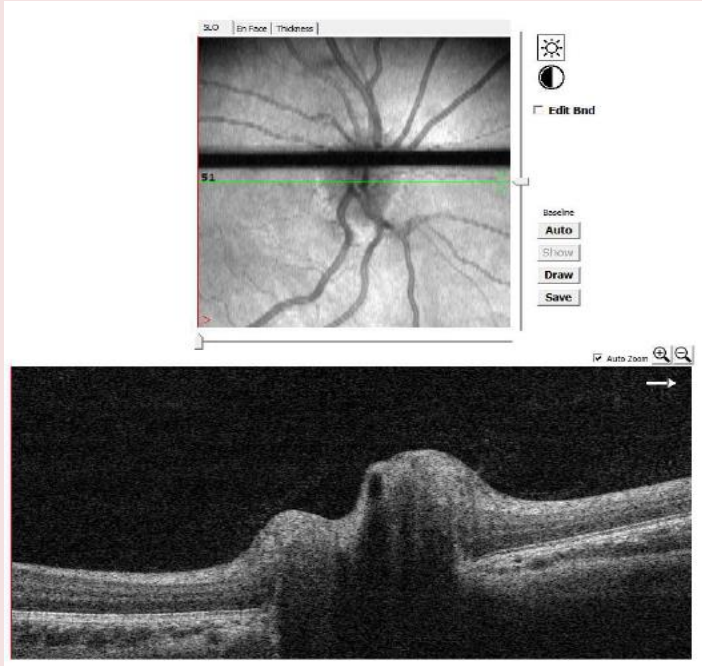


Ant Segment	Post Segment
1.Gahl Score	4.Macula
2.OCT (+/-Angio-OCT)	5.Optic nerve
3.IVCM	

4. OCT Macula



5. OCT optic nerve



Multimodal imaging system

1. Gahl Score 0-3

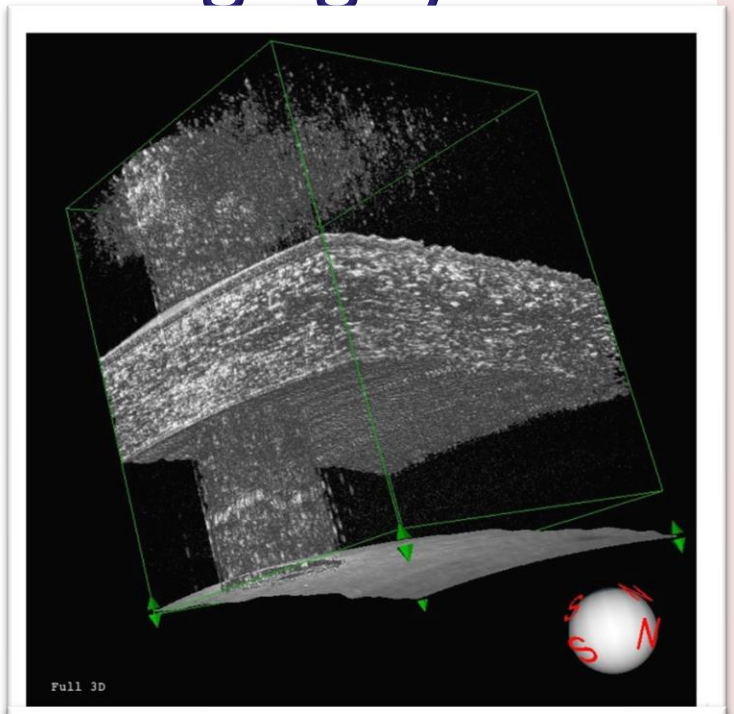
1.75 without cornea complications

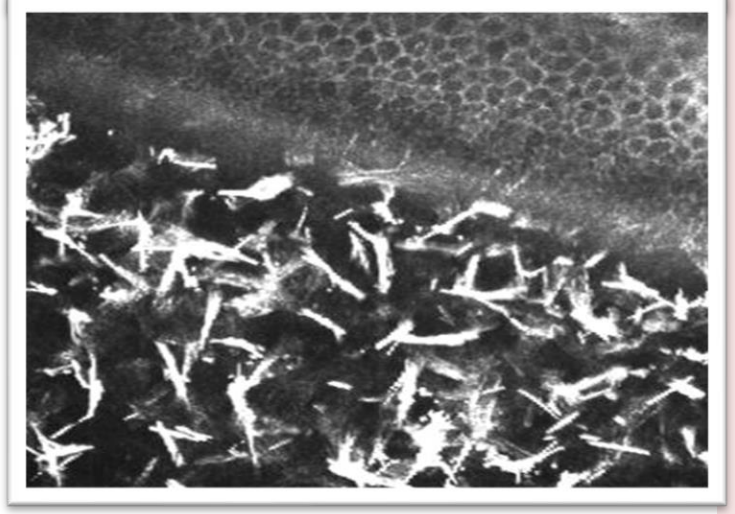
2. OCT cystinosis 0-100%

38%

3. IVCM score 0-28

8/28





4. OCT Macula

No Edema

5. OCT optic nerve

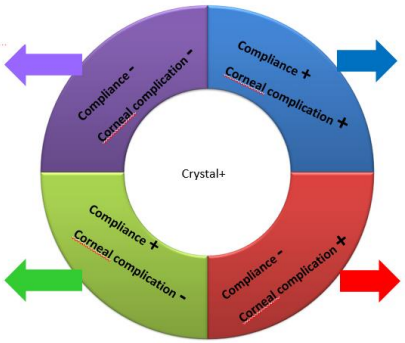
No Edema

No drusen

Conclusions

Eye complications in cystinosis

- Physiopathology: vicious cycle
- Cornea complications: don't forget inflammation and nerve damage
- Take in charge of all ocular structures including glaucoma and retina complications



Status of eye treatment

- Cysteamine + anti-inflamamtory/Cyclosporine/anti-odema treatments
- Real life: the balances of efficacity and tolerance
- Despite of the clinical challenges, need new therapeutic strategies=>

Already existed

-Cysteamine containing contact lens

=> Bad compliance patients

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Volume 85, Issue 3, Part A, November 2013, Pages 531-540

Research paper

Feasibility of corneal drug delivery of cysteamine using vitamin E modified silicone hydrogel contact lenses

Kuan-Hui Hsu [a] ✉, Richard C. Fentzke [b] ✉, Anuj Chauhan [a] ✉

-Genetic therpay

=> No eye drops

cells

MDPI

Review

Hematopoietic Stem Cell Gene Therapy for Cystinosis: From Bench-to-Bedside

Stephanie Cherqui

Thank you!