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LA RÉFÉRENCE TÊTE ET COU

CYSTOID MACULAR EDEMA AND CYSTOID MACULOPATHIES

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DIU Imagerie et Pathologie Rétiniennes Sept 2023

Disclosure

None

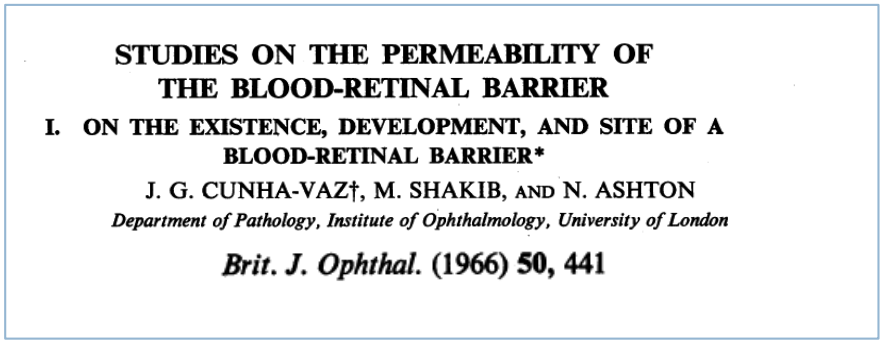
Edema: definition

- Edema (American English) or Œdema (British English) (/ɪˈdimə/; from the Greek οἴδημα—oídēma, "swelling"),
  - is an abnormal accumulation of fluid in the interstitium, which are locations beneath the skin or in one or more cavities of the body. It is clinically shown as swelling. …

  Wikipedia Engl
- In the retina,
  - The intercellular space is virtual,
  - It opens when the blood retinal barrier is broken, and edema occurs
- Macular edema has been defined for a long time, by fluorescein leakage and pooling within the macular retina.
- OCT has refocused this definition on macular thickening, more or less associated with cystic cavities
  - and Fluorescein Angiography is often no longer performed for the diagnosis.

Historical Perspective

- The history of Cystoid macular edema is closely related to BRB studies and FA use in the late 1960s



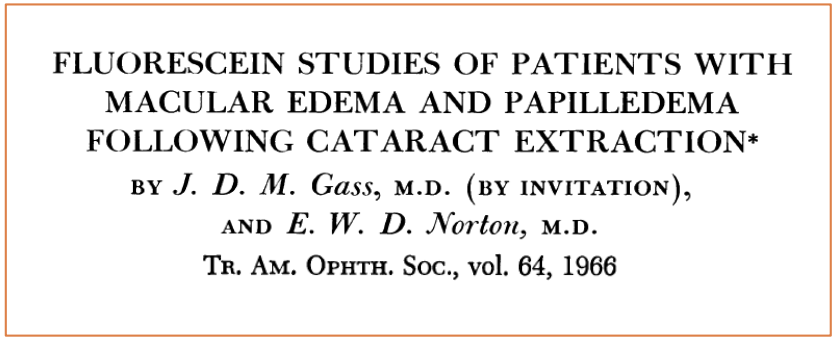
STUDIES ON THE PERMEABILITY OF THE BLOOD-RETINAL BARRIER

I. ON THE EXISTENCE, DEVELOPMENT, AND SITE OF A BLOOD-RETINAL BARRIER*

J. G. CUNHA-VAZ†, M. SHAKIB, AND N. ASHTON

Department of Pathology, Institute of Ophthalmology, University of London

Brit. J. Ophthal. (1966) **50**, 441



FLUORESCEIN STUDIES OF PATIENTS WITH MACULAR EDEMA AND PAPILLEDEMA FOLLOWING CATARACT EXTRACTION*

BY *J. D. M. Gass*, M.D. (BY INVITATION), AND *E. W. D. Norton*, M.D.

TR. AM. OPHTH. SOC., vol. 64, 1966

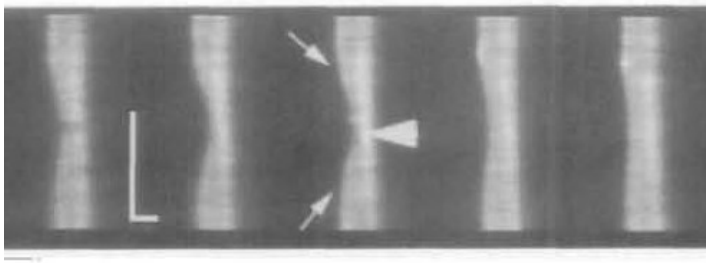
Historical Perspective

- For years, CME has been synonymous of dye pooling in cystoid spaces on late phase angiograms
- At the end of the 80s emerged the first attempts to correlate macular thickness and VA , before the advent of OCT.

Macular Thickening and Visual Acuity

ROBERT B. NUSSENBLATT, MD,* STEVEN C. KAUFMAN, MD,†
ALAN G. PALESTINE, MD,* MATTHEW D. DAVIS, MD,‡
FREDERICK L. FERRIS III, MD†

Ophthalmology 1987,94:1134



Retinal Thickness Analysis for Quantitative Assessment of Diabetic Macular Edema

Mahnaz Shahidi, PhD; Yuichiro Ogura, MD; Norman P. Blair, MD; Mark M. Rusin, MS; Ran Zeimer, PhD

Arch Ophthalmol 1991, 109,1115

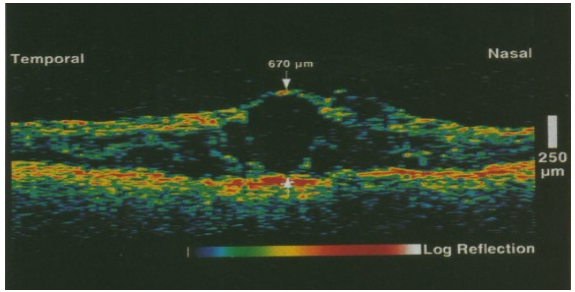
Historical Perspective

- Eventually the advent of OCT in 1995 made possible to routinely measure macular thickness.
- Quantitative assessment of macular edema was the object of the first publication on the use of OCT in a clinical setting.

Quantitative Assessment of Macular Edema With Optical Coherence Tomography

Michael R. Hee, MS; Carmen A. Puliafito, MD; Carlton Wong, MS; Jay S. Duker, MD; Elias Reichel, MD; Bryan Rutledge, MD; Joel S. Schuman, MD; Eric A. Swanson, MS; James G. Fujimoto, PhD

(Arch Ophthalmol. 1995;113:1019-1029)



VA /Macular thickness

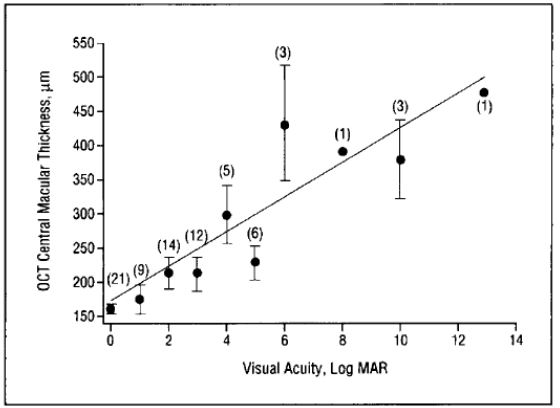
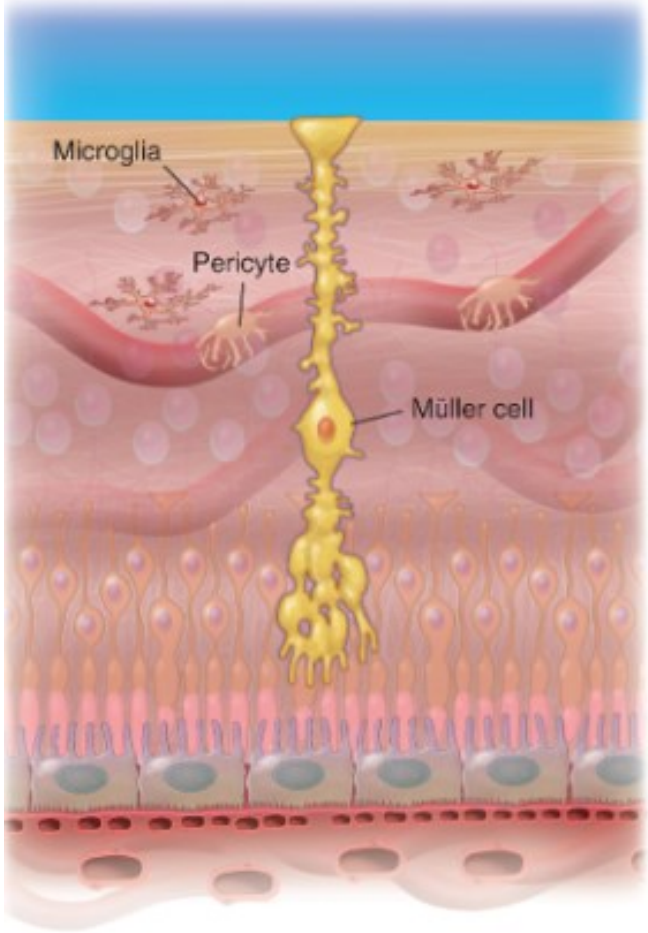
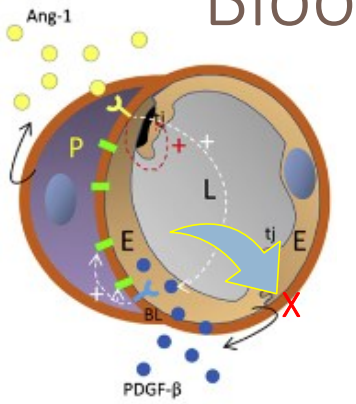


Figure 8. *Central macular thickness vs visual acuity in patients with diabetes (five eyes) and diabetic retinopathy (70 eyes). Data are plotted as*

Blood Retinal Barrier

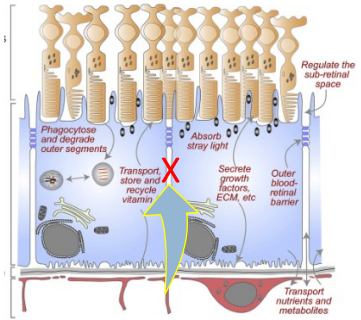


Inner Blood-Retinal Barrier



Pericytes and endothelial cell tight-junctions prevent the free diffusion of fluid from blood to the retinal tissue, under the control of various molecular signaling

Outer Blood-Retinal Barrier

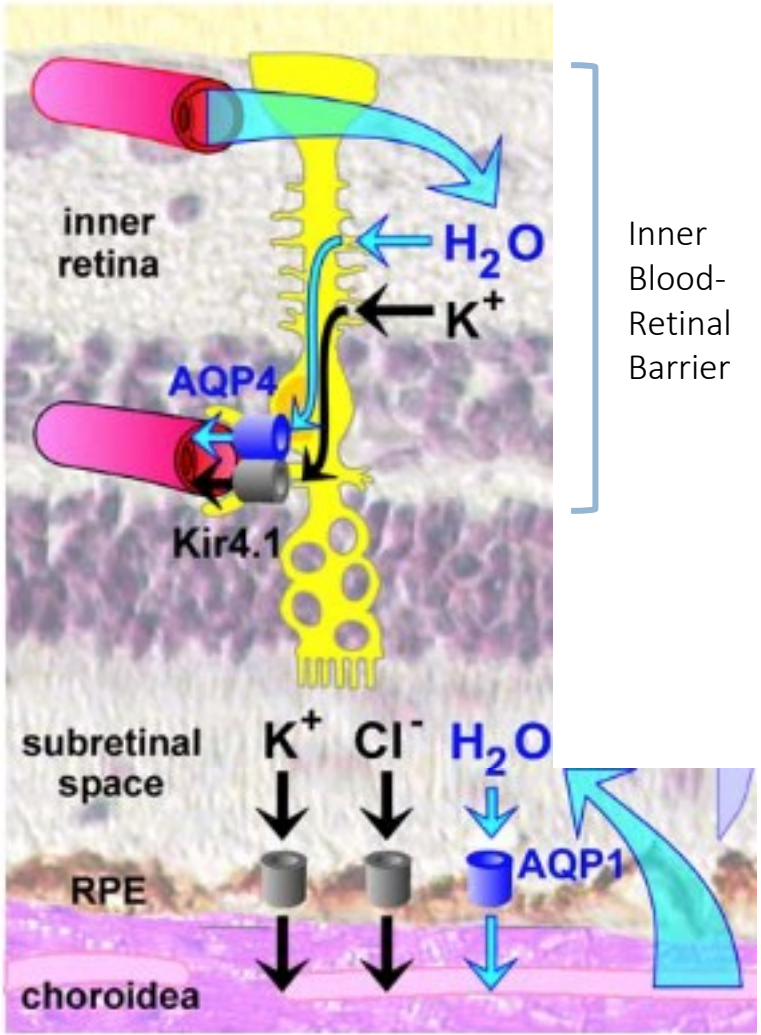


Tight-junctions between RPE cells also prevent the passage of fluid from the choriocapillaris to the outer retina

1. Klaassen I, et al .. Prog Retin Eye Res. 2013;34:19-48.

2. Lakkaraju A et al . Prog Retin Eye Res. 2020;78:100846.

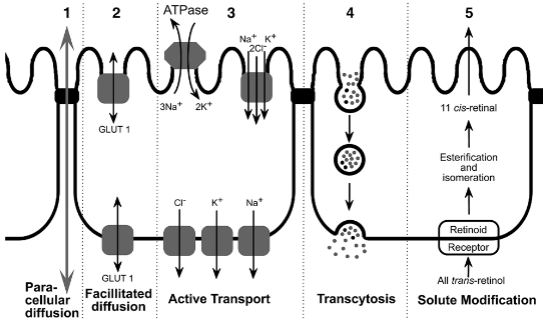
Blood Retinal Barrier



Inner Blood-Retinal Barrier

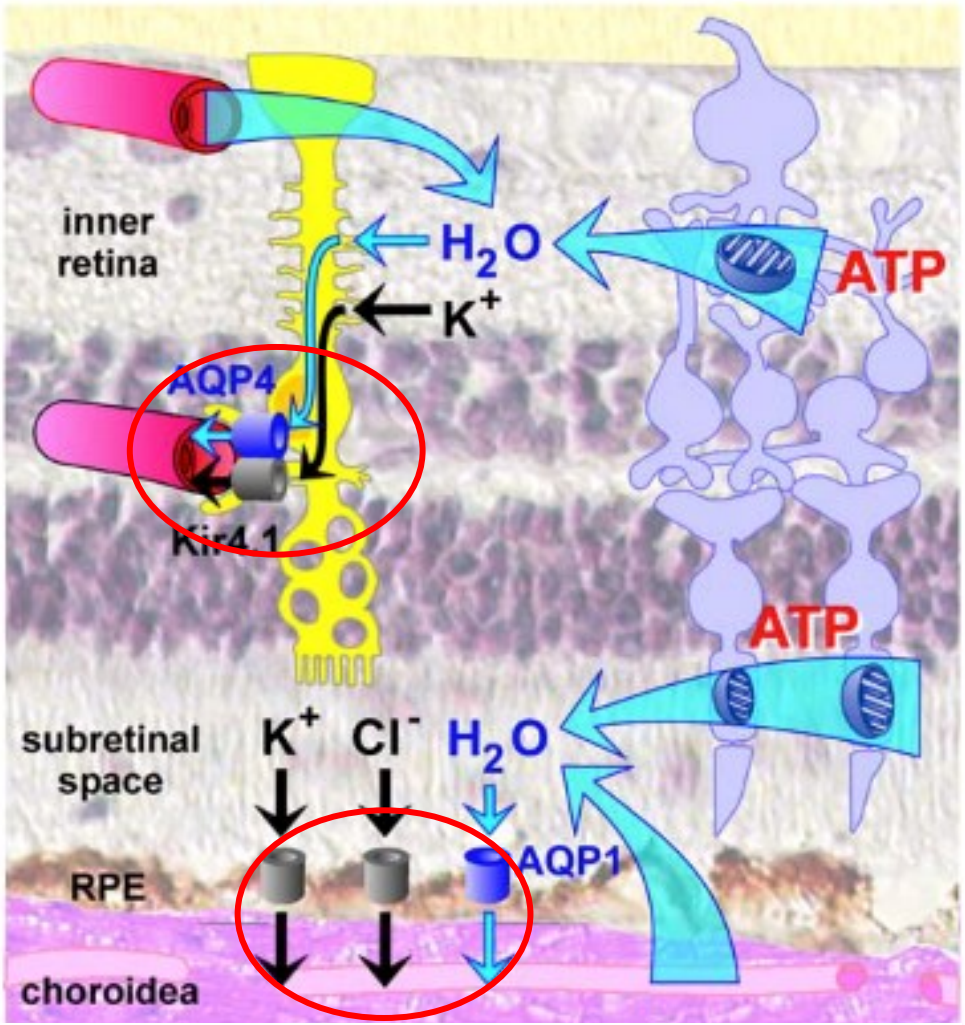
Outer Blood-Retinal Barrier

- Tight junctions form a dynamic opening and closing system between the capillary lumen and the retinal cells.
- In the normal BRB, the transcellular pathway is the preferred route for active transport of macromolecules whereas water and ions are preferentially transported via the via the paracellular pathway .



Rizzolo LJ, et al. Prog Retin Eye Res. 2011;30(5):296-323.

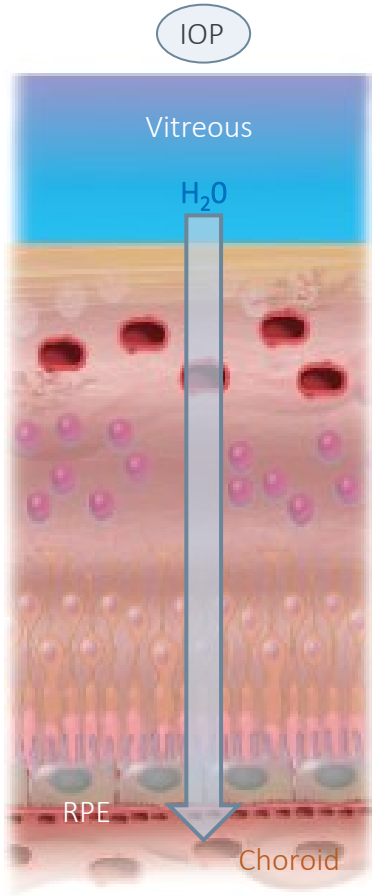
Reichenbach A, et al . Graefe's Arch Clin Exp Ophthalmol 2007;245(5):627-636.

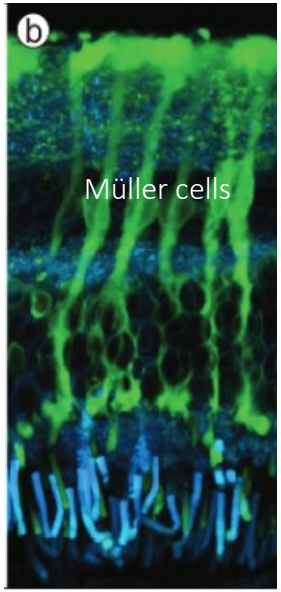


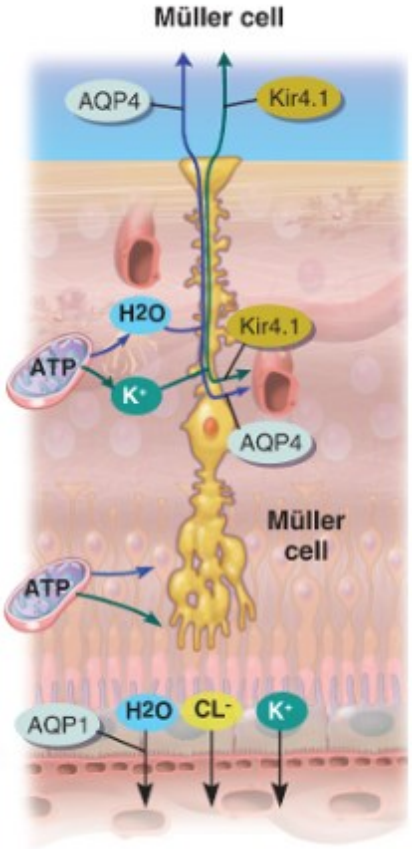
Blood Retinal Barrier

- Retinal water homeostasis is not only maintained by the BRB
- Active mechanisms continuously dehydrate the retina
- In addition to H_2O transferred from the blood, endogenous H2O is produced by neuronal and photoreceptor metabolism
- Müller cells and the RPE, contribute to transretinal fluid transfers
  - to deep capillary plexus
  - and to choriocapillaris

Reichenbach A, et al . Graefe's Arch Clin Exp Ophthalmol 2007;245(5):627-636.



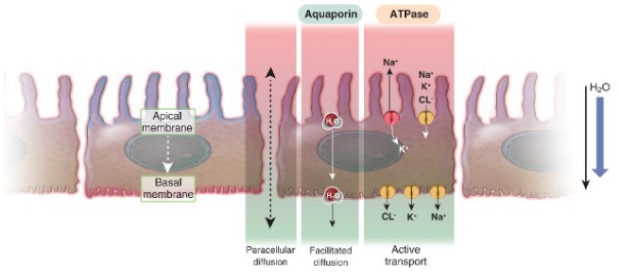




Fluid homeostasis

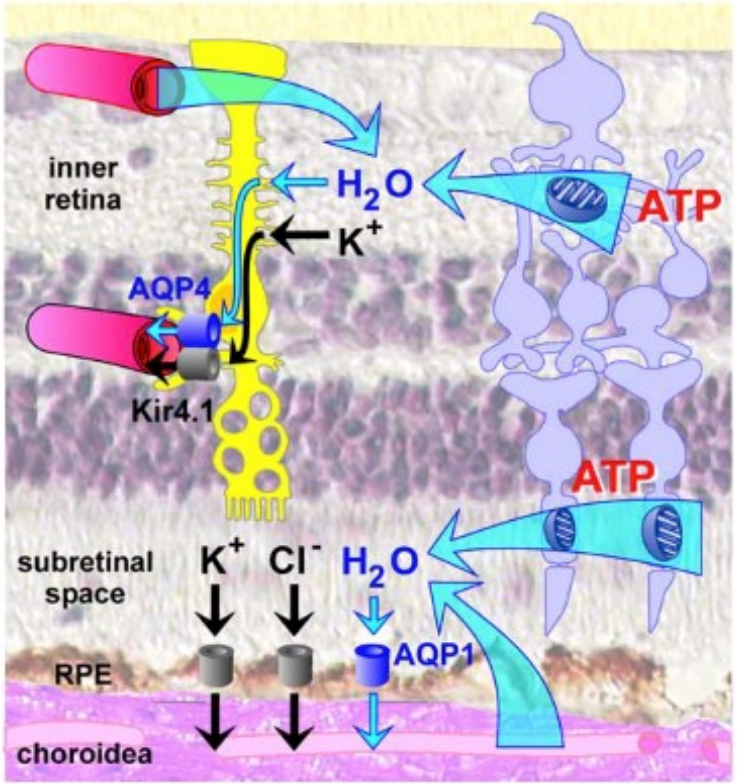
- Water coming from the vitreous crosses the retina permanently
- and is drained into the choroid
  - transported by Müller cells
  - by the active pumping of the RPE
  - and the osmotic pressure of the choroid
  - and the IOP

(Cunha-Vaz, 1984, Marmor 1999)



Joussen AM et al in Ryan's Retina 6th Ed 2018, Chapter 30

Role of Müller cells in macular edema



- Müller cell dysfunction as a promoter of macular edema in retinal vascular disease has been suspected on a histological basis.

"CME lacking the characteristic FA findings has been reported in nicotinic acid intocication…X-linked retinoschisis.. and RP.."

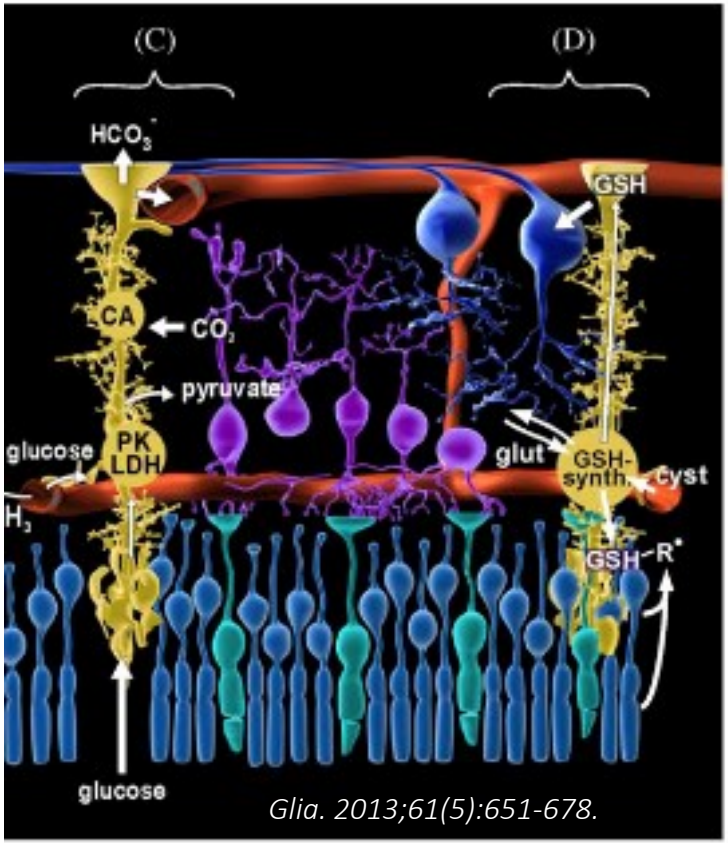
MACULAR EDEMA AND CYSTOID MACULAR EDEMA

BEN S. FINE, M.D.
Washington, D.C.
AND
ALEXANDER J. BRUCKER, M.D.
Philadelphia, Pennsylvania

Fine BS, Brucker AJ. Macular edema and cystoid macular edema. Am J Ophthalmol. 1981;92(4):466-481.

"The[se] observations indicated that the edematous process apparently begins with intracytoplasmic swelling of Müller cells, itself probably secondary to the vascular abnormalities"

Role of Müller cells in macular edema



Glia. 2013;61(5):651-678.

Pathomechanisms of Cystoid Macular Edema

Andreas Bringmann[a] Andreas Reichenbach[b] Peter Wiedemann[a]

[a]Department of Ophthalmology, Eye Clinic, and [b]Paul Flechsig Institute of Brain Research, University of Leipzig, Leipzig, Germany

Ophthalmic Research. 2004;36(5):241-249.

Müller cells in the healthy and diseased retina

Andreas Bringmann[a], Thomas Pannicke[b], Jens Grosche[b], Mike Francke[b], Peter Wiedemann[a], Serguei N. Skatchkov[c], Neville N. Osborne[d,*], Andreas Reichenbach[b]

Progress in Retinal and Eye Research. 2006;25(4):397-424.

New Functions of Müller Cells

Andreas Reichenbach[1] and Andreas Bringmann[2]

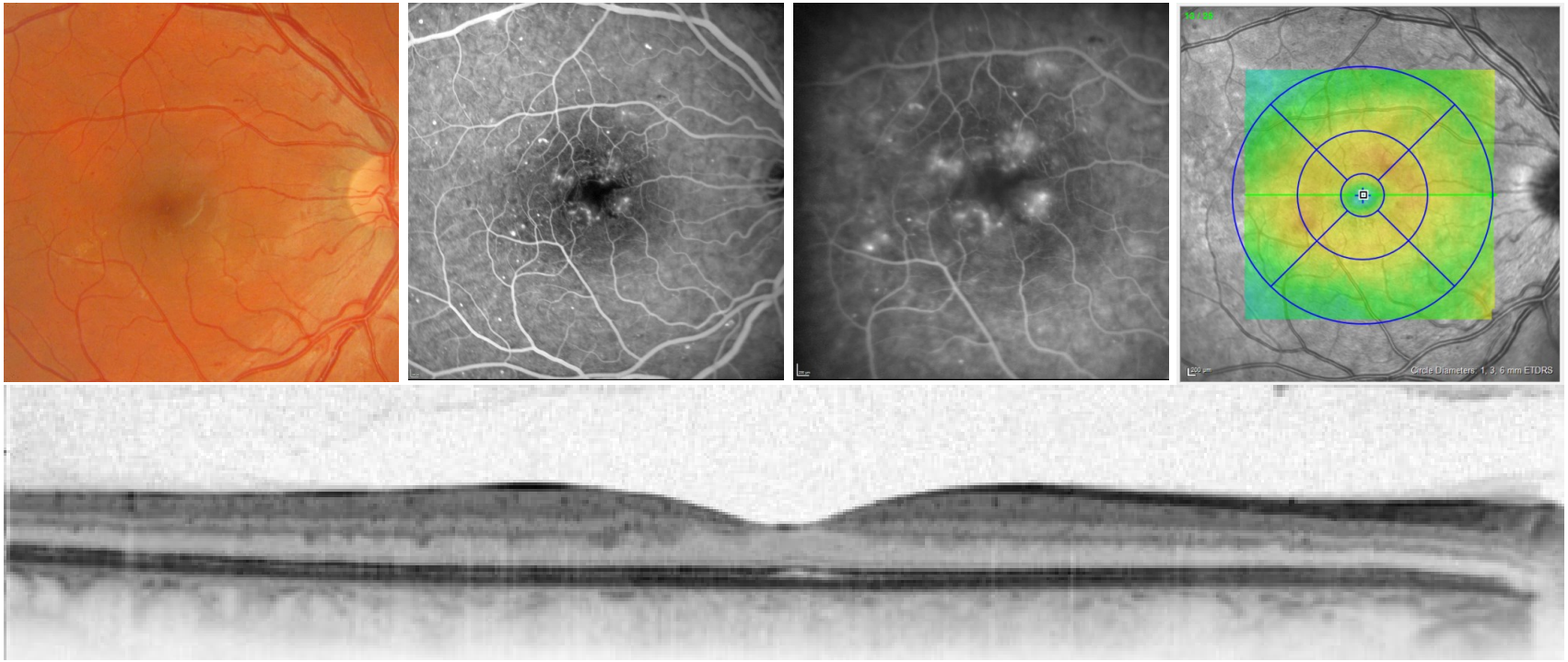
Glia. 2013;61(5):651-678.

OCT and Cystoid Macular Edema

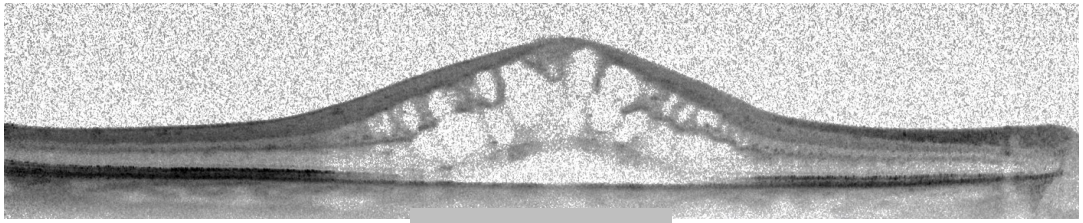
- OCT has changed our understanding of cystoid macular changes in many ways:
  - Leakage is not always associated with macular thickening
  - Cystoid cavities are not always associated with leakage
  - Cystoid cavities are associated with variable retinal tissue loss
  - Cystoid changes are not always associated with macular thickening

Leakage without edema

- It is well known that leakage may occur without resulting in CME



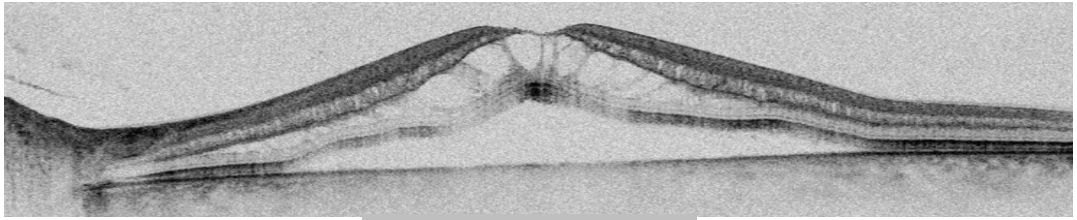
Leakage/no leakage and Cystoid Edema



LEAKAGE

Pseudophakic ME

Diabetic ME

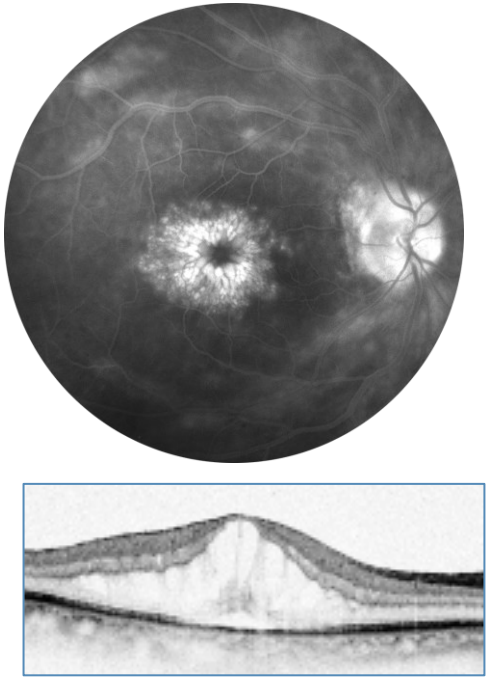


NO LEAKAGE

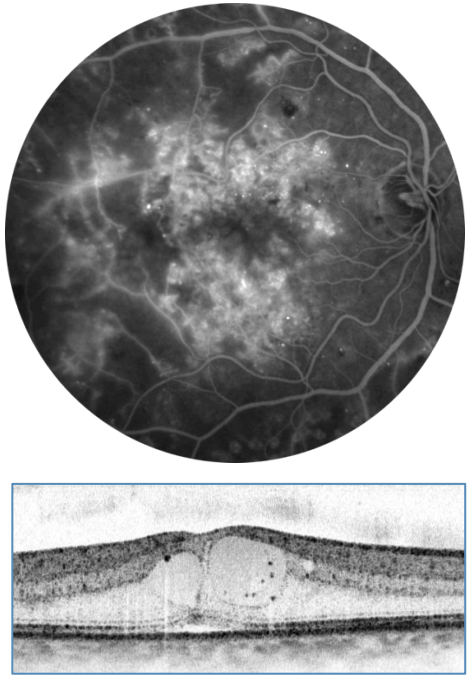
Acute Exudative Polymorphous Vitelliform maculopathy

CME with leakage

- Pseudophakic macular edema

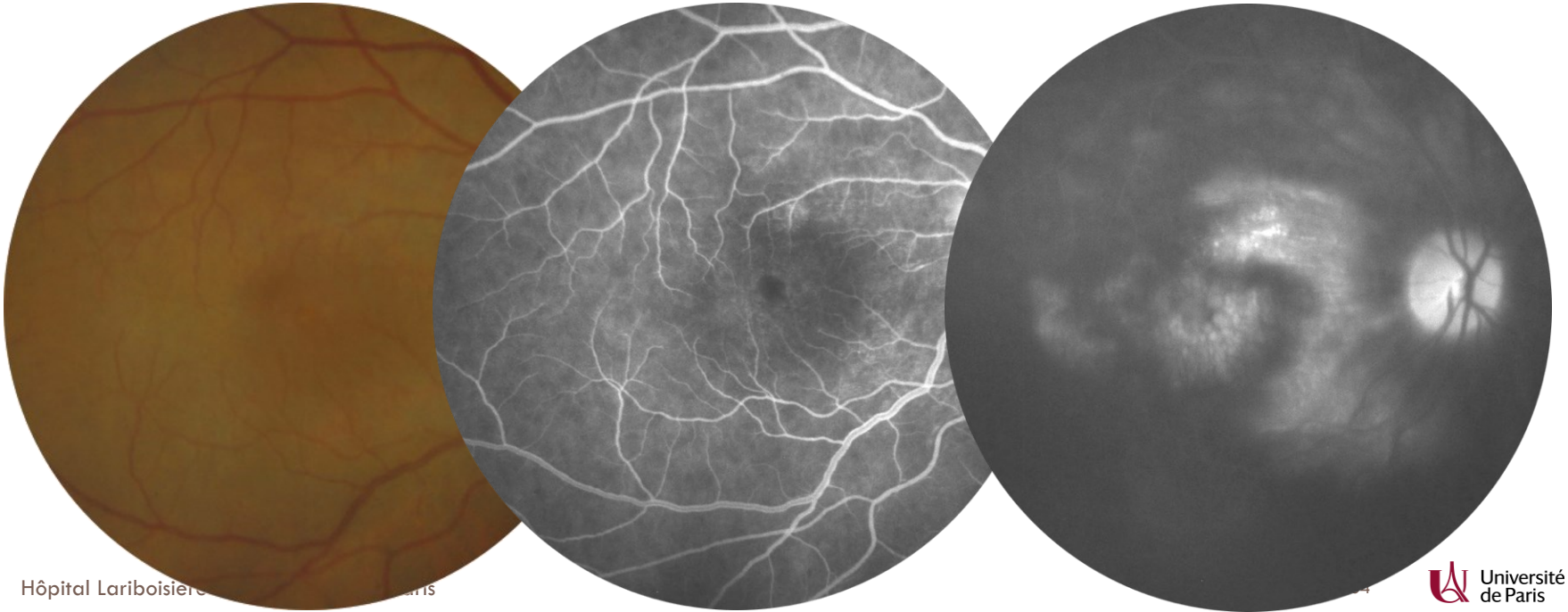


- Diabetic macular edema



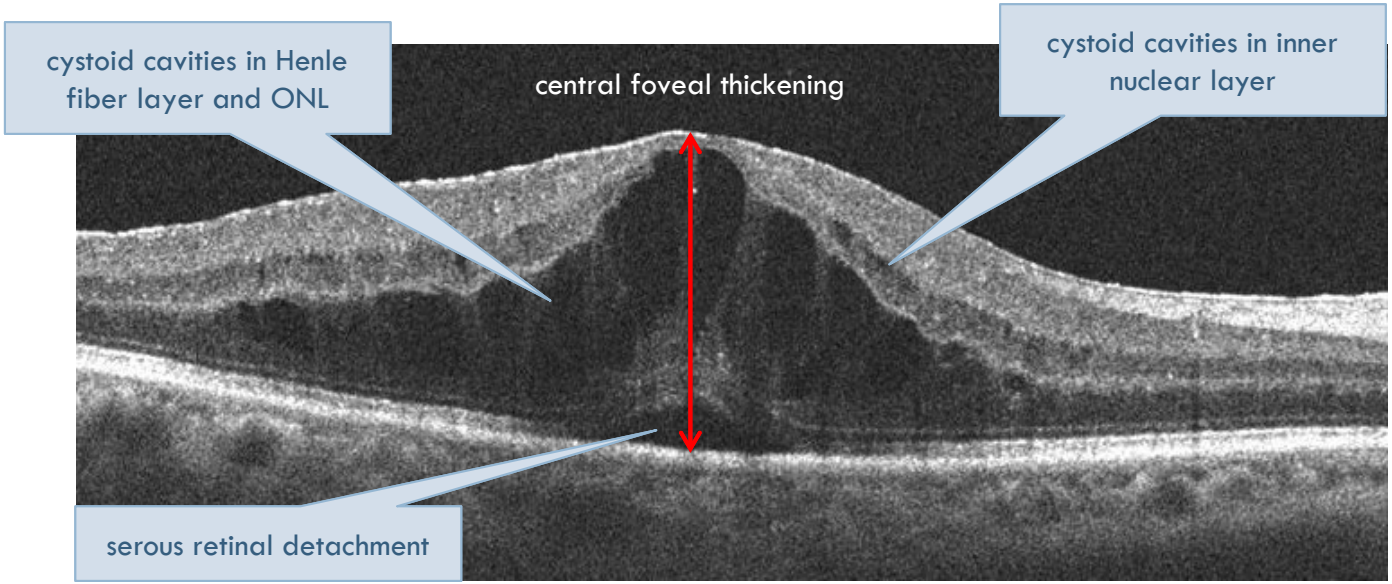
CME and leakage Pseudophakic ME

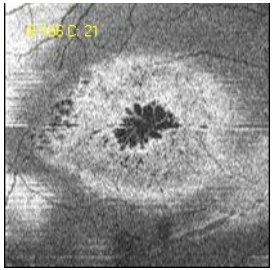
- Pseudophakic CME is typical of cystoid changes due to an acute inner BRB breakdown

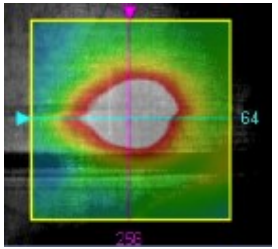


CME and leakage Pseudophakic ME

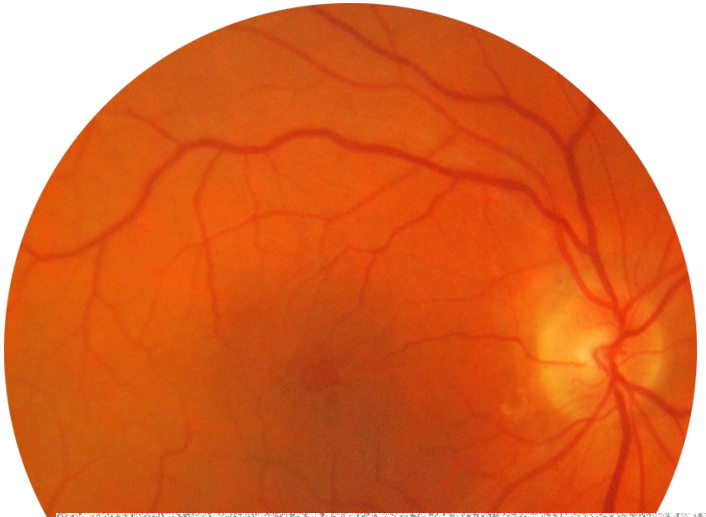
- OCT reveals the cystoid changes and macular thickening

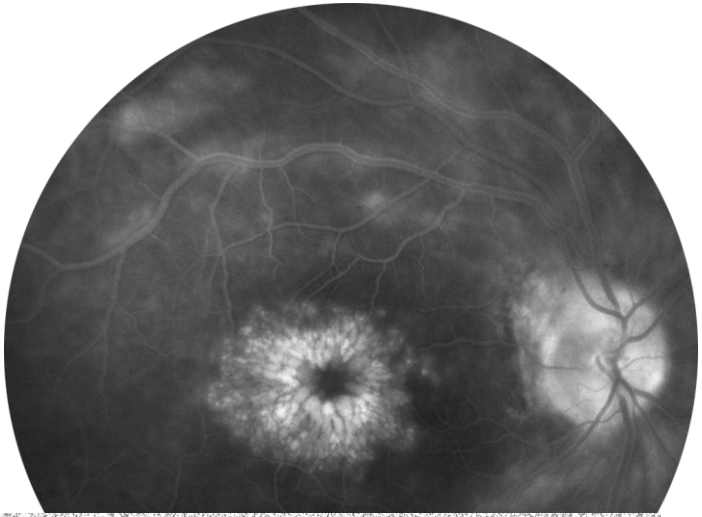


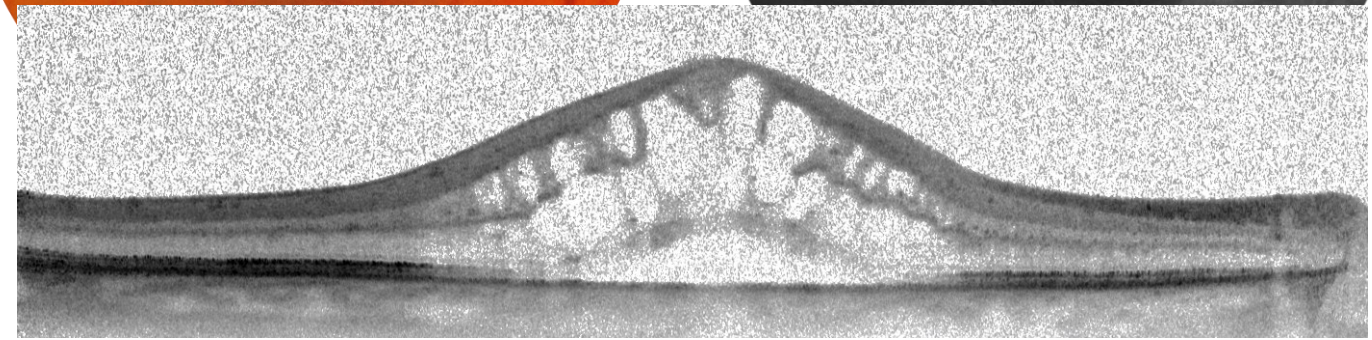




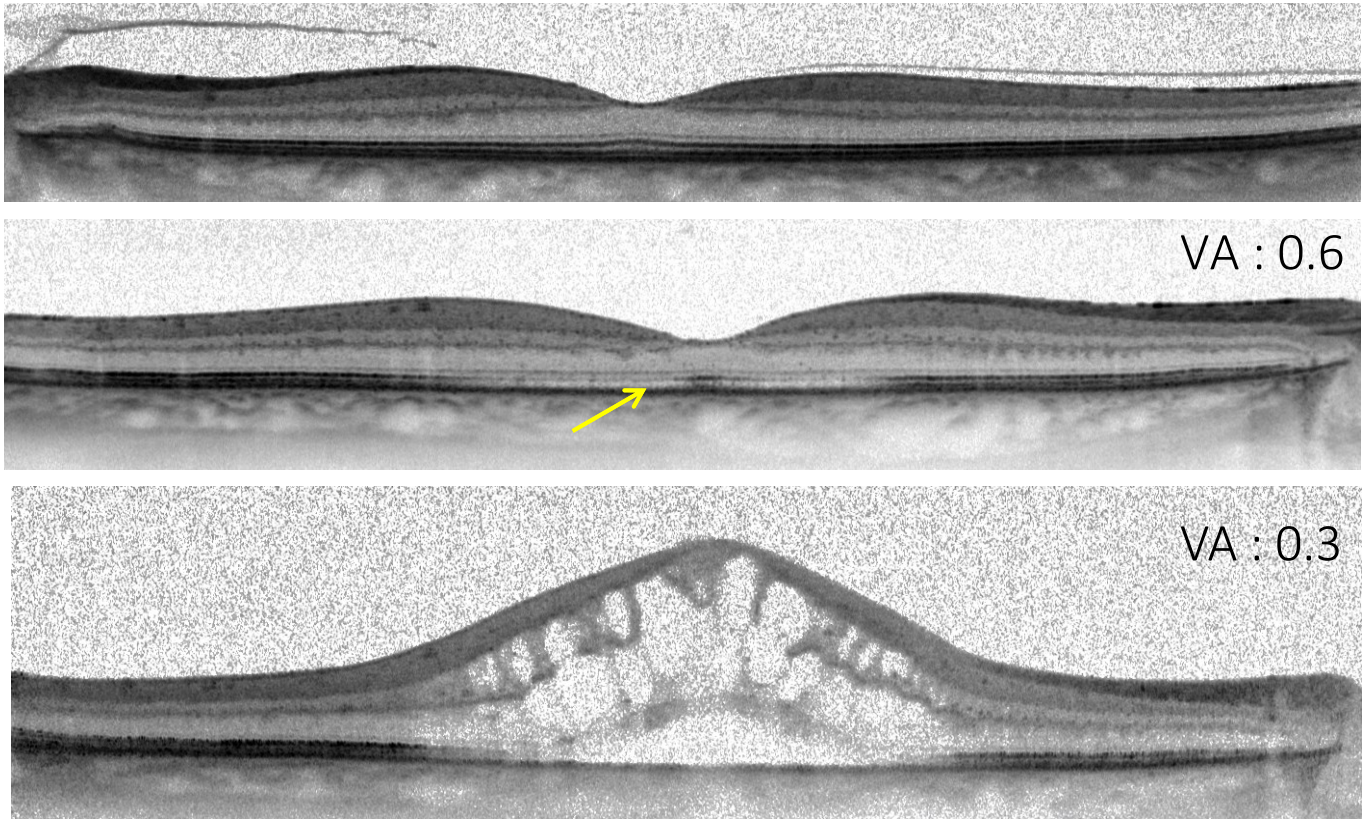
CME and leakage Pseudophakic ME . Evolution







CME and leakage Pseudophakic ME . Evolution



normal macula

after 2 months treatment

Pseudophakic CME and capillary density on OCTA

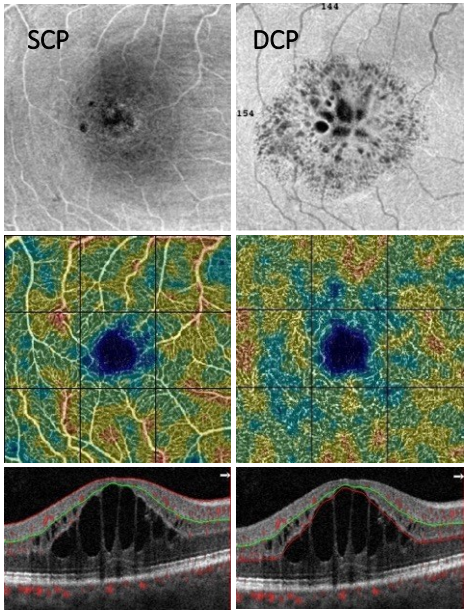
- Both SCP and DCP density remain normal during and after the edematous episode

ACUTE PSEUDOPHAKIC CYSTOID MACULAR EDEMA IMAGED BY OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

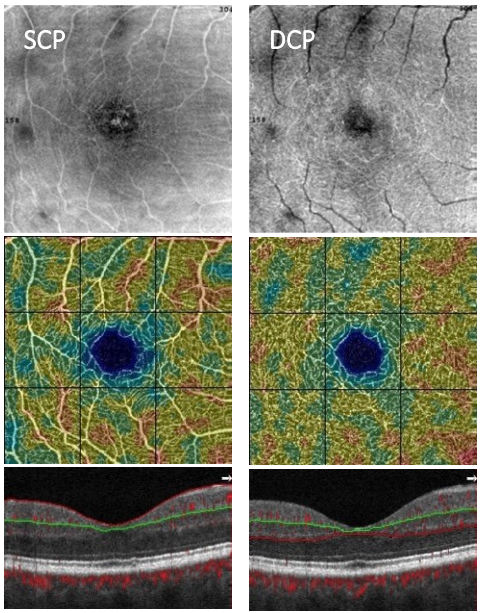
MARDOCHE CHETRIT, MD, SOPHIE BONNIN, MD, VALÉRIE MANÉ, MD, ALI ERGINAY, MD, RAMIN TADAYONI, MD, PHD, ALAIN GAUDRIC, MD, AUDE COUTURIER, MD

RETINA. 2018;38(10):2073-2080.

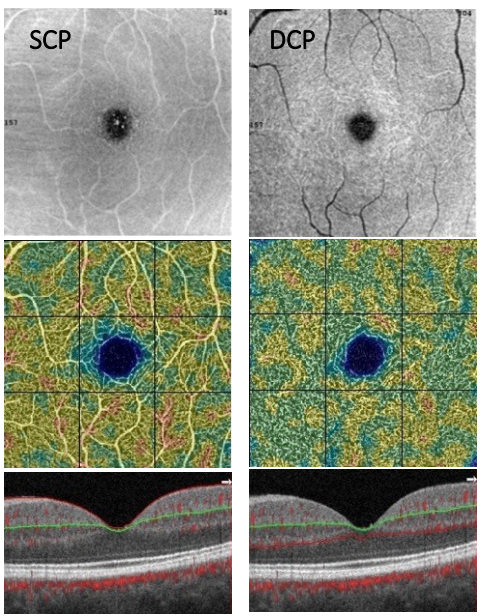
ACUTE PHASE



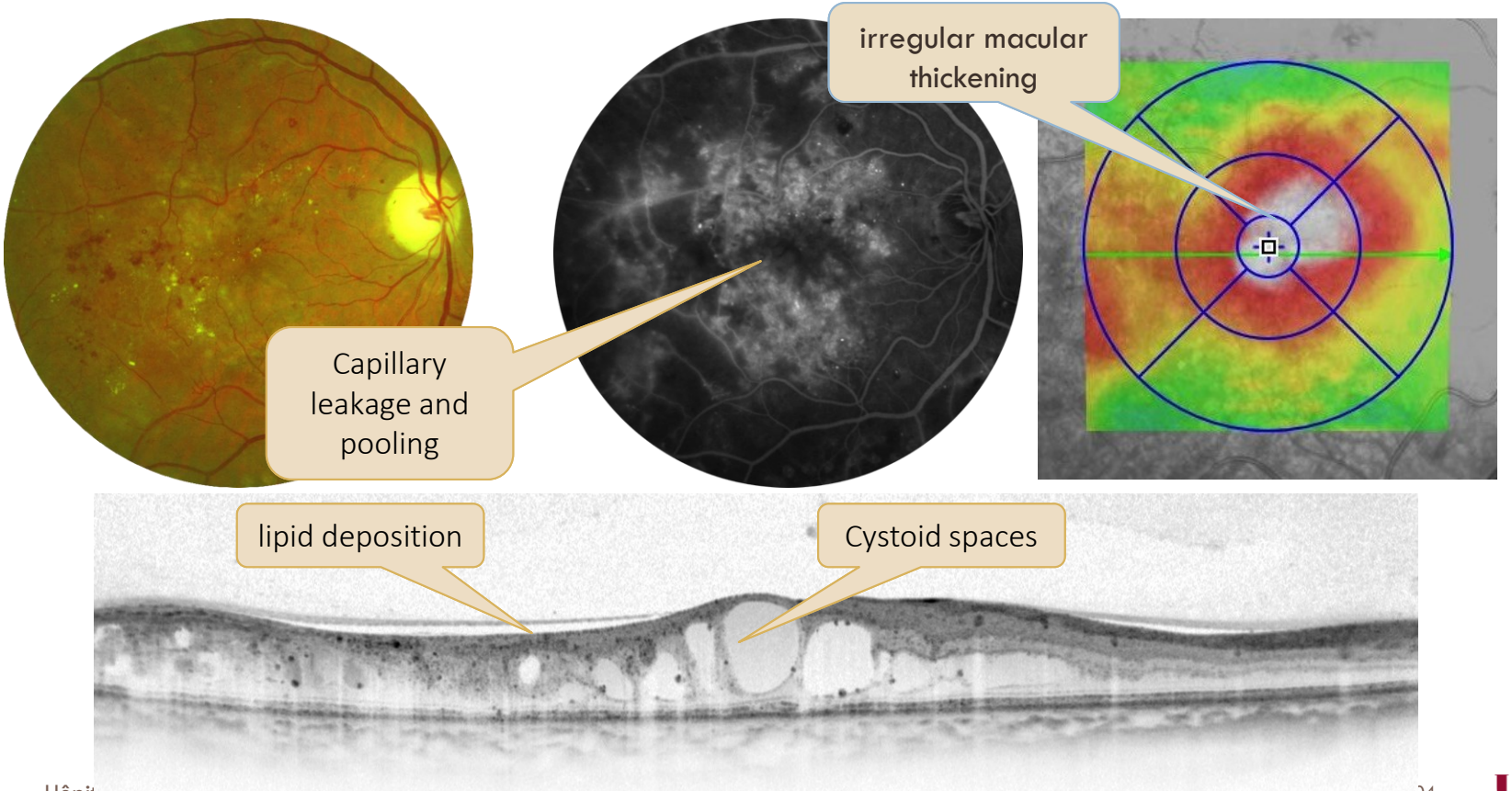
POST-TREATMENT



CONTROL



CME and leakage Diabetic Macular Edema



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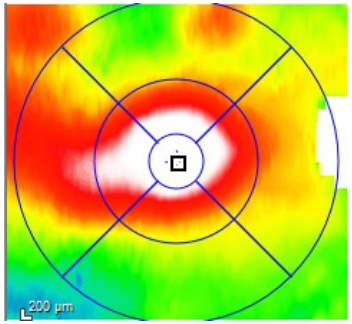
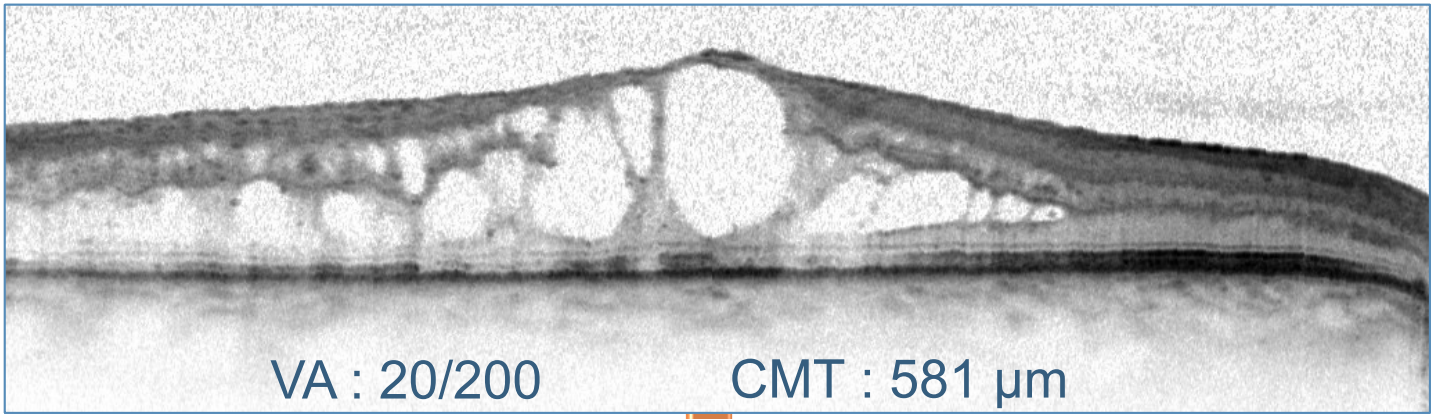
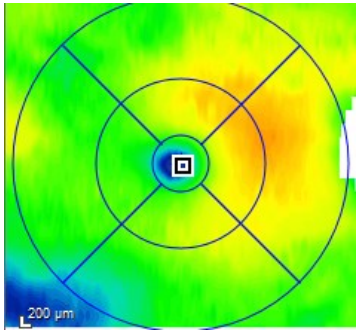
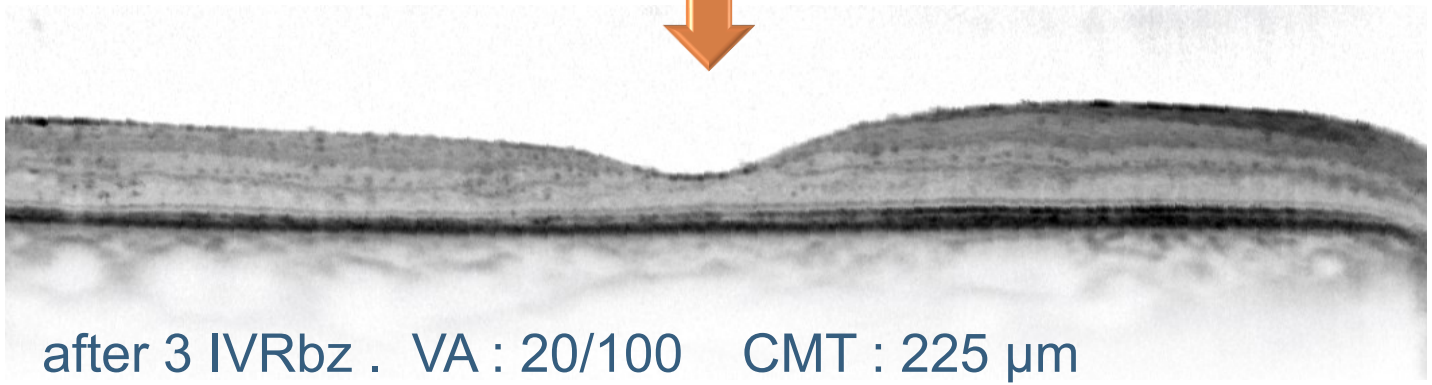
Diabetic CME: neuronal atrophy





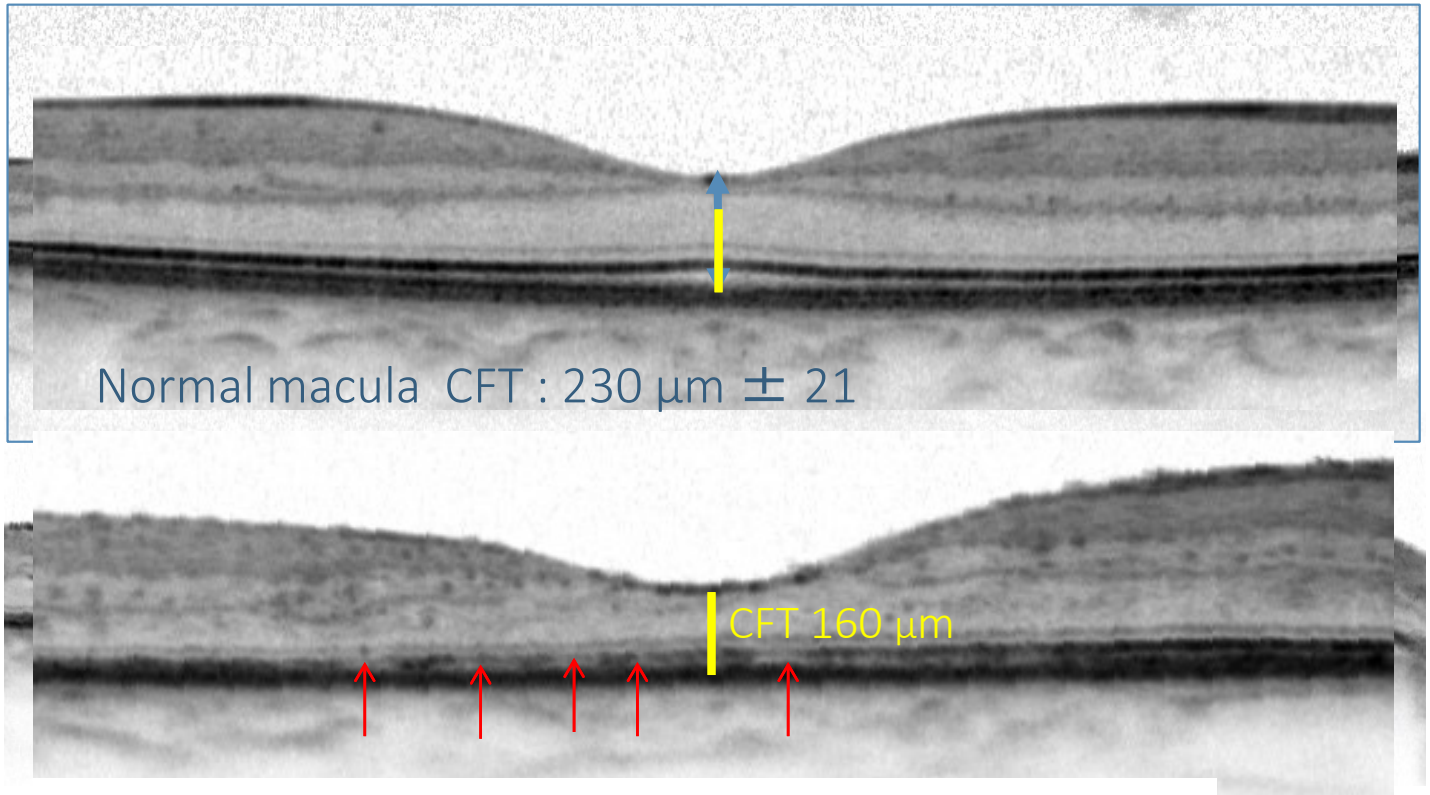




Diabetic CME: neuronal atrophy

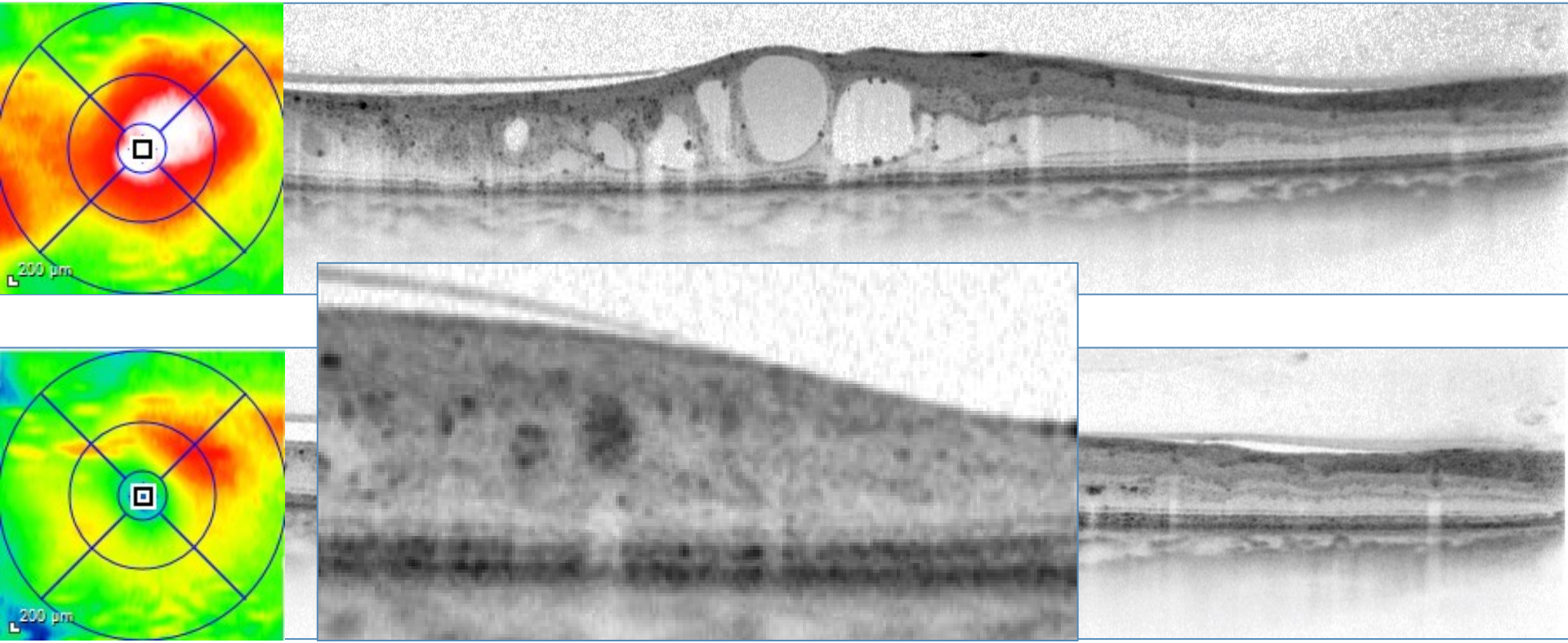
Cystoid cavities may be associated with cellular death.

Some degree of retinal atrophy is hidden in retinal thickening



1. Pelosini L,et al IOVS2011;52(5):2741-2748.
2. Deák GG, Schmidt-Erfurth UM, Jampol LM. JAMA Ophthalmol. 2018;136(11):1215–2.

Diabetic CME : DRIL



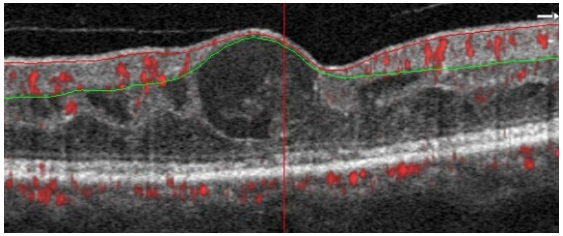
after treatment

Sun JK, et al. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. JAMA Ophthalmol. 2014;132(11):1309-1316

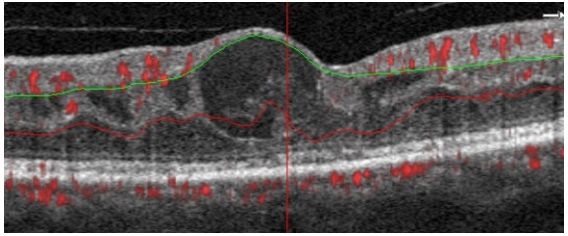
DME and capillary drop-out on OCTA

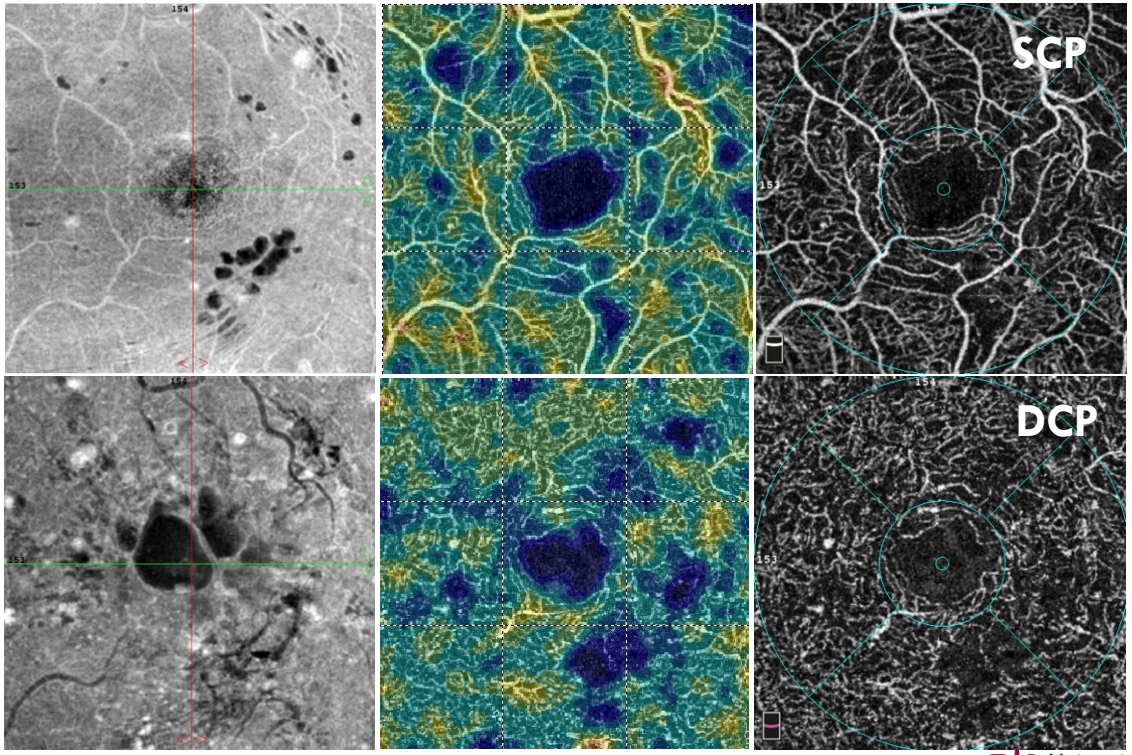
- Capillary drop-out both in the SCP and the DCP is always associated with cystoid edema

Superficial Capillary Plexus



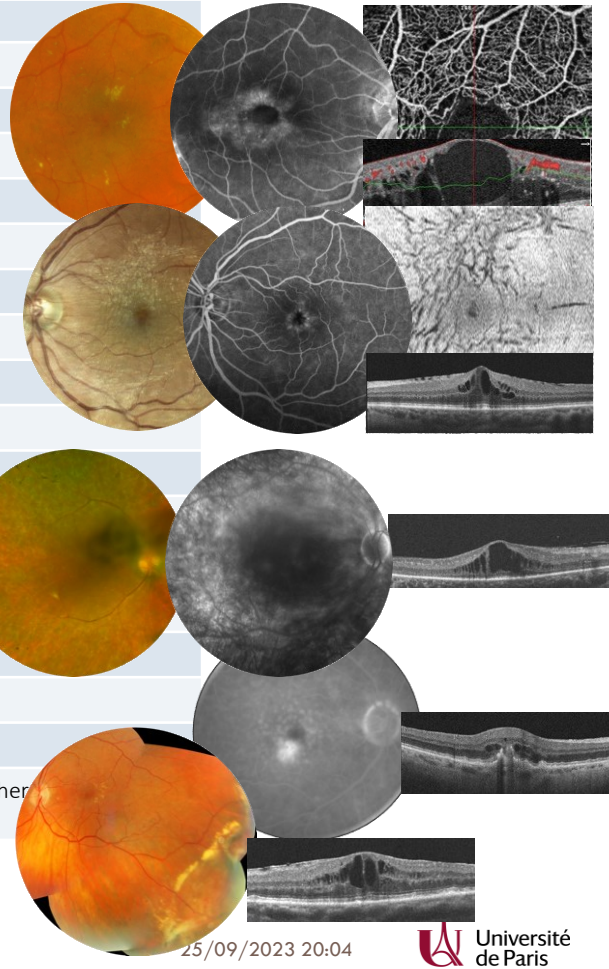
Deep Capillary Plexus





CYSTOID MACULAR EDEMA WITH LEAKAGE

Retinal vasculopathy	Diabetic retinopathy
	Retinal Vein Occlusion
	Macular Telangiectasia Type 1
	Radiation Retinopathy
Inflammation	Pseudophakic Macular Edema
	Birdshot retinochoroidopathy
Vitreo-Retinal Interface diseases	Epiretinal membrane
	Vitreo-macular traction
Drug tocicity	Fingolimod
	Acitretin (retinoid)
	Tropical Latanoprost, Epinephrin
	Vemurafenib
Retinal dystrophies	Retinitis Pigmentosa
Tumors	Choroidal Melanoma
	Choroidal Hemangioma
	Retinal Reactive Astrocytic Tumor (Vaso Proliferative Tumor)
Age Macular Degeneration	Macular New Vessels
	PEHC : Peripheral Exudative Hemorrhagic Chorioretinopathy (Peripher neovascularisation)
Inflammation	intermediate uveitis, vasculitis, Behcet disease, etc.



Vasogenic macular edema

- The mechanisms of ME have been extensively studied in several Reviews

Graefe's Arch Clin Exp Ophthalmol (2007) 245:627–636
DOI 10.1007/s00417-006-0516-y

REVIEW ARTICLE

Müller cells as players in retinal degeneration and edema

Andreas Reichenbach · Antje Wurm · Thomas Pannicke · Ianors Iandiev · Peter Wiedemann · Andreas Bringmann

Received: 29 November 2006 / Accepted: 2 December 2006 / Published online: 12 January 2007

Abstract
Background Under normal conditions, Müller cells support neuronal activity and the integrity of the blood-retinal barrier, whereas gliotic alterations of Müller cells under pathological conditions may contribute to retinal degeneration and edema formation. A major function of Müller cells is the fluid absorption from the retinal tissue, which is mediated by transcellular water transport coupled to currents through potassium channels.
Methods Alterations of retinal Müller cells under pathological conditions were investigated by immunohistochemistry and recording their behavior under osmotic stress.
Results In animal models of various retinopathies, e.g., retinal ischemia, ocular inflammation, retinal detachment, and diabetes, it was found that Müller cells decrease the expression of their major potassium channel (Kir4.1). This alteration is associated with an impairment of the rapid water transport across Müller cell membranes, as recognizable in the induction of cellular swelling under hypoosmolar conditions. Osmotic swelling of Müller cells is also induced by oxidative stress and by inflammatory mediators such as arachidonic acid and prostaglandins.
Conclusions The data suggest that a disturbed fluid transport through Müller cells is (in addition to vascular leakage) a pathogenic factor contributing to the development of retinal edema. Pharmacological re-activation of the retinal water clearance by Müller cells may represent an approach to the development of new edema-resolving drugs. Triamcinolone acetonide, which is clinically used to resolve edema, prevents osmotic swelling of Müller cells as it induces the release of endogenous adenosine and subsequent A1 receptor activation which results in the opening of ion channels. Apparently, triamcinolone resolves edema by both inhibition of vascular leakage and stimulation of retinal fluid clearance by Müller cells.

Keywords Diabetes · Edema · Fluid transport · Ischemia · Müller cells · Triamcinolone acetonide

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Mechanisms of macular edema: Beyond the surface

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ARTICLE INFO

Keywords:
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Edema
Mechanisms
Diabetes
Retina
Cysts

ABSTRACT

Macular edema consists of intra- or subretinal fluid accumulation in the macular region. It occurs during the course of numerous retinal disorders and can cause severe impairment of central vision. Major causes of macular edema include diabetes, branch and central retinal vein occlusion, choroidal neovascularization, posterior uveitis, postoperative inflammation and central serous chorioretinopathy. The healthy retina is maintained in a relatively dehydrated, transparent state compatible with optimal light transmission by multiple active and passive systems. Fluid accumulation results from an imbalance between processes governing fluid entry and exit, and is driven by Starling equation when inner or outer blood-retinal barriers are disrupted. The multiple and intricate mechanisms involved in retinal hydro-ionic homeostasis, their molecular and cellular basis, and how their deregulation lead to retinal edema, are addressed in this review. Analyzing the distribution of junction proteins and water channels in the human macula, several hypotheses are raised to explain why edema forms specifically in the macular region. "Pure" clinical phenotypes of macular edema, that result presumably from a single causative mechanism, are detailed. Finally, diabetic macular edema is investigated, as a complex multifactorial pathogenic example. This comprehensive review on the current understanding of macular edema and its mechanisms opens perspectives to identify new preventive and therapeutic strategies for this sight-threatening condition.

RETINAL VASCULAR CYSTOID MACULAR EDEMA

Review and New Theory

RICHARD F. SPAIDE, MD

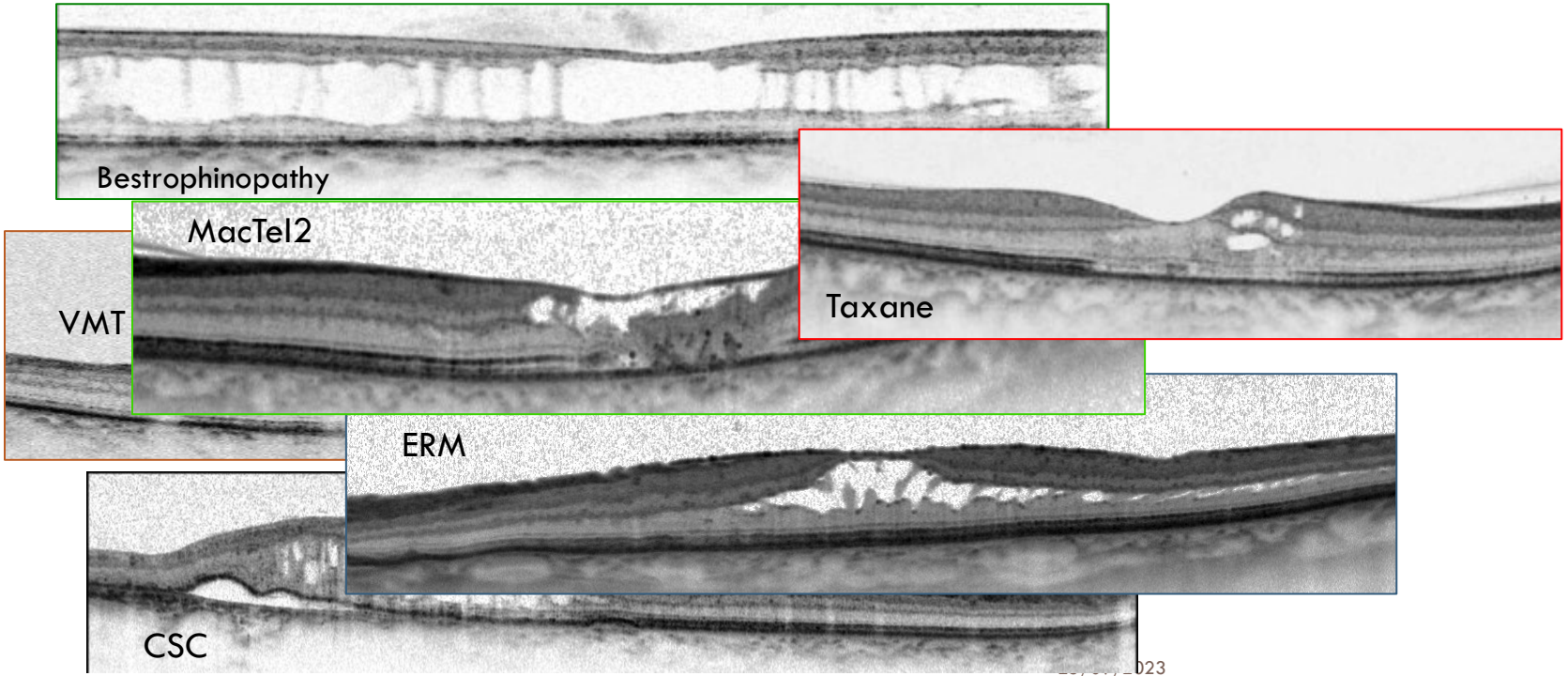
Retinal vascular disease has the potential to affect hundreds of millions of people, with the inherent risk of vision loss related to cystoid macular edema. Although there have been histologic evaluation of eyes having cystoid macular edema, the most recent paper was published more than 30 years ago. In retinal vascular cystoid macular edema fluorescein angiography, a modality that images the superficial vascular plexus, shows increased leakage. Optical coherence tomography angiography has provided unprecedented resolution of retinal vascular flow in a depth resolved manner and demonstrates areas of decreased or absent flow in the deep vascular plexus colocalizing with the cystoid spaces. There has been a large amount of research on fluid management and edema in the brain, much of which may have analogues in the eye. Interstitial flow of fluid as managed by Müller cells may occur in the retina, comparable in some ways to the bulk flow in brain parenchyma, which is managed by astrocytes. Absent blood flow in the deep retinal plexus may restrict fluid management strategies in the retina, to include transport of excess fluid out of the retina into the blood by Müller cells. Application of this theory may help in increasing understanding of the pathophysiology of retinal vascular cystoid macular edema and may lead to new therapeutic approaches.

RETINA 36:1823–1842, 2016

Non-vasogenic cystoid maculopathy

- Cases in which there is
  - NO BRB breakdown , no fluorescein leakage
  - NO retinal capillary anomalies on OCTA
- The term "CME" is too co-noted to "BRB breakdown"
- I propose the term "Cystoid Maculopathy"
  - to name those cases with cystoid spaces without fluorescein leakage

In many cases cystoid spaces are present on OCT without any leakage on FA



Tractional cystoid maculopathies

Retinal dystrophies and cystoid maculopathies

Chronic CSCR and cystoid maculopathy

Drug induced cystoid maculopathies

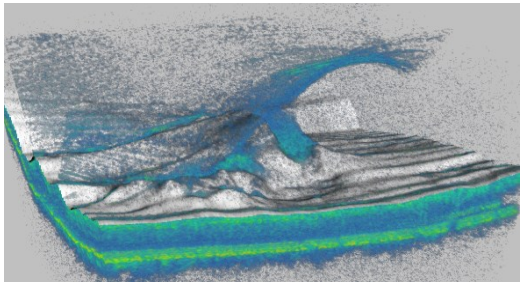
Miscellaneous

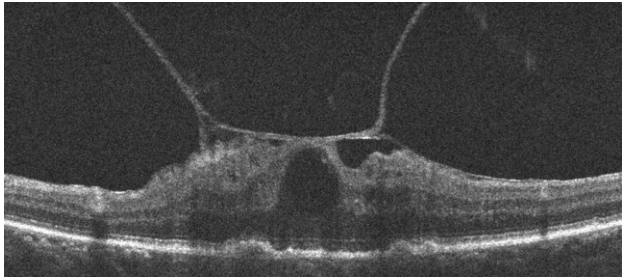
"Mechanical", "tractional" cystoid maculopathies

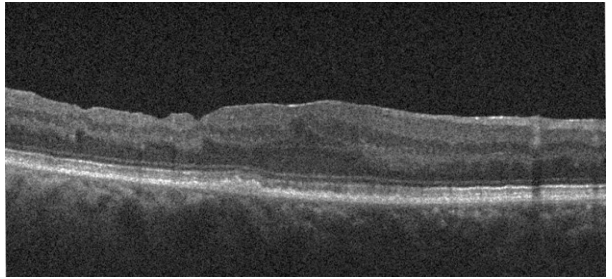
- May be caused
  - by antero-posterior traction, (VMT), or
  - tangential traction (ERM , Myopic foveoschisis)
- Various terminology:
  - intraretinal cystoid spaces
  - cystic degeneration
  - microcystic macular edema
  - Inner nuclear layer microcysts
  - Intraretinal fluid
  - foveoschisis

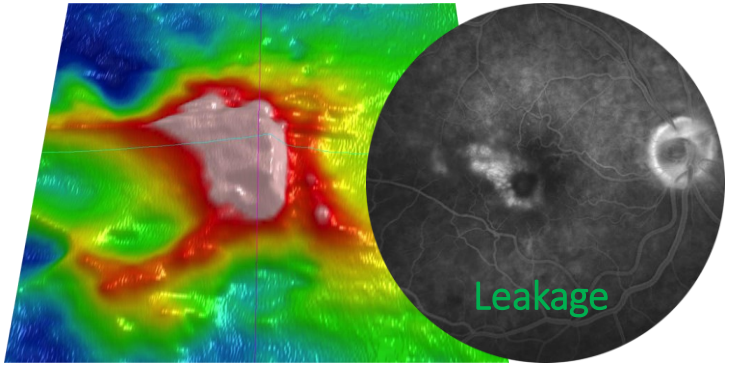
Cystoid maculopathy and VMT

With leakage

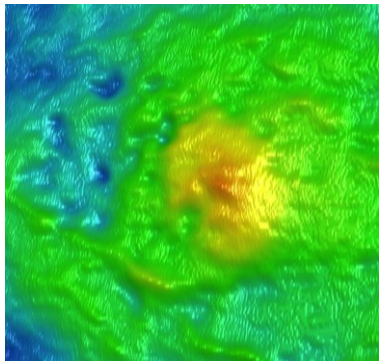








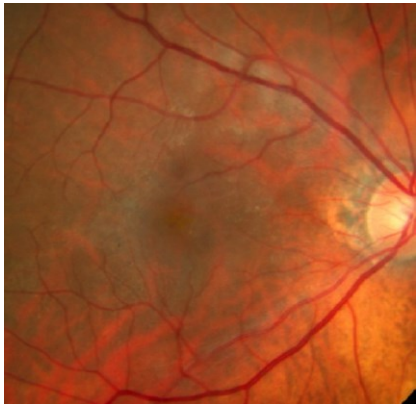
Capillary leakage may be associated with VMT in some cases , which does not prevent edema resolution after surgery

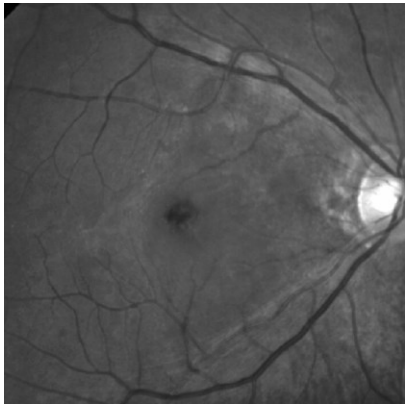


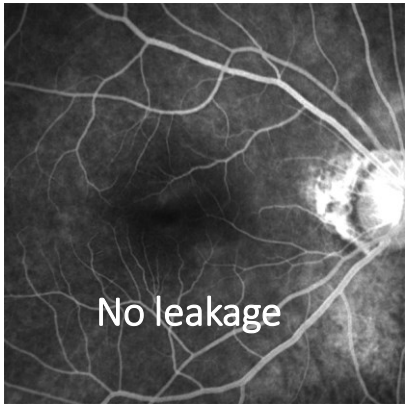
Post surgery

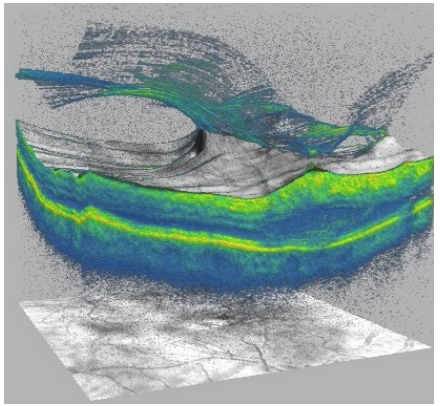
Cystoid maculopathy and VMT

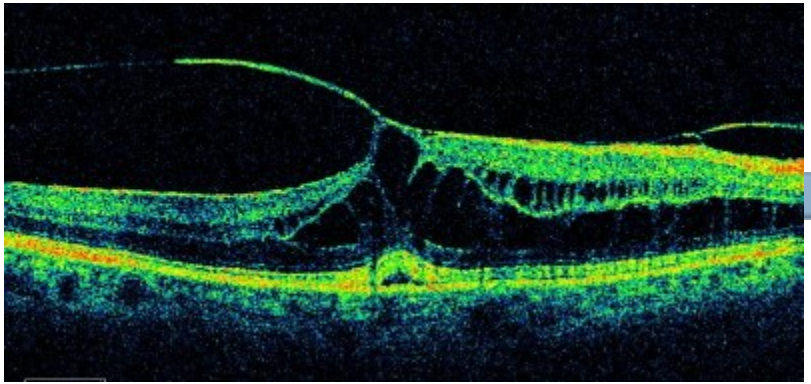
No leakage

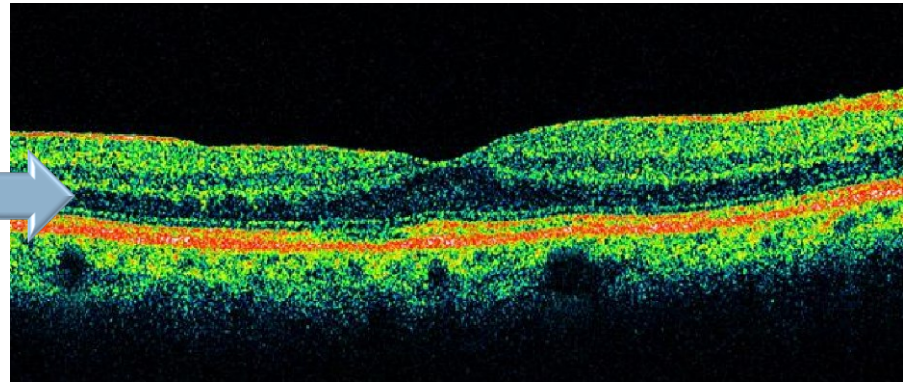








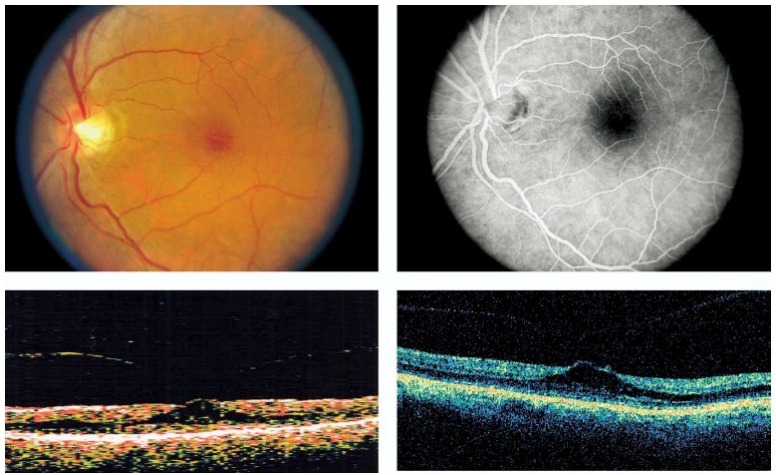




Cystoid maculopathy and VMT

Tractional Cystoid Macular Edema: A Subtle Variant of the Vitreomacular Traction Syndrome

MARK W. JOHNSON, MD



Fluorescein angiography revealed no leakage of perifoveal capillaries in eight eyes (72.7%)

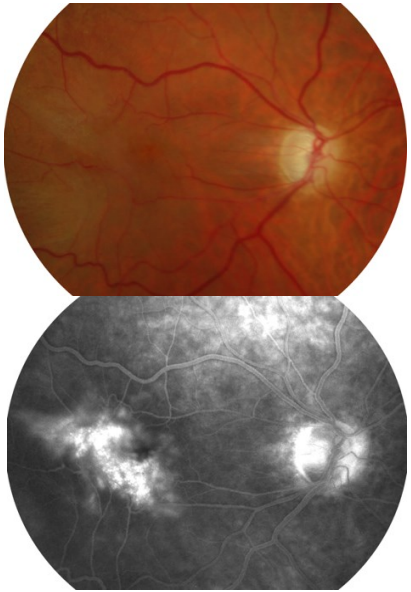
As defined in this study, tractional CME is a subtle variant of the vitreomacular traction syndrome that can easily be confused with postoperative or uveitic CME.

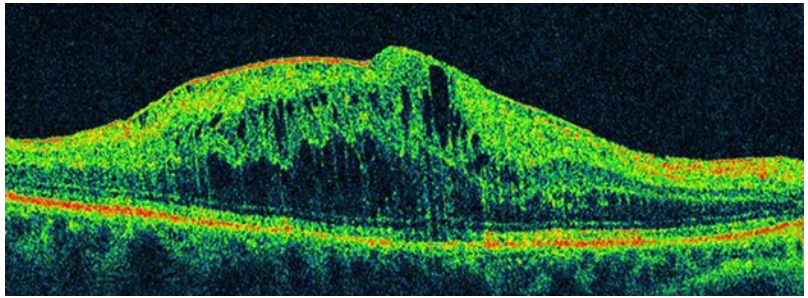
Johnson MW. Tractional cystoid macular edema: a subtle variant of the vitreomacular traction syndrome. Am J Ophthalmol 2005;140(2):184-192.

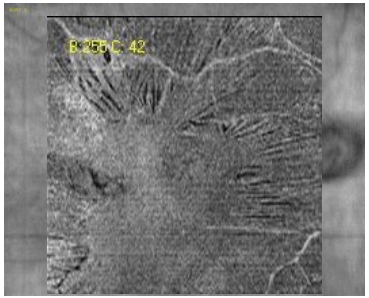
Cystoid maculopathy and ERM

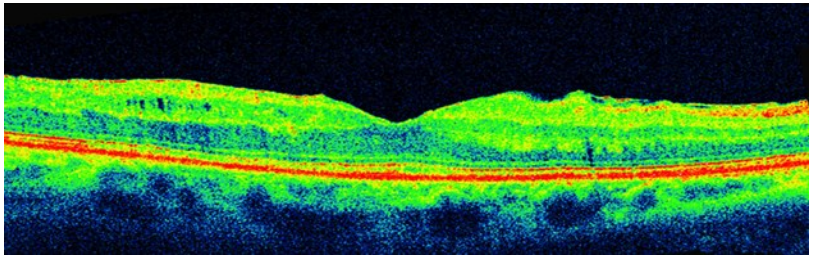
With leakage

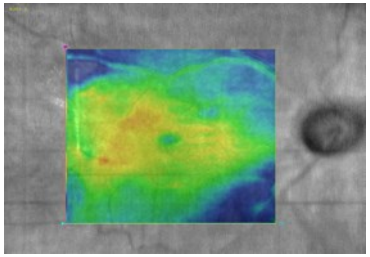
- ERM and capillary leakage
- Cystoid cavities disappear after ERM/ILM peeling





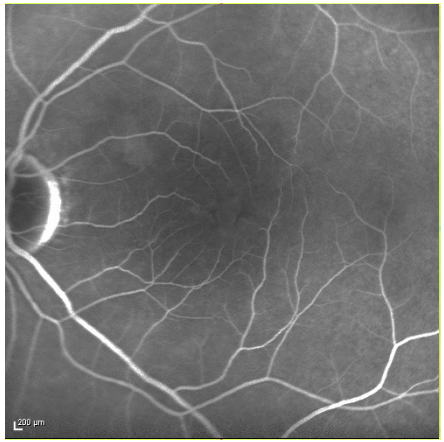


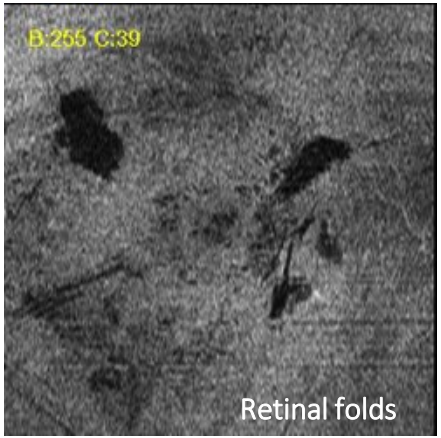




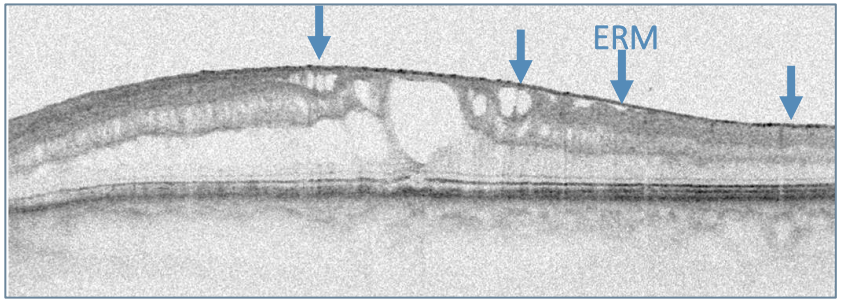
Cystoid maculopathy and ERM

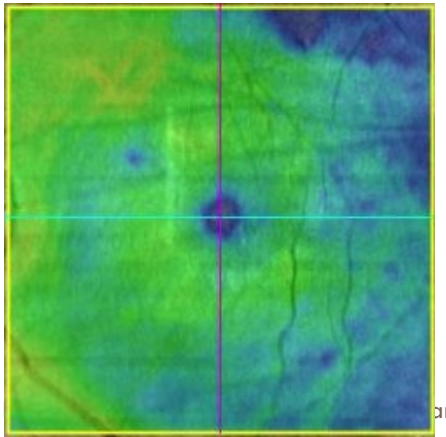
No leakage

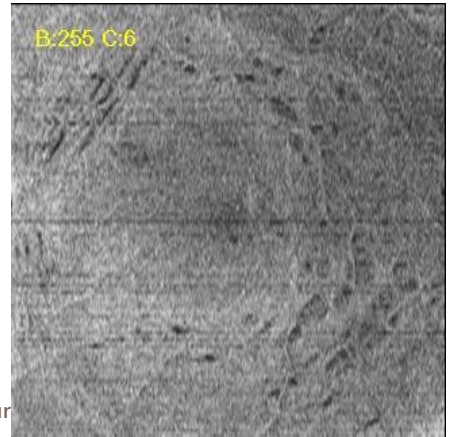


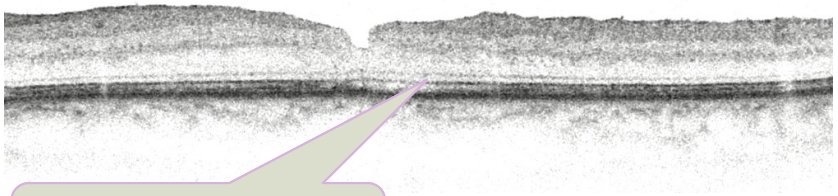


pre-operative tangential contraction







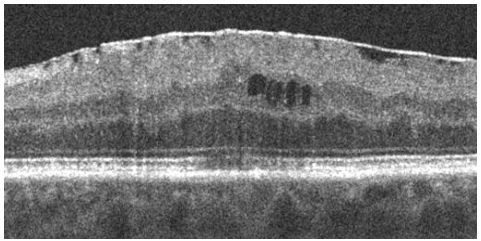


Normalization after ERM peeling

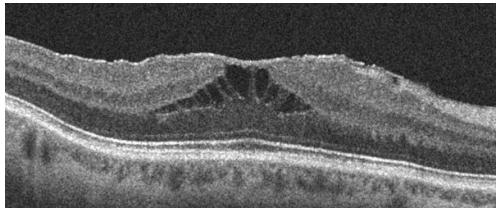
Cystoid maculopathy and ERM

No leakage

- ERM may be associated with preoperative cystoid spaces mainly located in the INL:
  - Meuer et al, Beaver Dam Study Ophthalmol, 2015, : 7.5%
  - Govetto et al, Am J Oph 2017 : 19.7% ,
    - of which 55% had concomitant Glaucoma



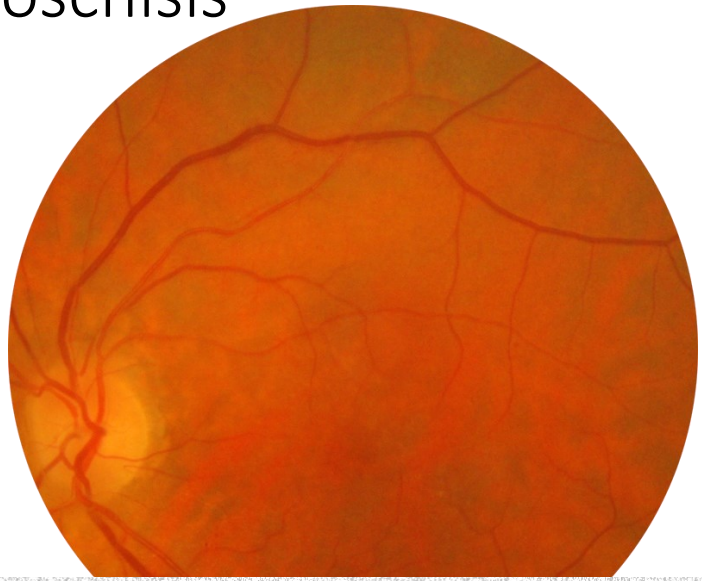
- A peculiar presentation is an aspect of foveoschisis
  - Govetto et al , Am J Oph 2020
  - Lam et al, Br J Oph 2021 : 3.1%

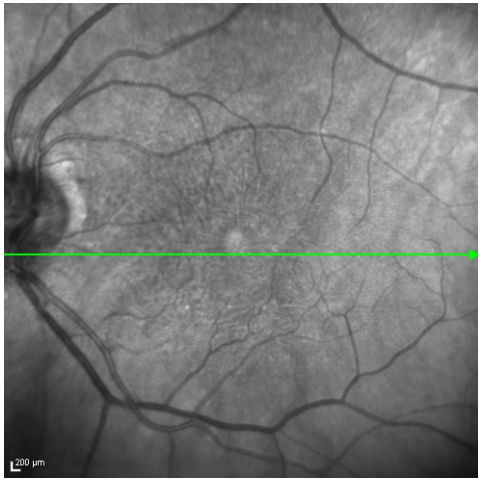


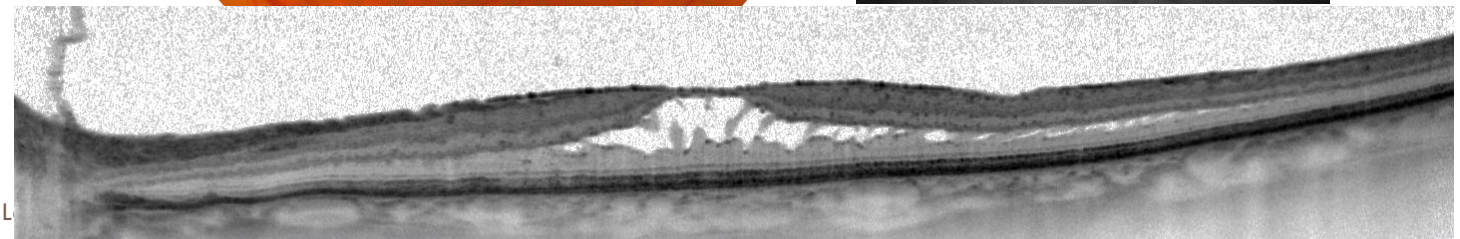
Cystoid maculopathy and ERM

No leakage

- Foveoschisis





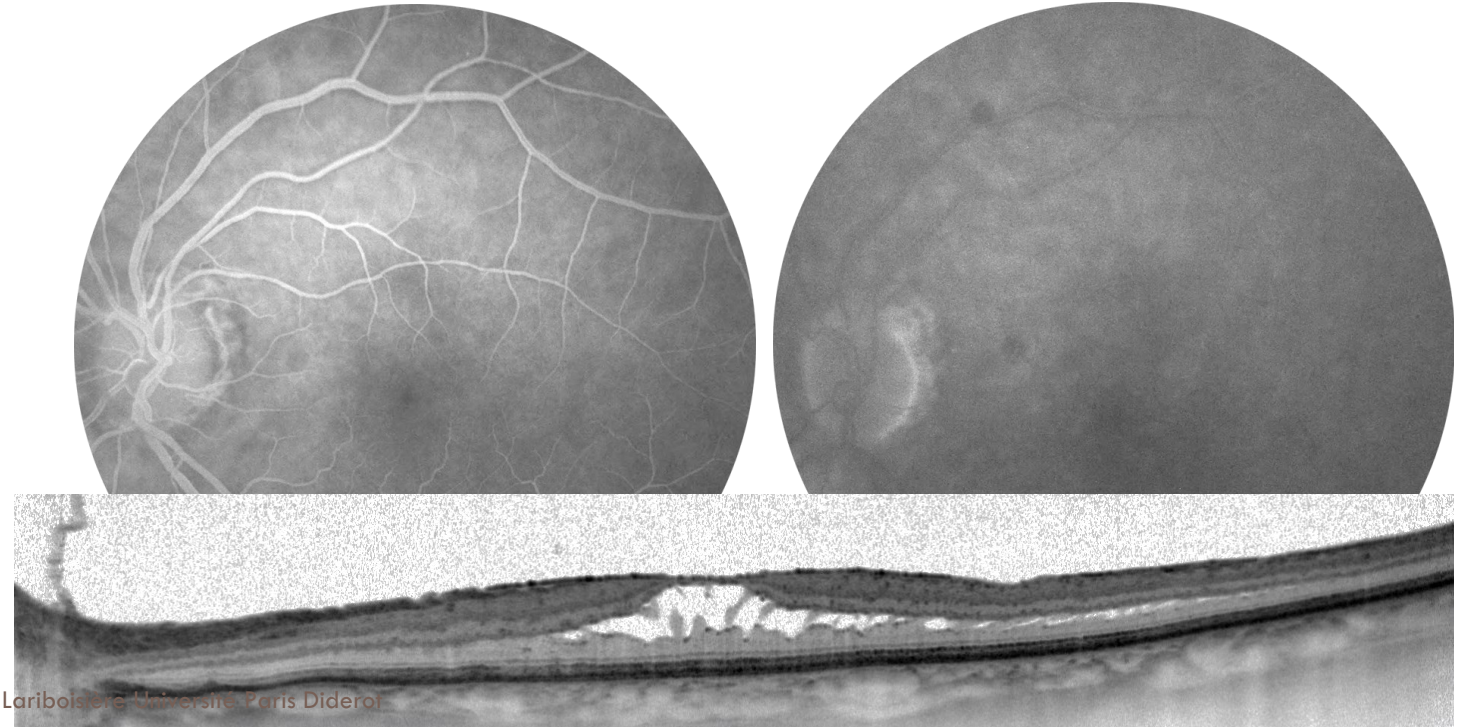


Université de Paris

Cystoid maculopathy and ERM

No leakage

- Foveoschisis, no leakage on FA

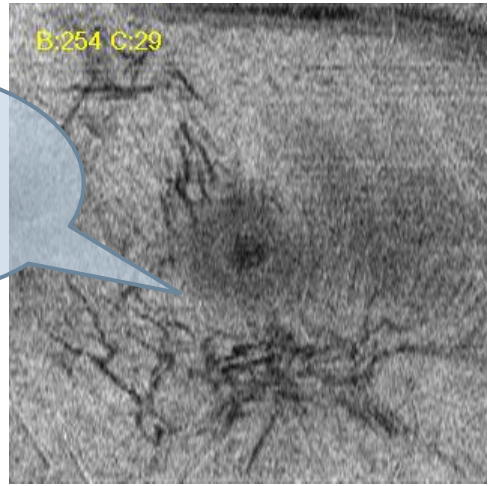


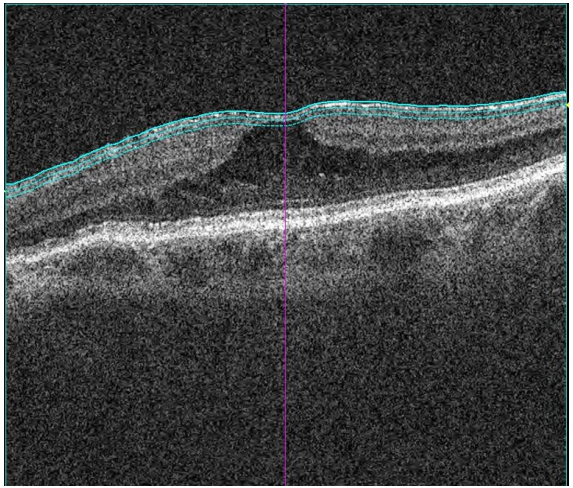
Cystoid maculopathy and ERM

No leakage

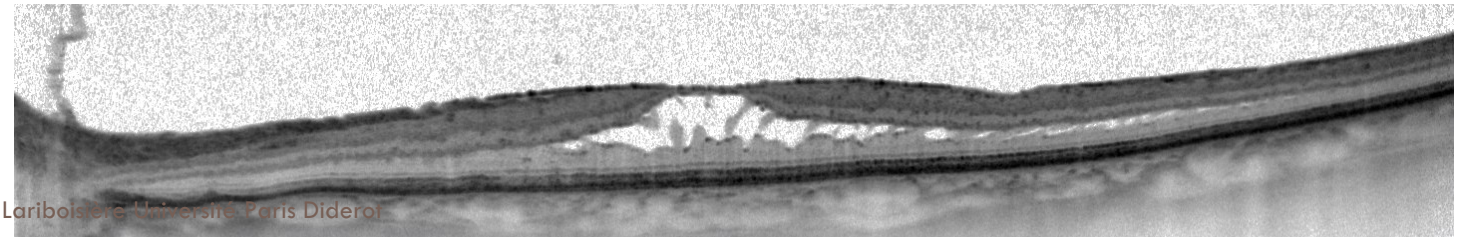
- Foveoschisis, tangential contraction of the ERM

which differenciate this case from SNIFR





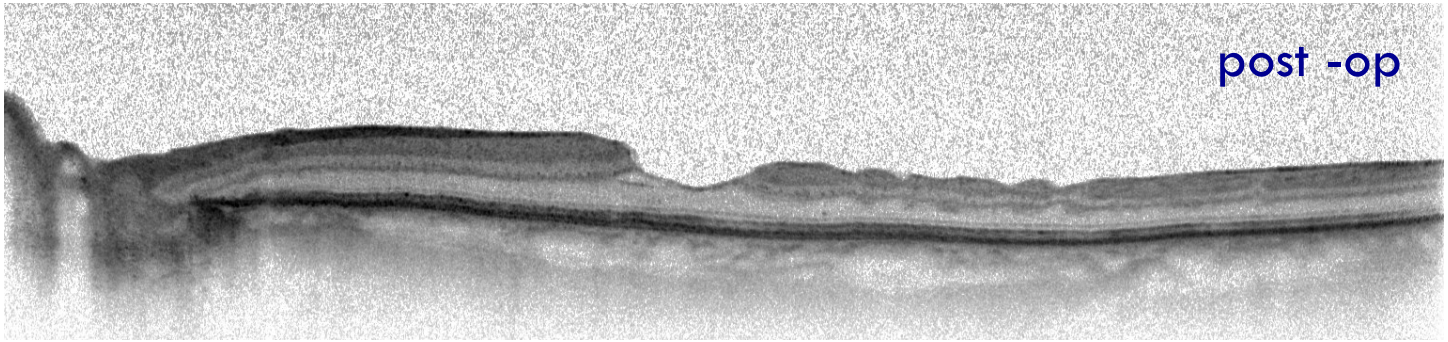
Stellate
Nonhereditary
Idiopathic
Foveomacular
Retinoschisis

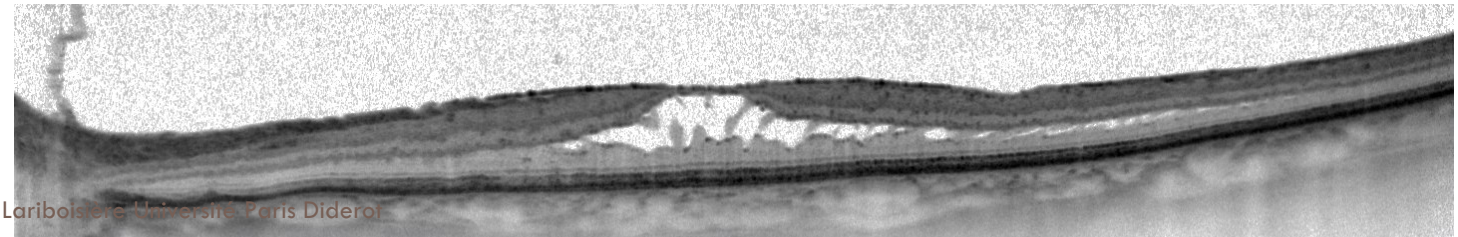


Cystoid maculopathy and ERM

No leakage

- Foveoschisis, flattens after ERM+ILM peeling

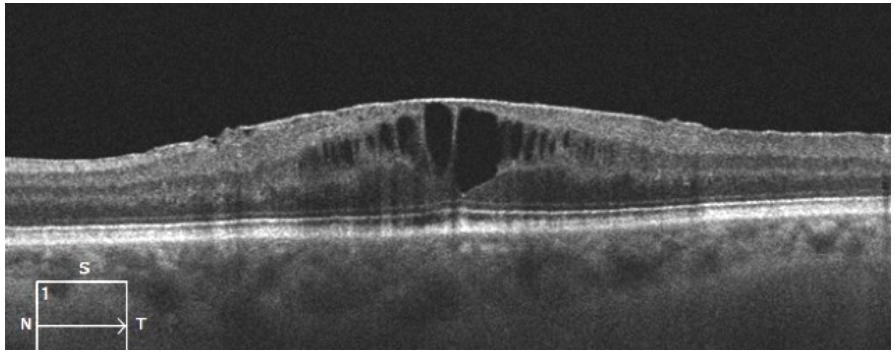


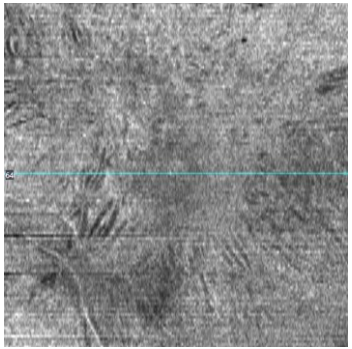


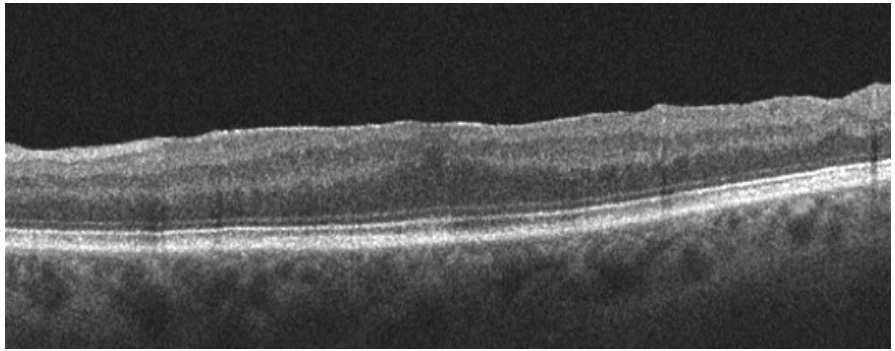
Cystoid maculopathy and ERM

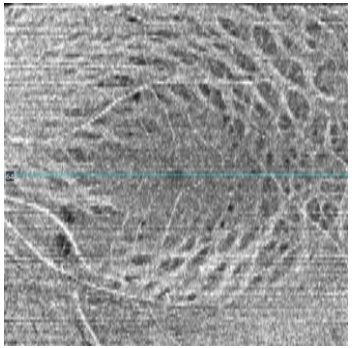
No leakage

- Central + INL cysts



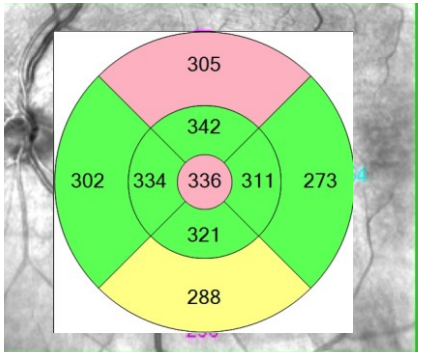






DONFL

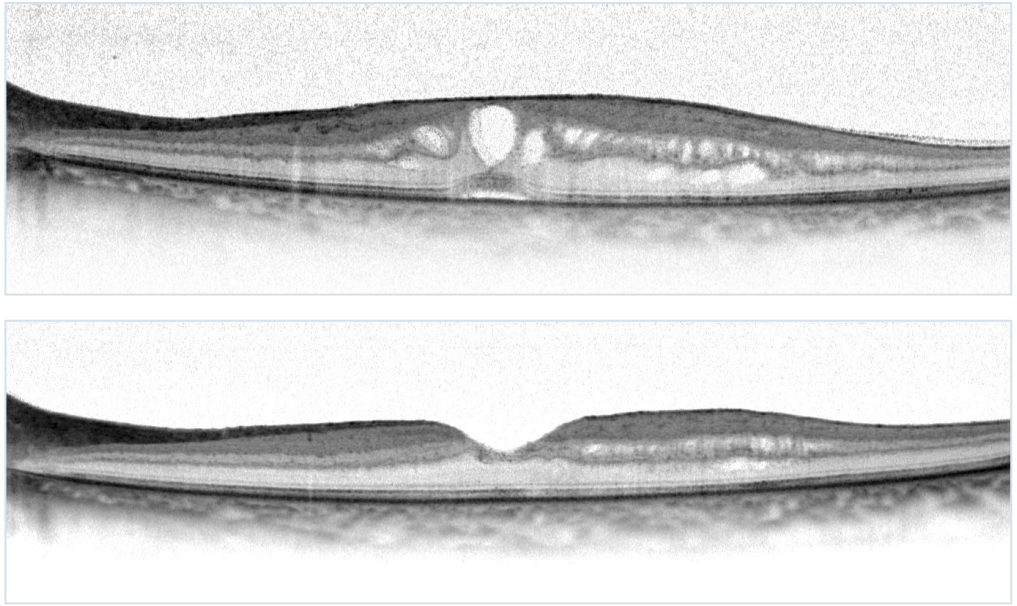
- Cysts regression after ERM and ILM peeling
- macula remains thicker than normal



Cystoid maculopathy and ERM

No leakage

- Post operative outcome
  - Some cystoid spaces may persist after surgery



6 months post surgery

Cystoid maculopathy and ERM

- Post operative outcome od associated foveoschisis
  - Most disappear after surgery

Postoperative outcomes of idiopathic epiretinal membrane associated with foveoschisis

Marion Lam,[1] Elise Philippakis ,[1] Alain Gaudric ,[1] Ramin Tadayoni,[1,2] Aude Couturier [1]

Brit J Ophthalmol. Published online 2021:bjo-2020-317982.

76 % of foveoschisis had disappeared completely after a one-year follow-up

In the other cases cystoid spaces were limited to the INL

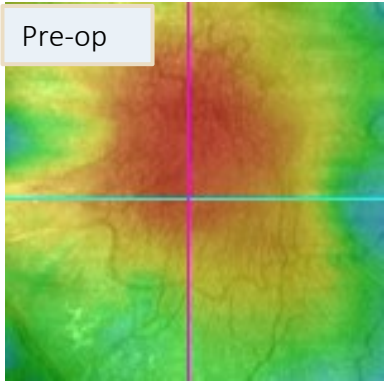
Interestingly , a CME with fluorescein leakage occurred in 24% of the cases after subsequent cataract surgery

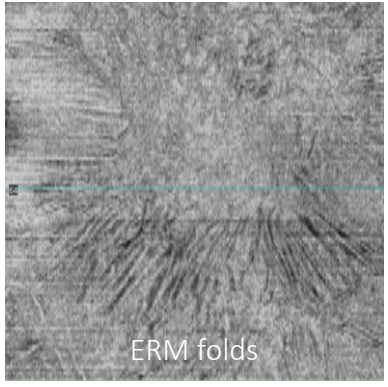
Cystoid maculopathy and ERM

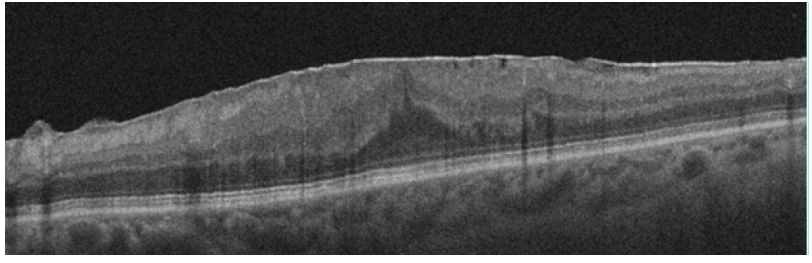
No leakage

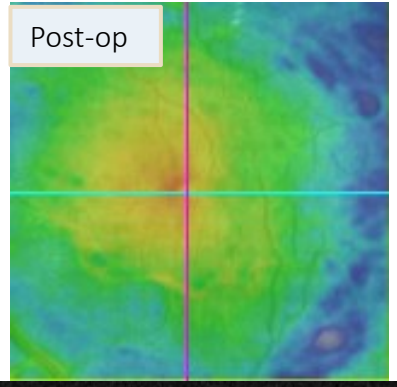
- Post operative outcome
  - Other may appear after surgery

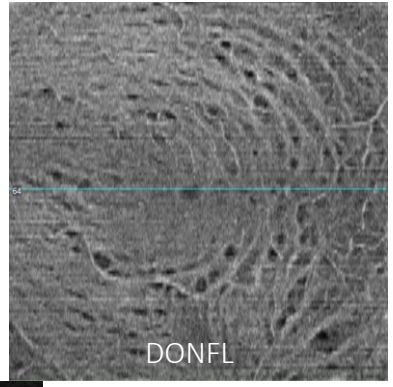
Hsieh, M.-H., et al , 2019.. Sci Rep 9, 11570 – 11577
Sigler, E.J., 2014.. Invest Oph Vis Sci 55, 3282-3284

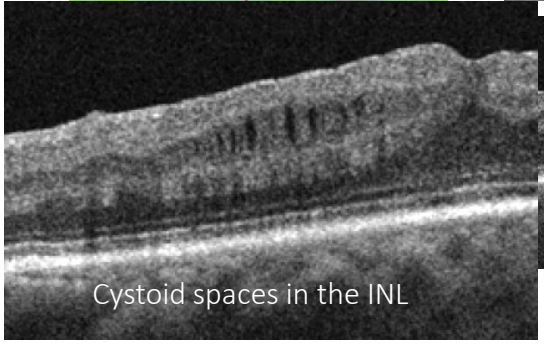


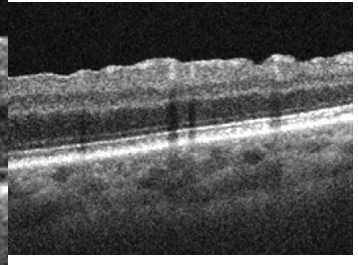






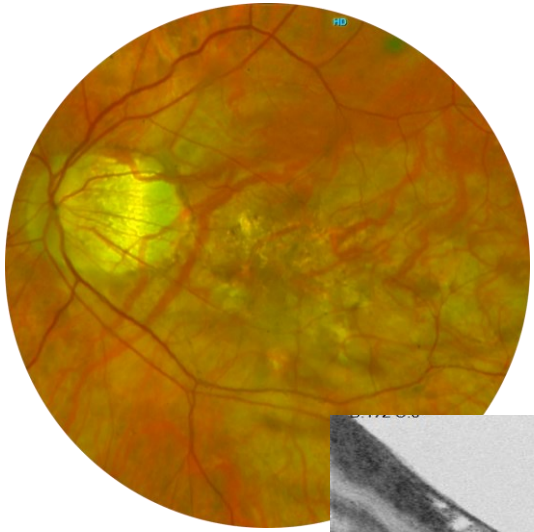


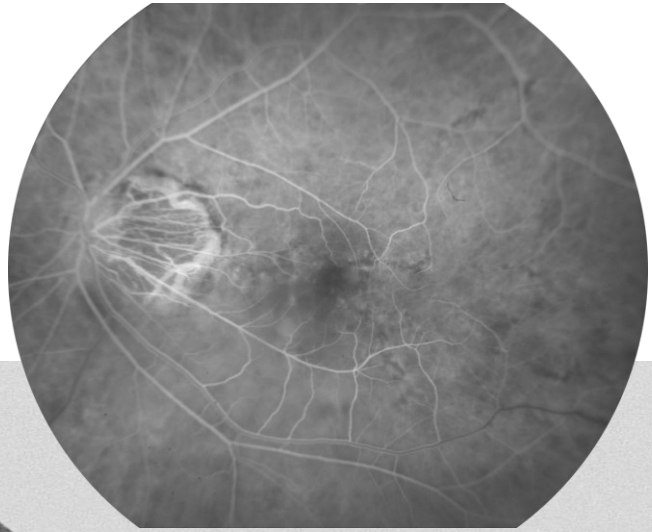


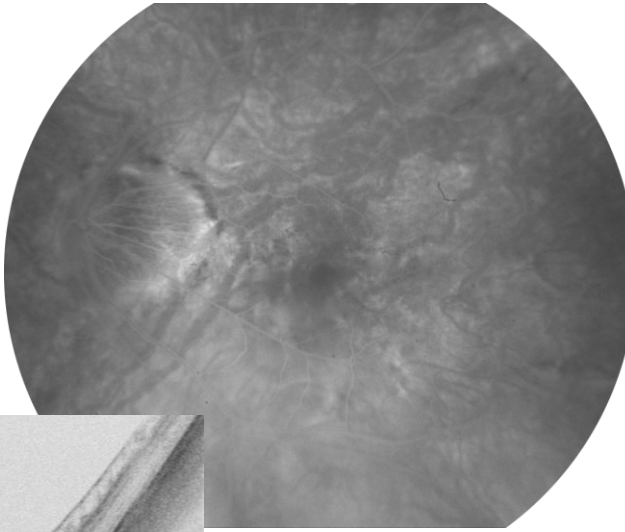


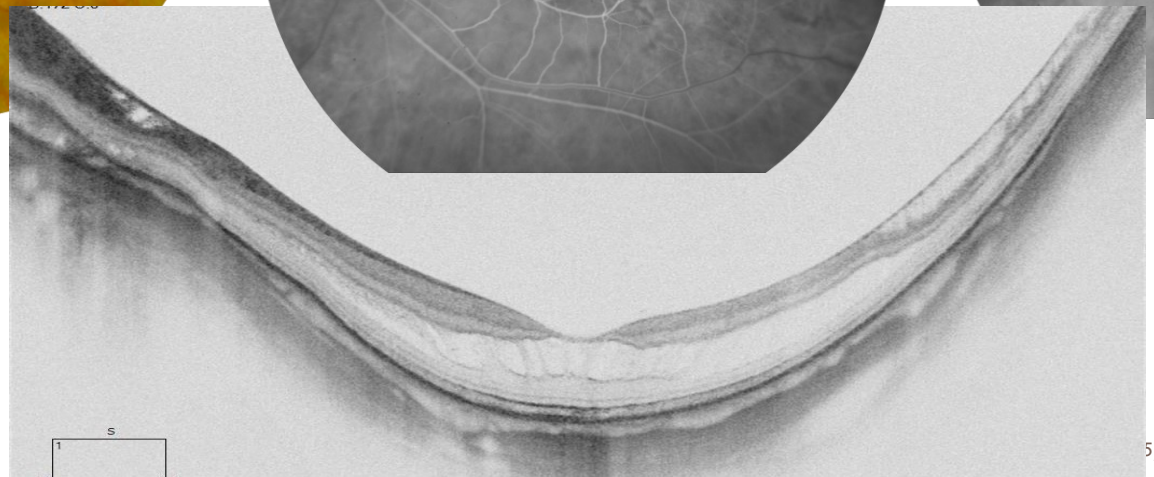
Myopic foveoschisis

No leakage



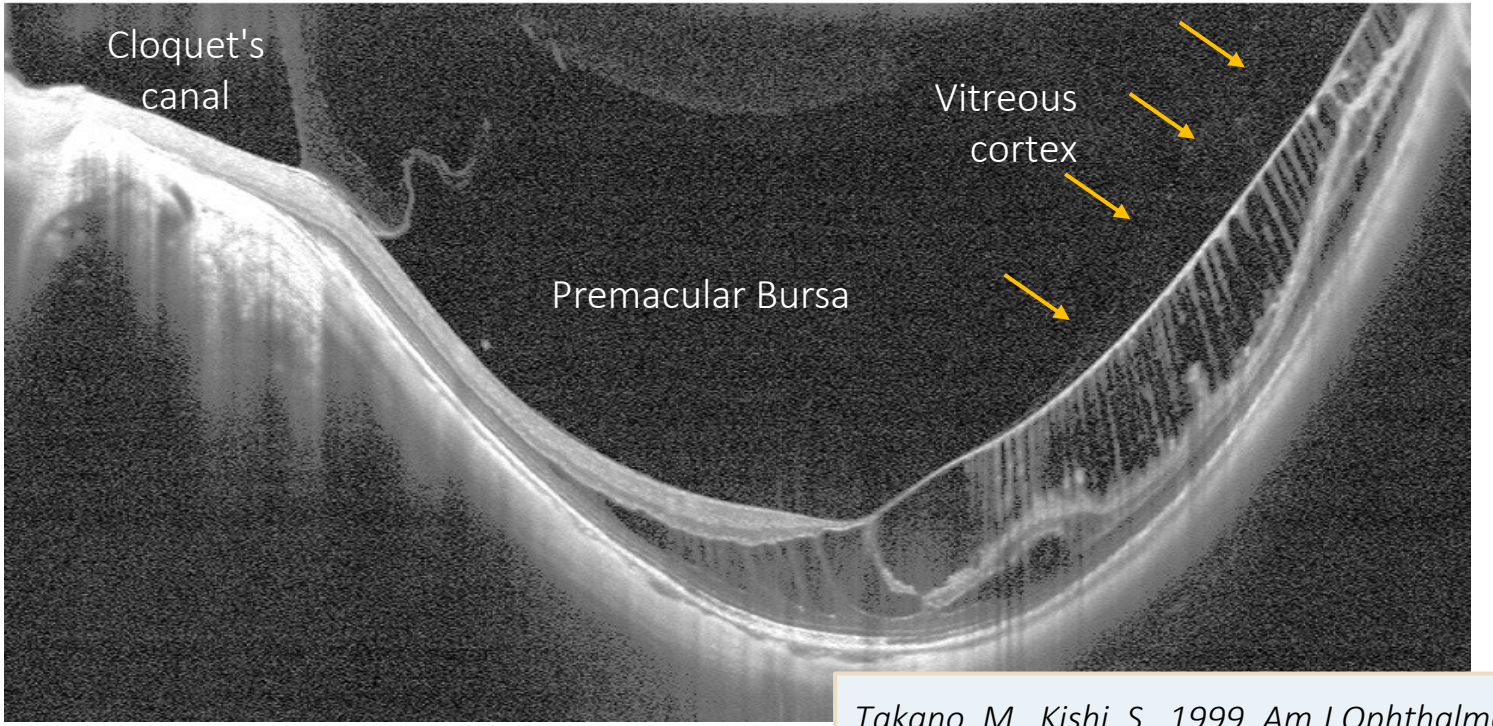






Myopic foveoschisis

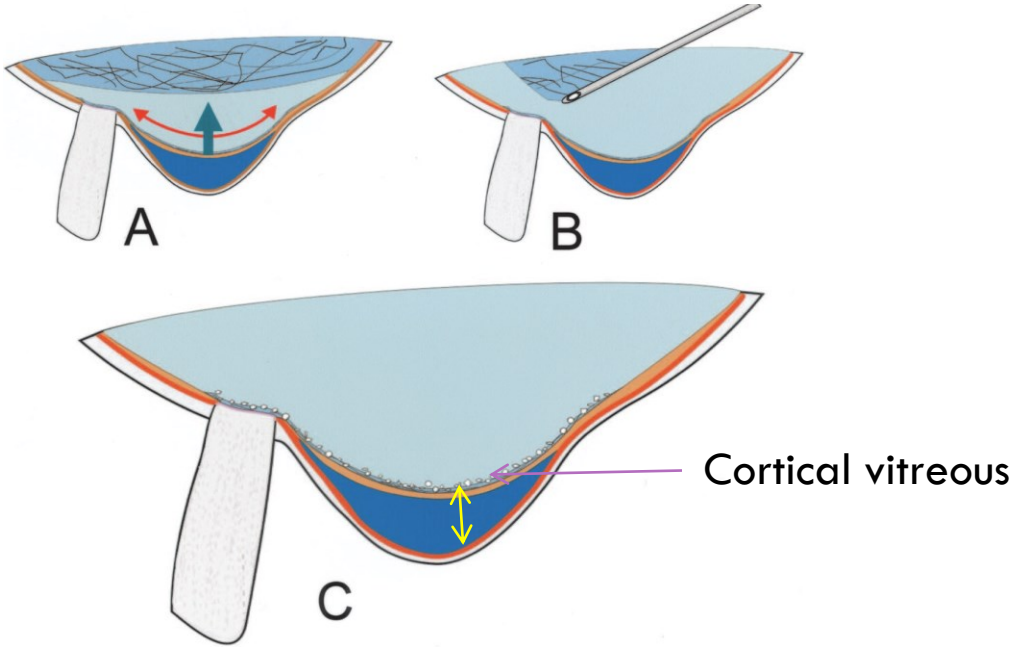
No leakage



Takano, M., Kishi, S., 1999. Am J Ophthalmol 128, 472-476,

Ikuno, Y., Tano, Y., 2006.. American J Ophthalmol141, 774-776,

Myopic foveoschisis, pathogenesis



REMOVAL OF ADHERENT CORTICAL VITREOUS PLAQUES WITHOUT REMOVING THE INTERNAL LIMITING MEMBRANE IN THE REPAIR OF MACULAR DETACHMENTS IN HIGHLY MYOPIC EYES

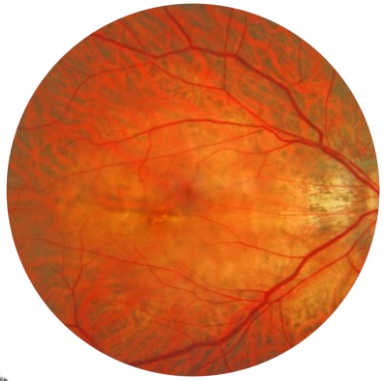
RICHARD F. SPAIDE, MD, YALE FISHER, MD

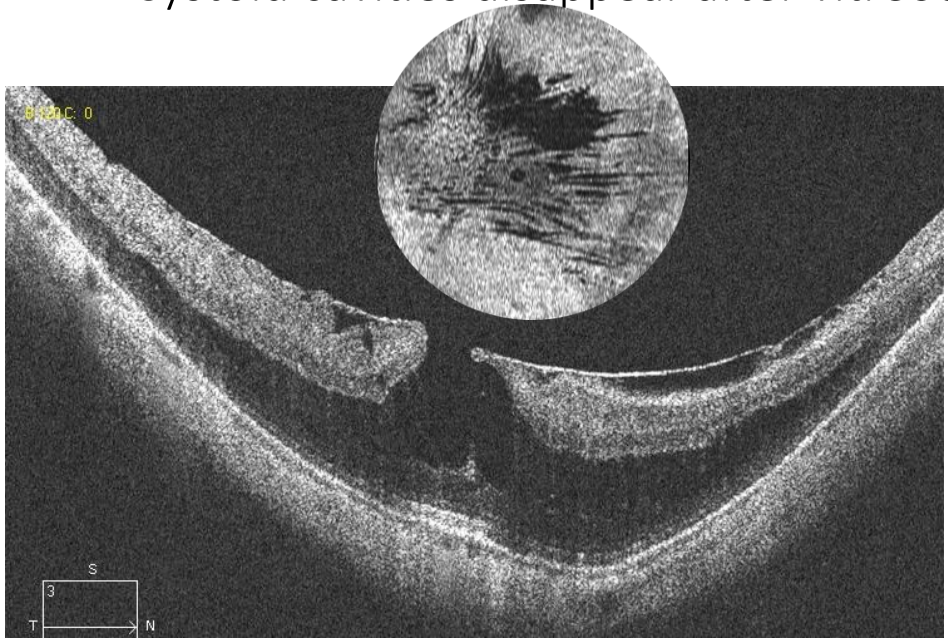
- The persistence of a layer of cortical vitreous adherent to the ILM may induce retinal surface stiffening, preventing it to conform to the staphylomatous curvature of the eyeball

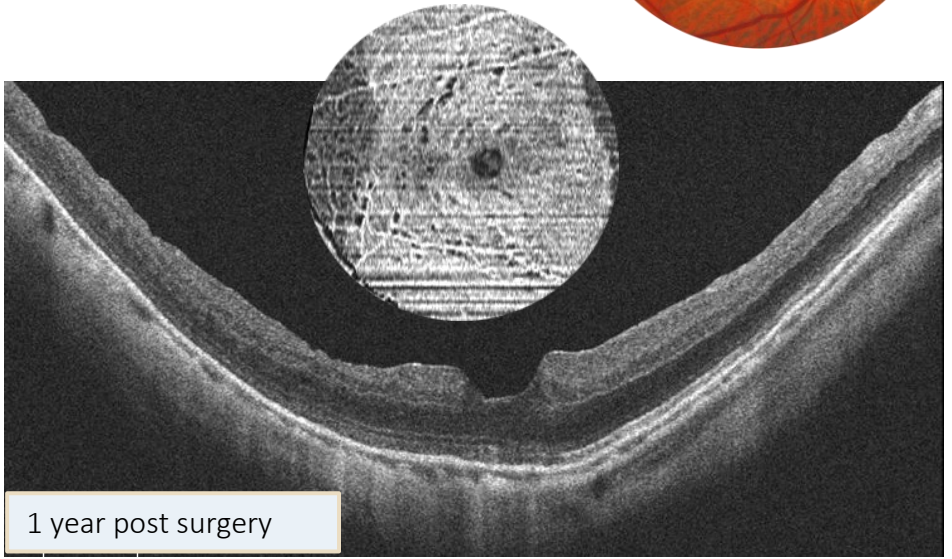
Myopic Foveoschisis

- Tangential contraction of vitreous cortex / ERM
- No leakage
- Cystoid cavities disappear after vitreous cortex/ERM/ILM peeling

No leakage

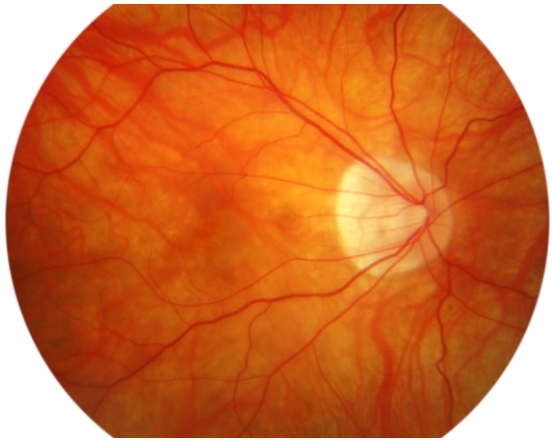


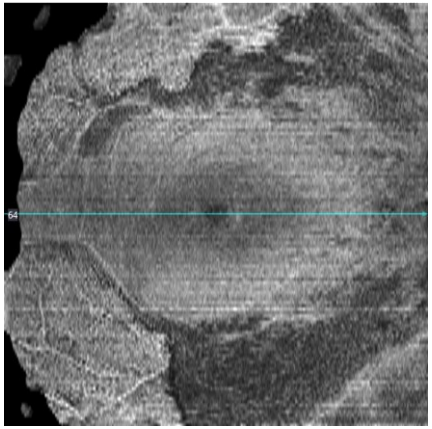


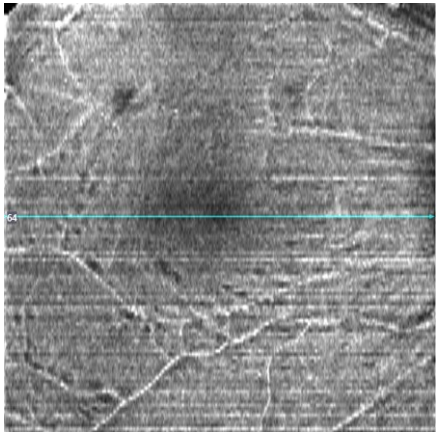


1 year post surgery

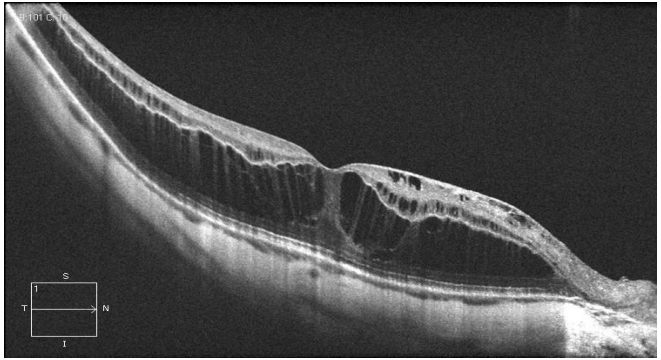
Myopic foveoschisis

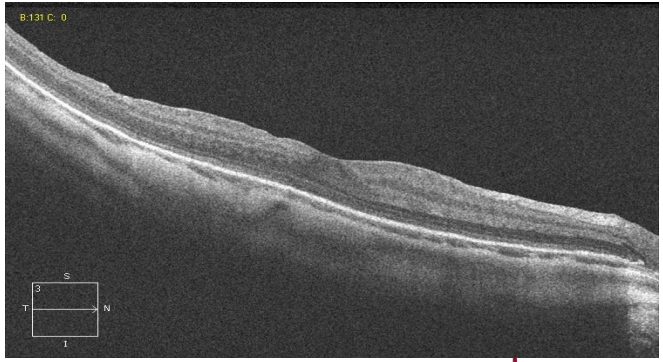




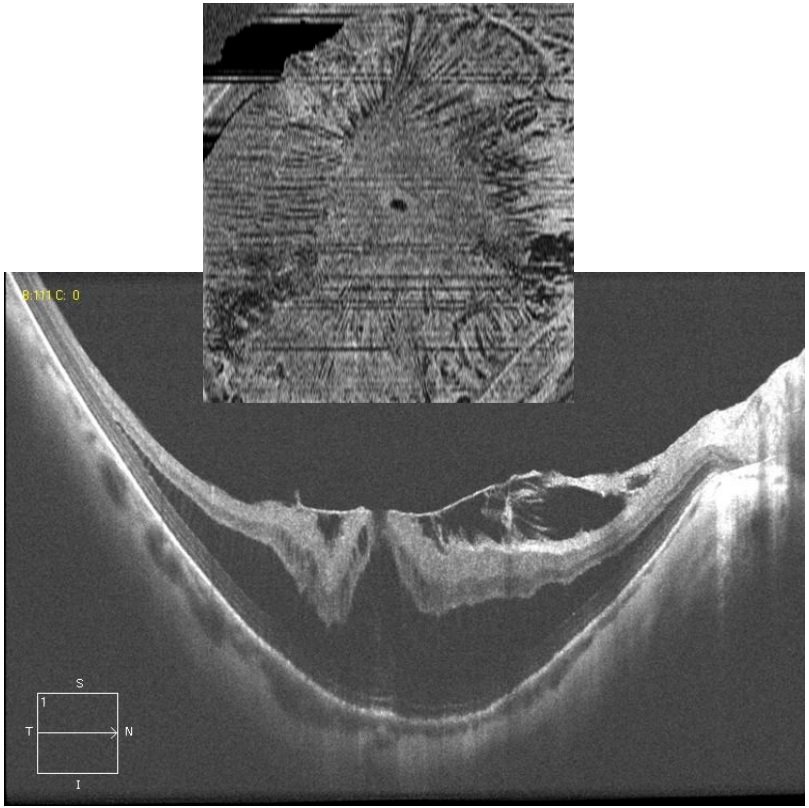


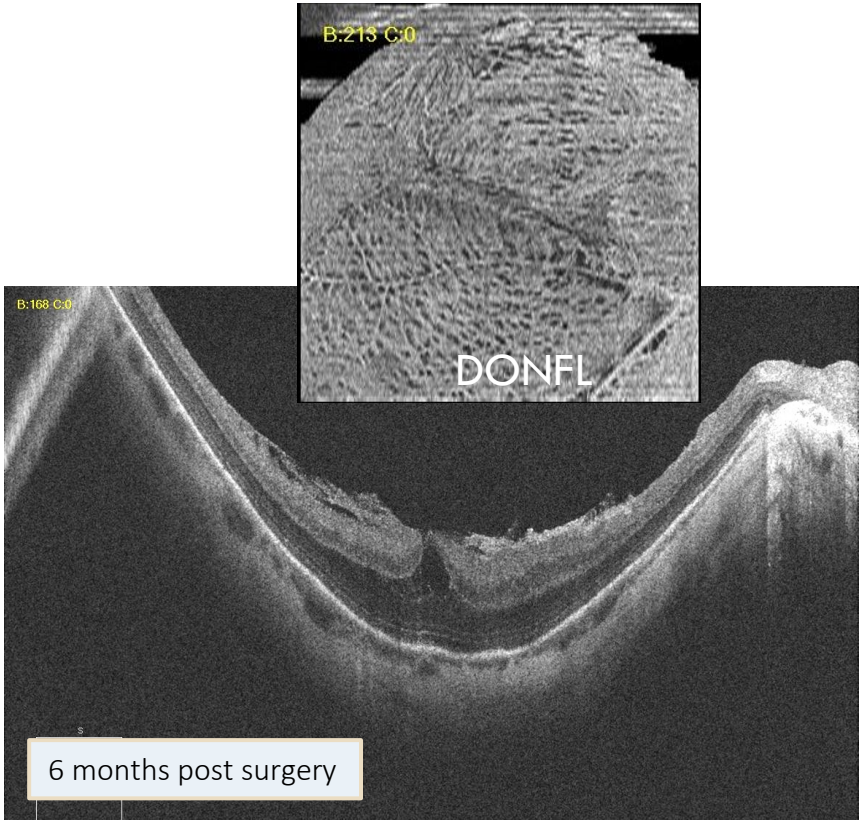
The removal of an ERM relieves the tangential traction and results in the progressive collapse of the inner and outer foveoschisis





Myopic Foveoschisis

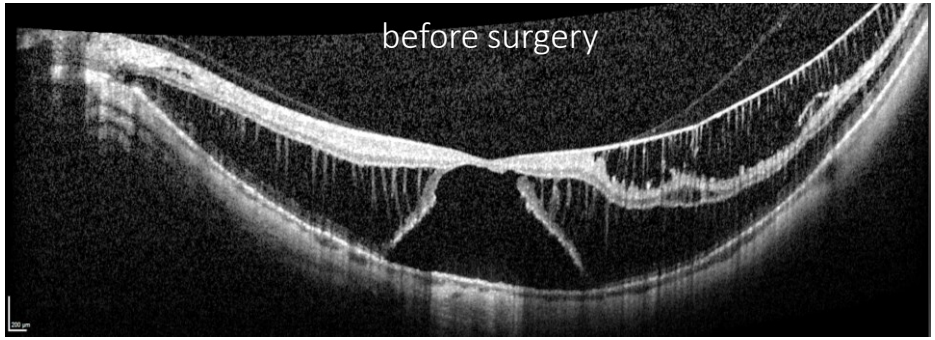


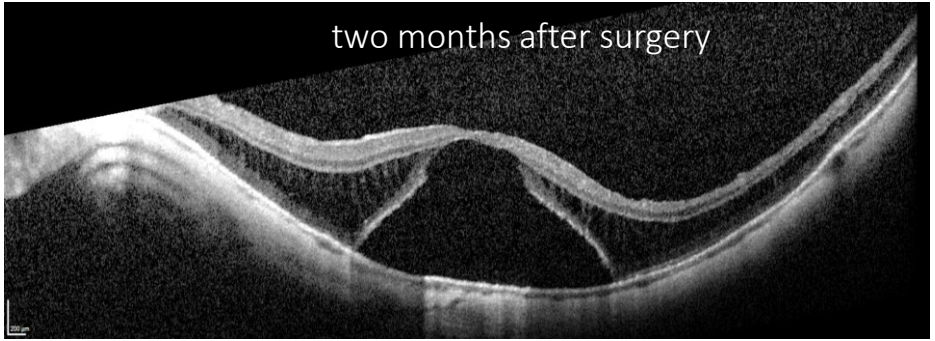


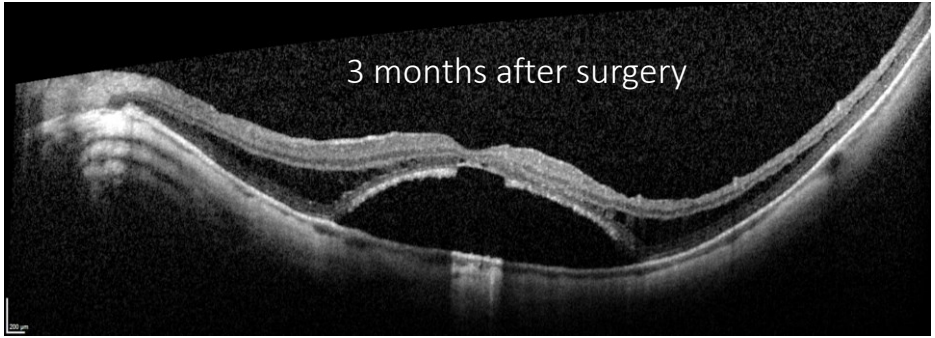
Université de Paris

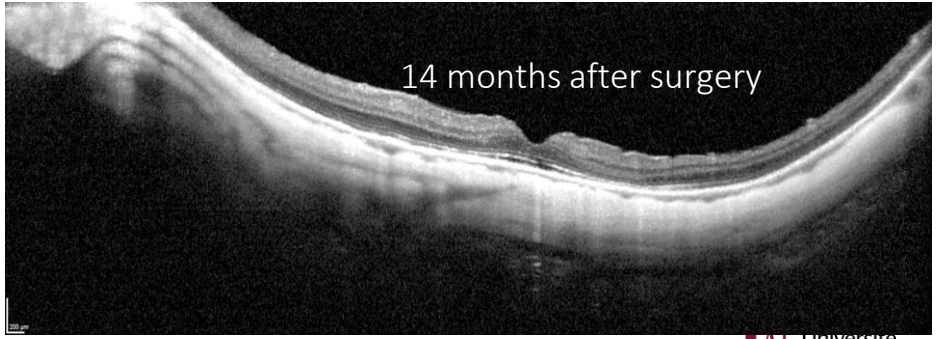
Myopic foveoschisis

- Inner schisis : median time to resorption 1month
- Outer schisis : median time to resorption 11 months

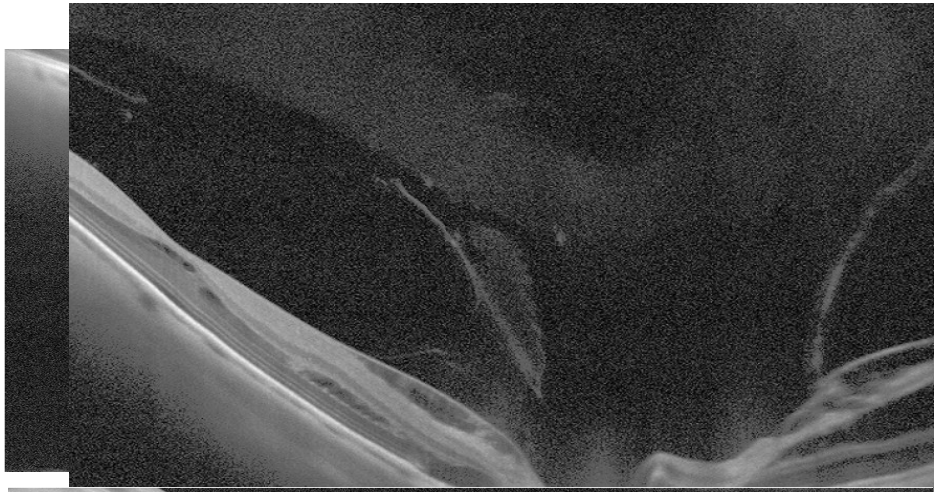


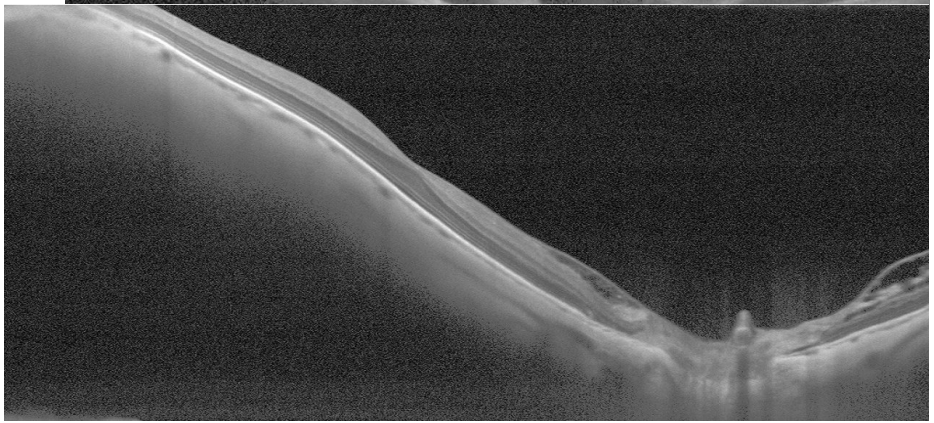


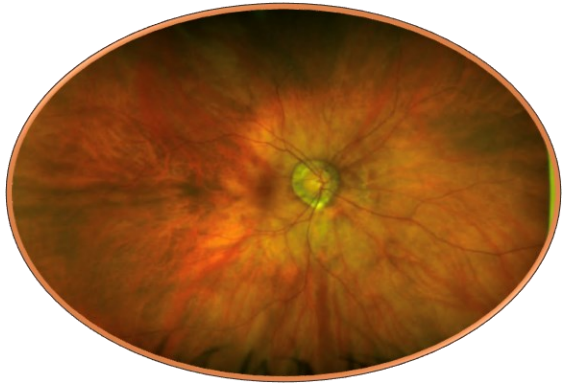


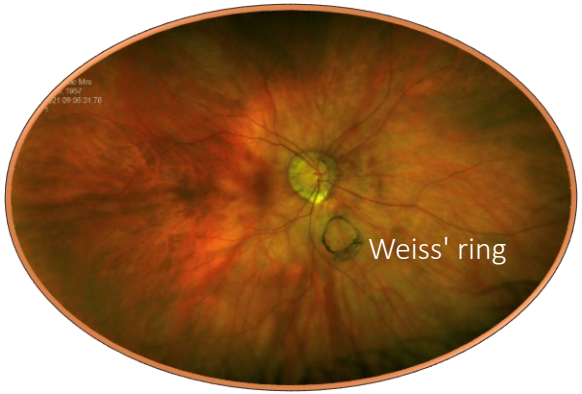


Myopic foveoschisis







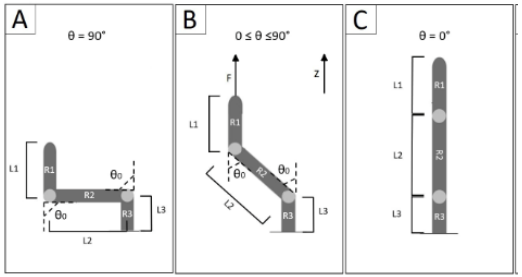


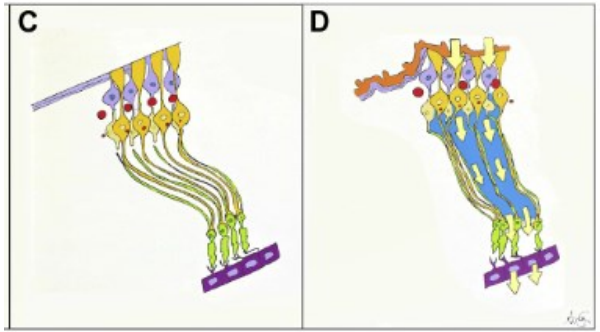
Five years later

Tractional Cystoid Maculopathy

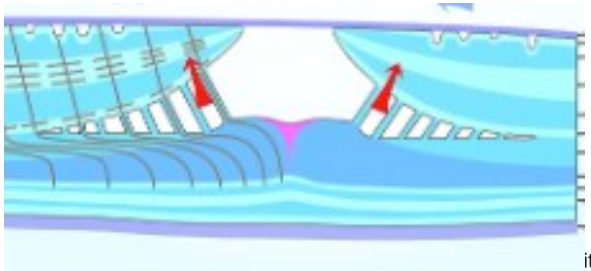
- What is the mechanism of tractional cysts induction?
  Verticalization of the Z-shaped Müller cells of the parafovea ?

Govetto A, et al. Am J Ophthalmol. 2019;212:43-56.





Govetto A et al. The role of Müller cells in tractional macular disorders: an OCT study and physical model of mechanical force transmission. Br J Oph. online July 20, 2019:



Bringmann A, et al. Müller cells and astrocytes in tractional macular disorders. Prog Retin Eye Res. Published online 2021

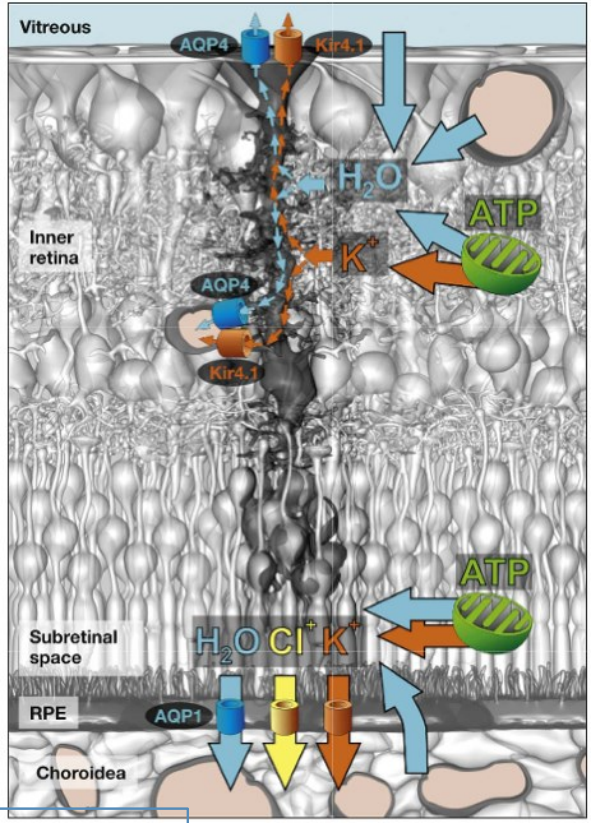
Tractional Cystoid Maculopathy

- Where does the fluid, in the cystoid cavities, come from, when there is no fluorescein leakage ?
  - from the vitreous ?
  - from the retinal cellular metabolism ?
- Are these cavities the sign of a retinal "degeneration"
  - Is there some cellular loss ?

- A mechanical dysfunction of Müller cells is probably involved
  - Reichenbach A, Bringmann A. New functions of Müller cells. *Glia*. 2013;61(5):651-678.

Müller cells and tractional cystoid maculopathy

- Several sources of H_2O, transit across the retina :
  - From the vitreous
  - From the capillaries, controlled by the BRB
  - From the retinal metabolism itself
    - *The areobic energy production results in the formation of 42 molecules of H_2O per molecule of glucose.*
- Müller cells, sense mechanical deformation of the retinal tissue, by calcium dependant mechanisms.
    - Reichenbach A, Bringmann A. New functions of Müller cells. Glia. 2013;61(5):651-678.
- Tractional forces on Müller cells may result in the dysfunction of its capacity to regulate water flux through the retina



Reichenbach A, et al. Graefes Arch Clin Exp Ophthalmol 2007;245:627–36.

Müller cells and tractional cystoid maculopathy

- What does alter intercellular adhesion?
- Why does it may take months to obtain a complete resolution of the intraretinal cystoid spaces ?
  - after relief of the epiretinal traction
    - in VMT
    - in ERM with foveoschisis
    - in myopic foveoschis

Tractional cystoid maculopathies

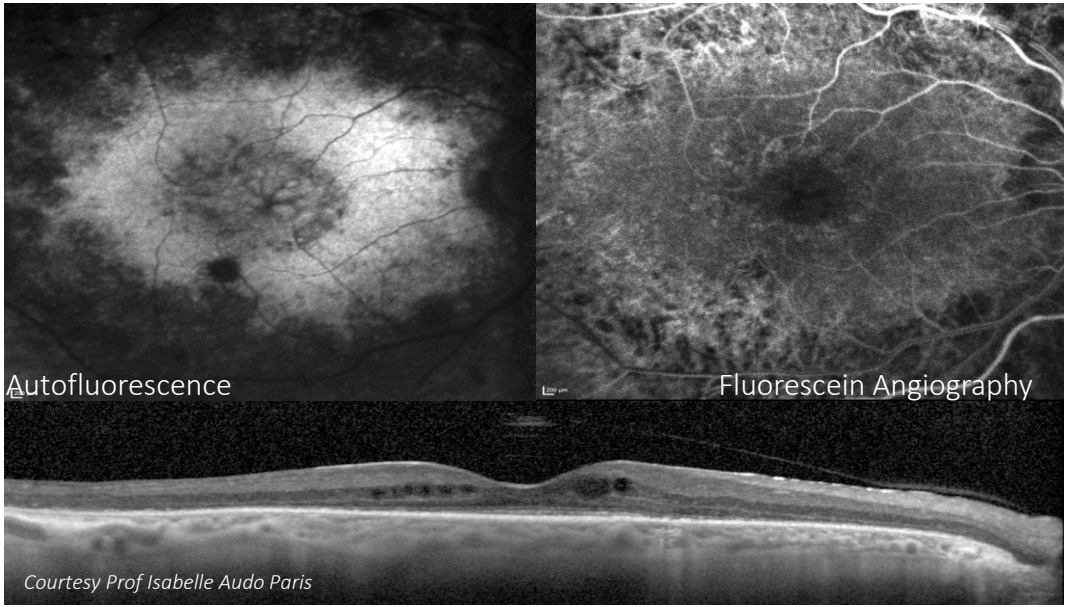
Retinal dystrophies and cystoid maculopathies

Chronic CSCR and cystoid maculopathy

Drug induced cystoid maculopathies

Miscellaneous

Retinitis Pigmentosa



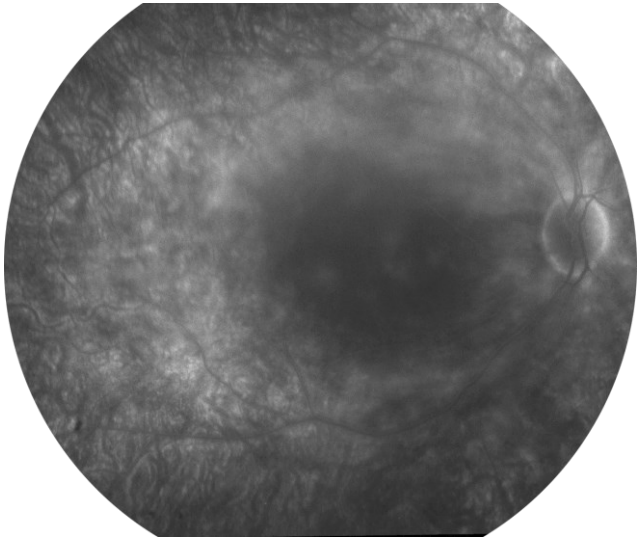
Cystoid maculopathy is present in 10 to 50% of cases [1].
More frequently associated with the CRB1 gene mutation [2]

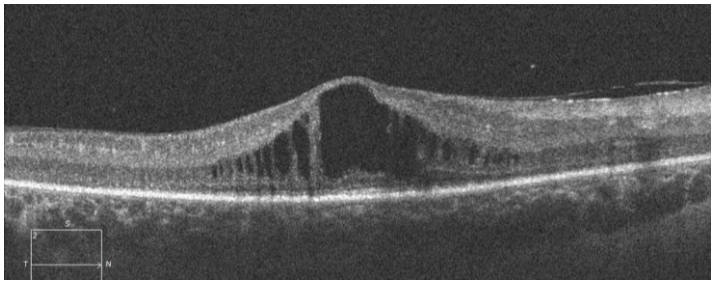
Most frequently without BRB breakdown.

The mechanism is unknown but could be due
- to an impaired fluid pumping function of the RPE
- to the presence of antiretinal antibodies, such as antienolase and anticarbonic anhydrase [3]

1. *Mrejen S, Audo I, Bonnel S, Sahel J-A. Retinitis Pigmentosa and Other Dystrophies. Dev Ophthalmol. 2017;58:191-201.*
2. *Bujakowska K, Audo I, Mohand-Saïd S, et al: CRB1 mutations in inherited reti- nal dystrophies. Hum Mutat 2012;33: 306–315.*
3. *Bakthavatchalam M, Lai FHP, Rong SS, Ng DS, Brelen ME. Treatment of cystoid macular edema secondary to retinitis pigmentosa: a systematic review. Surv Ophthalmol. 2018;63(3):329-339..*

Retinitis Pigmentosa





Oral acetazolamide should be the first-line treatment

Topical Dorzolamide , can be effective too

anti-VEGF or intravitreal corticosteroids could be considered only for patients with CME not responding to either oral or topical Carbonic Anhydrase Inhibitors. [3]

1. *Mrejen S, Audo I, Bonnel S, Sahel J-A. Retinitis Pigmentosa and Other Dystrophies. Dev Ophthalmol. 2017;58:191-201.*
2. *Bujakowska K, Audo I, Mohand-Saïd S, et al: CRB1 mutations in inherited reti- nal dystrophies. Hum Mutat 2012;33: 306–315.*
3. *Bakthavatchalam M, Lai FHP, Rong SS, Ng DS, Brelen ME. Treatment of cystoid macular edema secondary to retinitis pigmentosa: a systematic review. Surv Ophthalmol. 2018;63(3):329-339..*

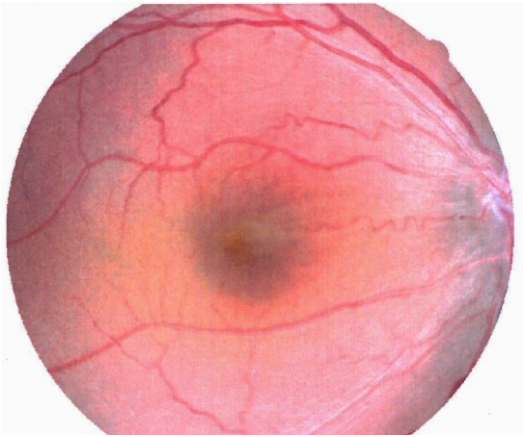
Posterior Microphthalmos, RP, foveoschisis and optic disc drusen

- Autosomic recessive hyperopia
  - Due to mutations on MFRP gene [1]
  - Associated with RP, Foveoschisis and optic disc drusen [2]

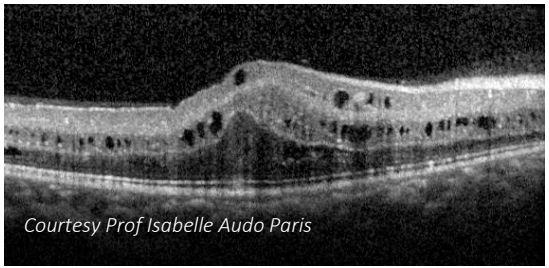
Peripheral retinal pigmentary changes in 50% of cases
Subnormal ERG rod and cones in 75% of cases
Non recordable ERG in 12% of cases
Crowded disc

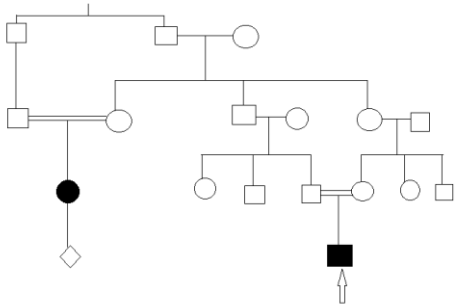
Almoallem, Sci Rep 2020 10(1): 1289

MRFP: Membrane-type Frizzled-Related Protein



10 y old boy . refraction + 16 D OU

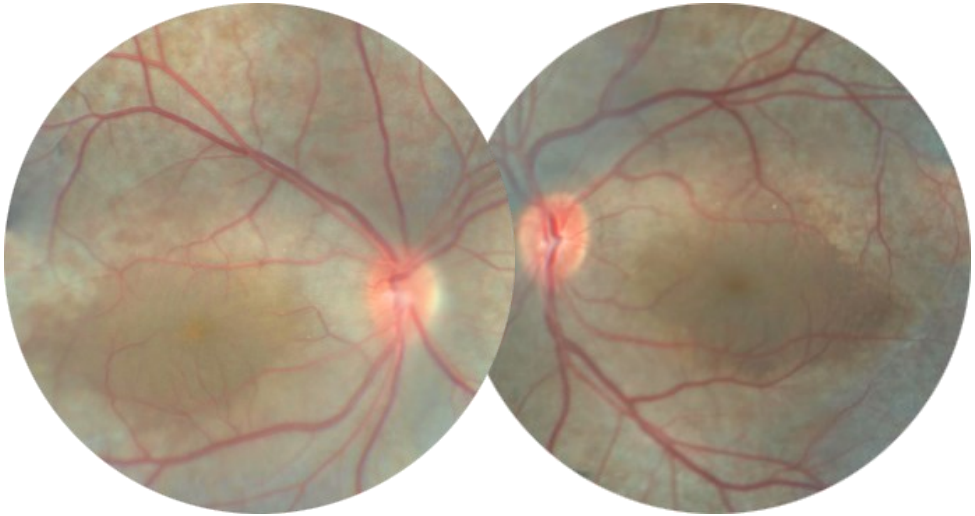




1. *Sundin, OH et al, PNAS102(27): 9553-9558.*

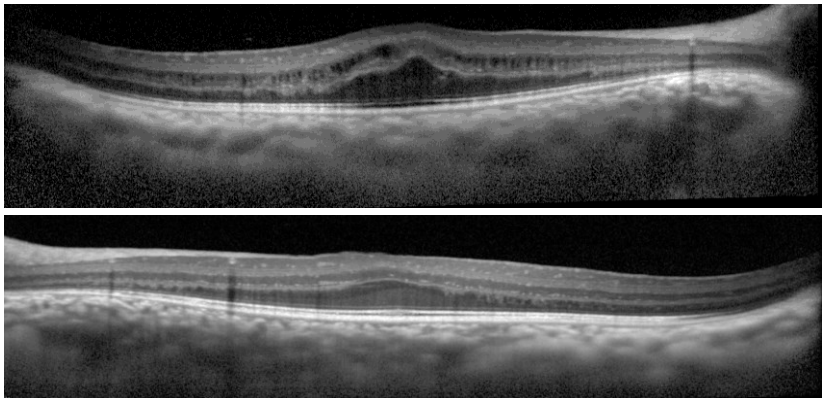
2. *Ayala-Ramirez R et al Molecular Vision 12: 1483-1489.*

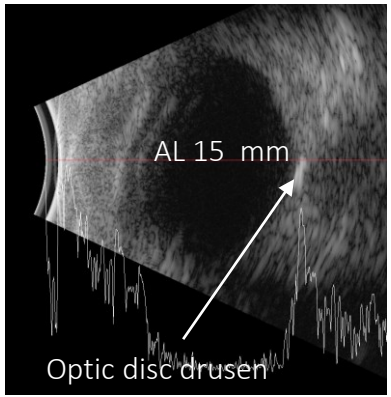
Posterior Microphthalmos, RP, foveoschisis and optic disc drusen



Recent studies have highlighted the importance of the retinal serine protease PRSS56 expressed by Müller cells, and transmembrane glycoprotein MFRP, a factor predominantly expressed in the retinal pigment epithelium (RPE), in ocular size determination. *Koli, SC et al PLoS Genet 2021. 17(3)*:

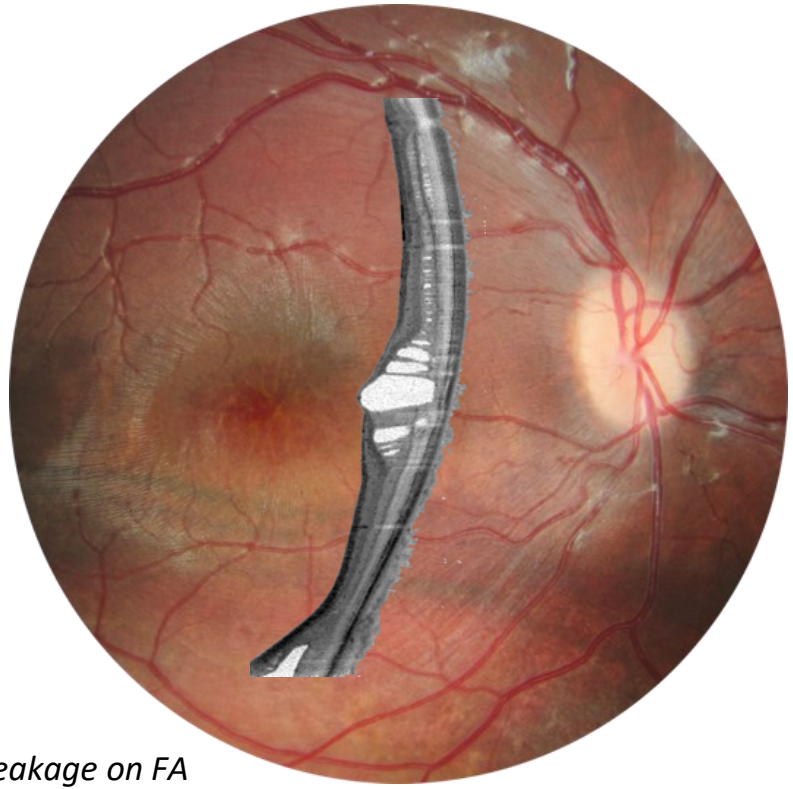
However , their role in the cystoid maculopathy remains unexplained





Cystoid maculopathy may be related or not to fluorescein leakage

X-linked retinoschisis



No leakage on FA

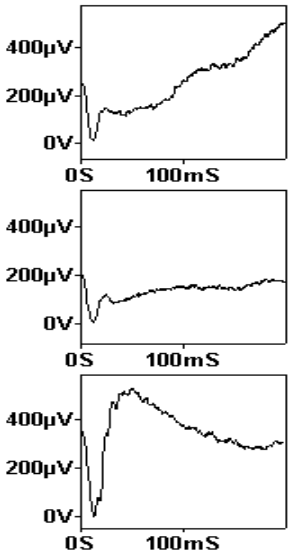
In X linked, retinoschisis is due to a mutation of RS1 gene (Xp22.2-p22.1),

Cystoid spaces develop in the OPL and INL

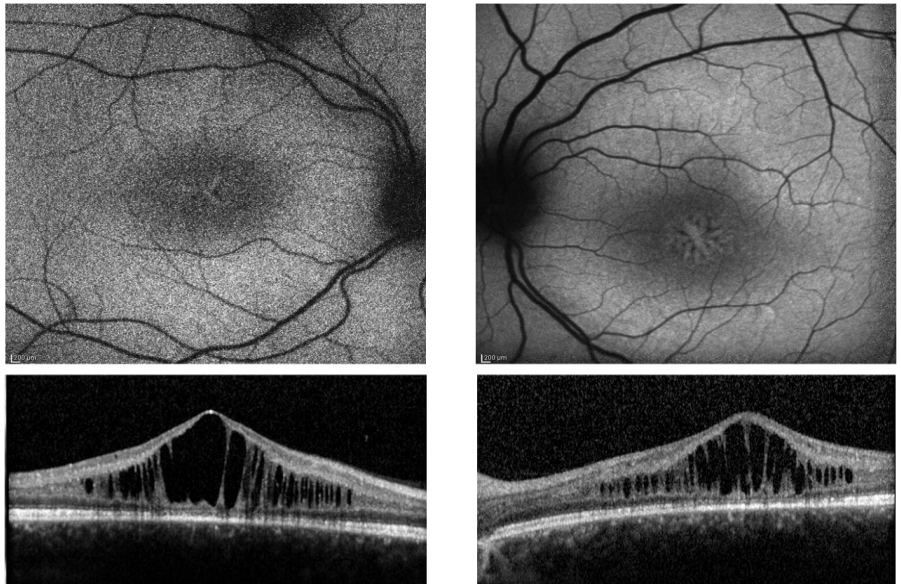
ERG typically electronegative

Acetazolamide may be be effective in flattening cystoid spaces

Dark-adapted ERG
3cd.s/m²



X-linked retinoschisis



RS1 gene therapy might be successful is applied early in the development of the disease

Vijayasarathy C, Gene Ther. 2021;32(13-14):667-681

The RS1 gene encodes RETINOSCHISIN (RS1) a secreted protein that has a crucial role in maintaining cellular organization of the retina.

Retinal photoreceptors and bipolar cells express and secrete RS1 into the extracellular space.

The XLRS has been attributed to RS1 loss of function as a cell adhesion protein.

Molday. Prog Retin Eye Res. 2012;31(3):195-212.

However , no in vivo evidence exists that RS1 can link two neighboring cells.

Another possible role of retinoschisin may be to help regulate the fluid balance between the intracellular and extracellular environment particularly within the photoreceptor and bipolar cell layers

Stellate Nonhereditary Idiopathic Foveomacular Retinoschisis . SNIFR

Stellate Nonhereditary Idiopathic Foveomacular Retinoschisis

Michael D. Ober, MD,[1] K. Bailey Freund, MD,[2] Manthan Shah, MD,[3] Shareef Ahmed, MD,[3] Tamer H. Mahmoud, MD, PhD,[4] Thomas M. Aaberg, Jr., MD,[5] David N. Zacks, MD,[6] Hua Gao, MD,[3] Krishna Mukkamala, MD,[2] Uday Desai, MD,[3] Kirk H. Packo, MD,[7] Lawrence A. Yannuzzi, MD[2]

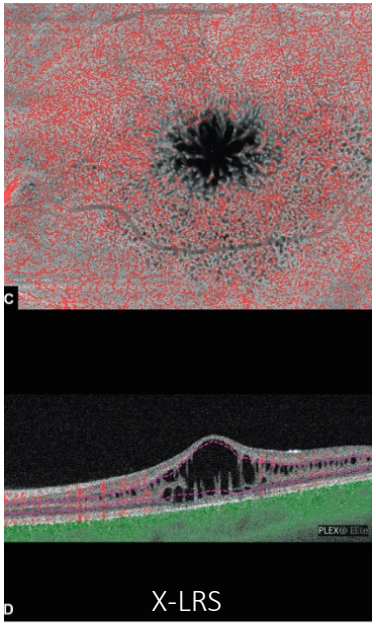
Ophthalmology. 2014;121(7):1406-1413.

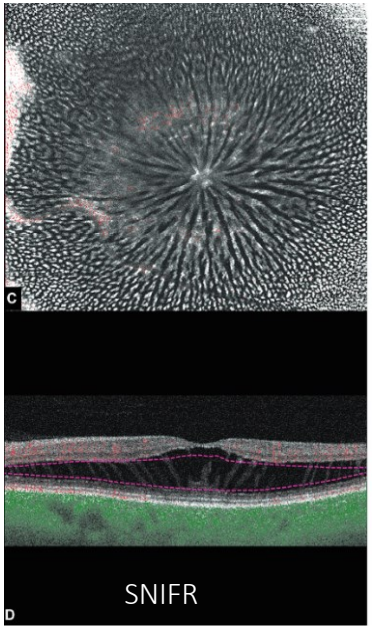
17 patients (16 F, 1 M) with foveoschisis , bilateral in 5
No familial history, no mutation on RS 1 gene

A proposed mechanism influencing structural patterns in X-linked retinoschisis and stellate nonhereditary idiopathic foveomacular retinoschisis

Serena Fragiotta[1,2,3,4] · Belinda C. S. Leong[1,2,3] · Talia R. Kaden[1,2,3,5] · Sherry J. Bass[6] · Jerome Sherman[6] · Lawrence A. Yannuzzi[1,2,3,5] · K. Bailey Freund[1,2,3,5]

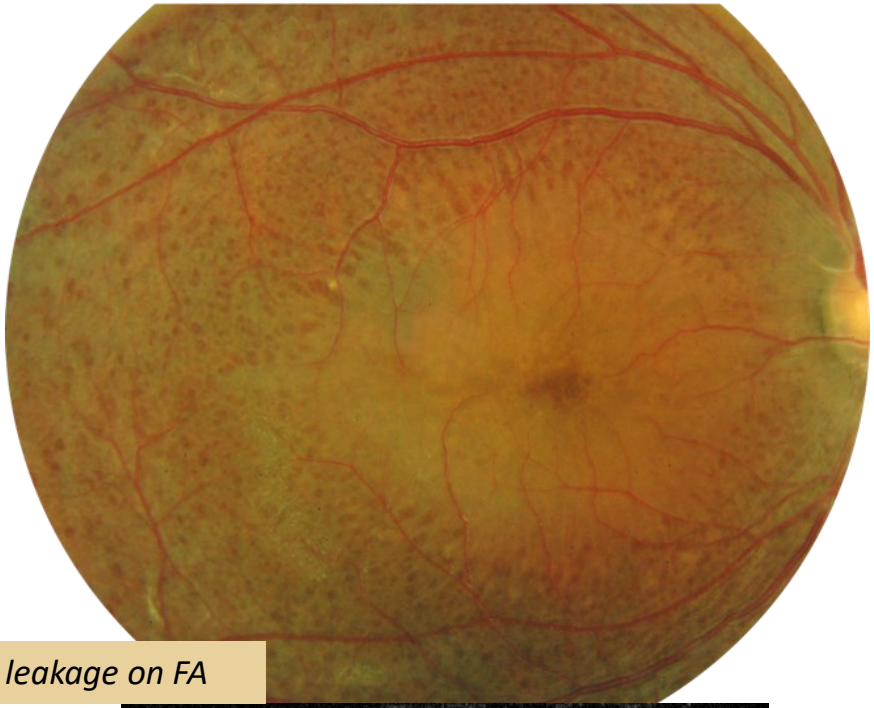
Fragiotta, S., B. Eye (Lond) 33(5): 724-728.



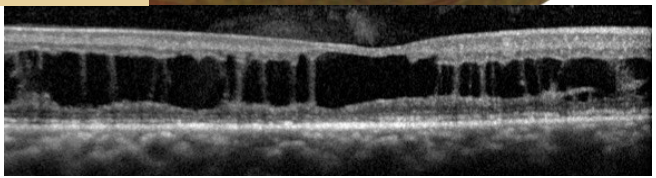


in SNIFR : cystoid spaces in the ONL
in X-LRS : cystoid spaces in both OPL and INL

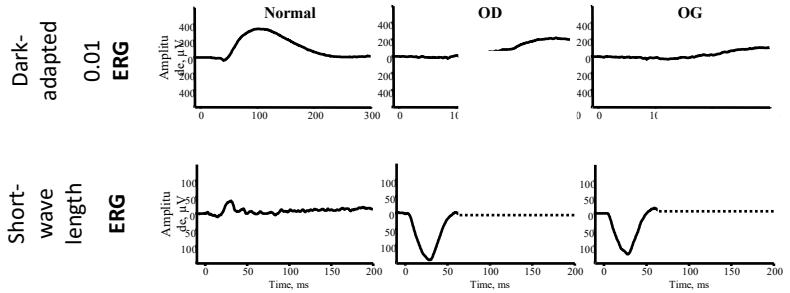
Enhanced S-cone syndrome /Goldman-Favre



No leakage on FA



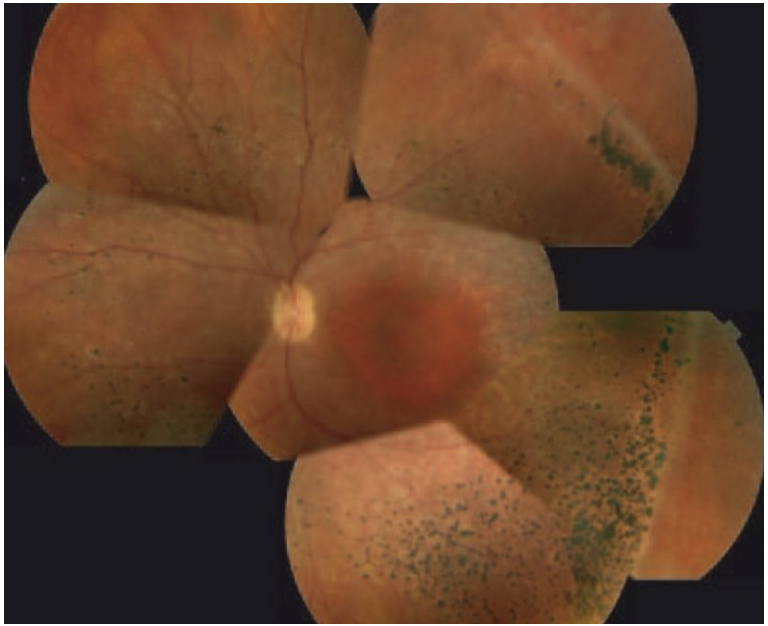
Enhanced S-cone Syndrome (ESCS) is due to an Autosomal Recessive Mutation on NR2E3 gene (15q23)
resulting in an abnormal differentiation of rods and an excess of S-cones .

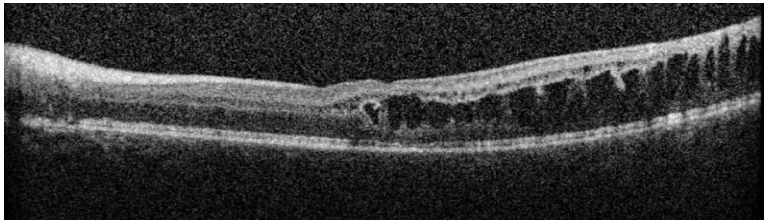


The ERG shows the loss of rod function and an high-amplitude response of S-cones to short wavelength

Audo I, Michaelides M, Robson AG, et al.
Phenotypic Variation in Enhanced S-cone Syndrome.
IOVS. 2008;49(5):2082–12.

Enhanced S-cone syndrome /Goldman-Favre





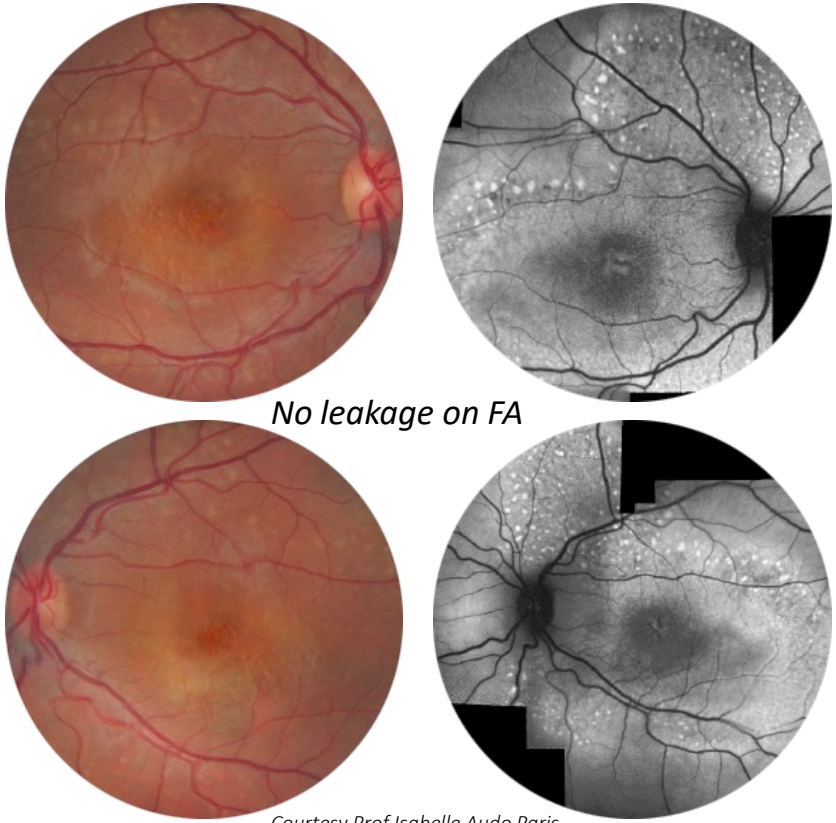
In a series of 56 patients, 13/18 with severe visual outcomes showed moderate to advanced foveomacular schisis.

The cause of cystoid spaces formation is uknown

Carvalho ER de, Ophthalmol Retin. 2021;5(2):195-214.

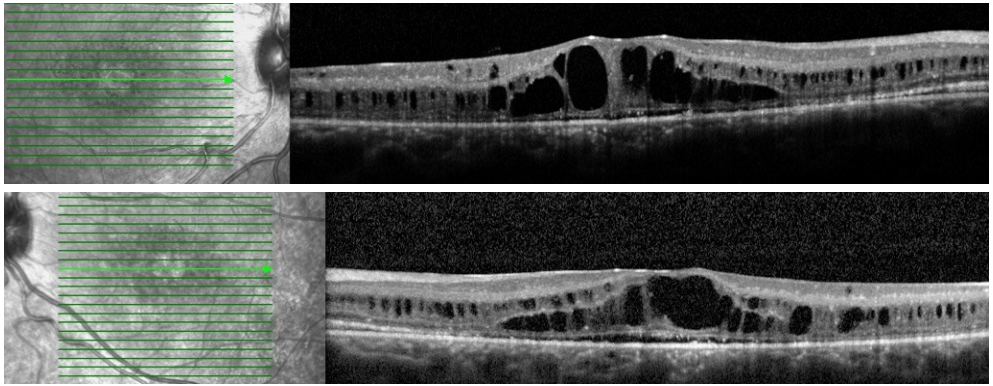
Acetazolamide has been effective in flattening cystoid spaces in some cases , without visual benefit

Recessive Autosomal Bestrophinopathy



No leakage on FA

Courtesy Prof Isabelle Audo Paris



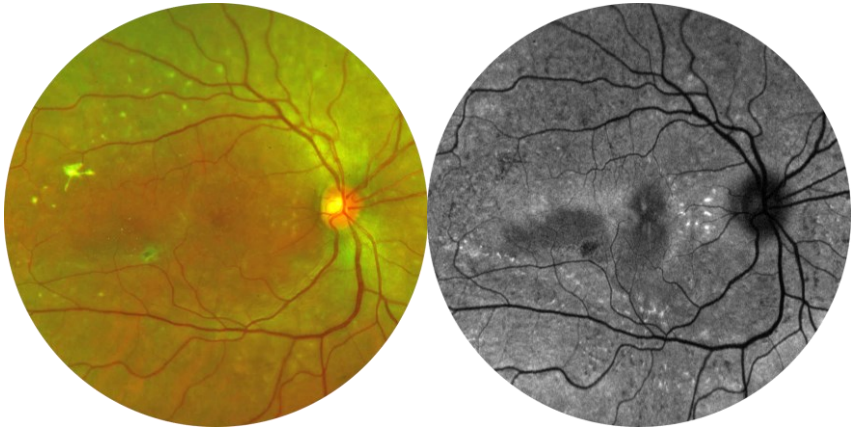
Recessive Autosomal Bestrophinopathy is due to mutations on BEST1 encoding a defective Bestrophine1 protein. These mutations give a broad spectrum of clinical presentations .

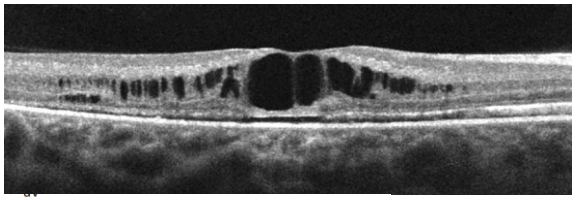
Best1 is predominantly expressed in the retinal pigment epithelium (RPE)

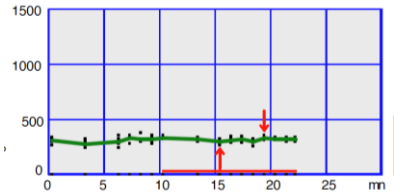
Best1 functions are to regulate calcium homeostasis and mediate anion transport in the RPE.

1. *Toto L, Boon CJF, Di Antonio L, et al. RETINA. 2016;36(8):1586-1595.*
2. *Guziewicz KE, Sinha D, Gómez NM, et al. Prog Retin Eye Res. 2017;58:70-88.*

Recessive Autosomal Bestrophinopathy







Hôpital Lariboisière

EOG is usually flat

More than one half of the eyes demonstrate cystoid maculopathy at presentation, which remains relatively stable over time.[1]

Cystoid spaces are not associated with focal leakage on FA[2]

The pathogenesis of cystoid maculopathy is less understood than this of the macular neuroretinal detachment.
Anomalies of RPE apical microvilli and the IPM weaken the adherence between RPE and PR [3]

Cystoid formation and fluid retention within the retina could be due a defective function of Best1 which normally both regulate calcium homeostasis and mediate anion transport in the RPE[4]

1.Casalino G, et al. Ophthalmology. Published online 2020.

2.Dijk EHC van, et al. Prog Retin Eye Res. Published online 2021:.

3.Guziewicz KE, et al. Prog Retin Eye Res. 2017;58:70-88.

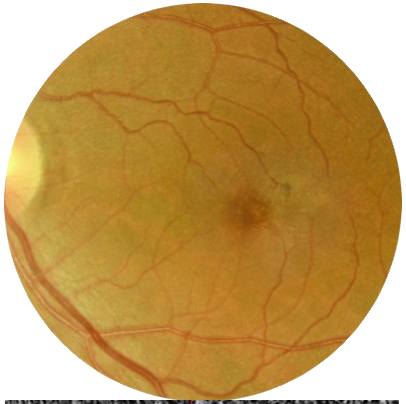
4.Johnson AA et al . Prog Retin Eye Res. 2017;58:45-69.

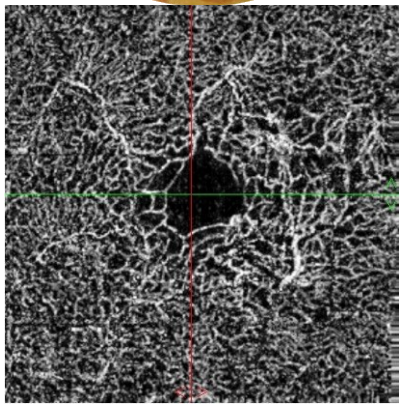
Other retinal dystrophies with cystoid maculopathy

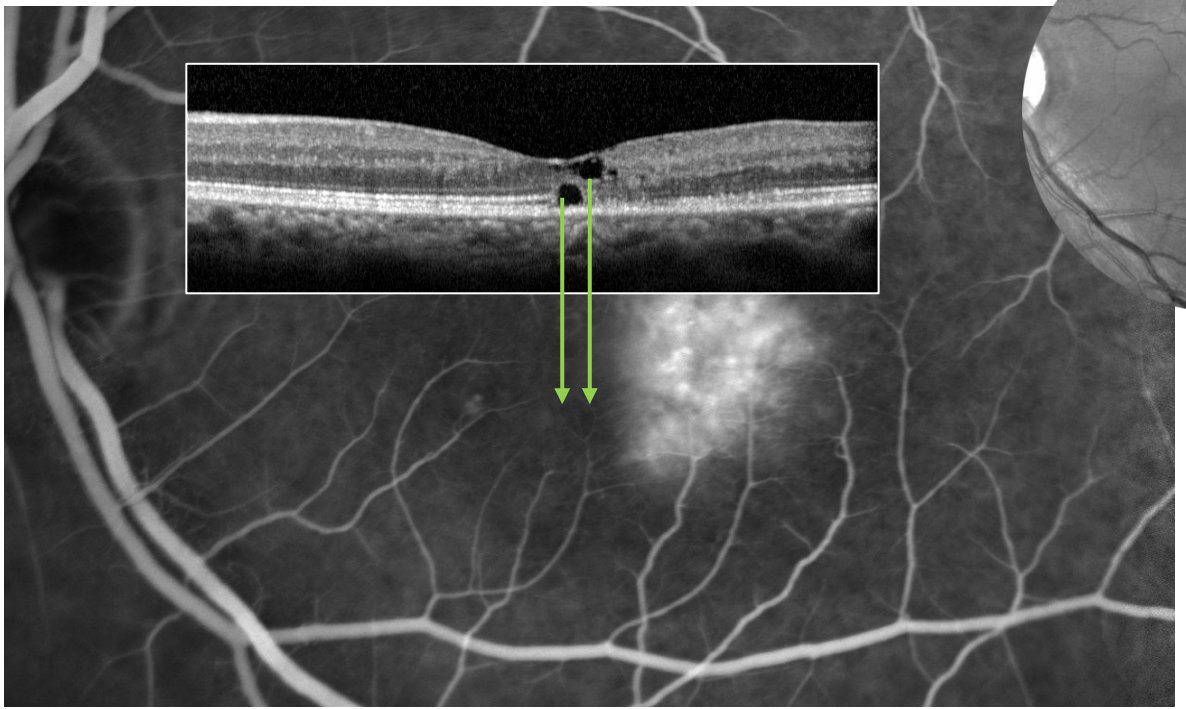
- Rare occurrences of cystoid maculopathy
  - Bietti crystalline dystrophy
    - *fluorescein leakage*
      - *Saatci, A. O., H. C. Doruk and A. Yaman (2014). "Cystoid Macular Edema in Bietti's Crystalline Retinopathy." Case Rep Ophthalmol Med 2014: 964892.*
  - Dominant Cystoid macular dystrophy
    - *Pinckers, A., A. F. Deutman and J. G. Notting (1976). Acta Ophthalmol 54(5): 579-590.*
    - *Saksens, N.T., van Huet, R.A., van Lith-Verhoeven, J.J., den Hollander, A.I., Hoyng, C.B., Boon, C.J., 2015. Dominant cystoid macular dystrophy. Ophthalmology 122, 180-191 .*
  - Gyrate atrophy
    - *Goel, N., P. Jain, S. Arora and B. Ghosh (2015). "Gyrate atrophy of the choroid and retina with cystoid macular edema and unilateral optic disc drusen." J Pediatr Ophthalmol Strabismus 52(1): 64.*
  - Müller Cell Sheen Dystrophy
    - *Renner, A.B., Radeck, V., Kellner, U., Jagle, H., Helbig, H., 2014. Ten-year follow-up of two unrelated patients with Muller cell sheen dystrophy and first report of successful vitrectomy. Doc Ophthalmol 129, 191-202.*
  - Cohen syndrome
    - *Gabrielle, P.-H., Faivre, L., Audo, I., Zanlonghi, X., Dollfus, H., Thiadens, A.A.H.J., Zeitz, C., Mancini, G.M.S., Perdomo, Y., Mohand-Saïd, S., Lizé, E., Lhussiez, V., Nandrot, E.F., Acar, N., Creuzot-Garcher, C., Sahel, J.-A., Ansar, M., Thauvin-Robinet, C., Duplomb, L., Costa, R.D., 2021. Cystoid maculopathy is a frequent feature of Cohen syndrome-associated retinopathy. Scientific Reports 11,*

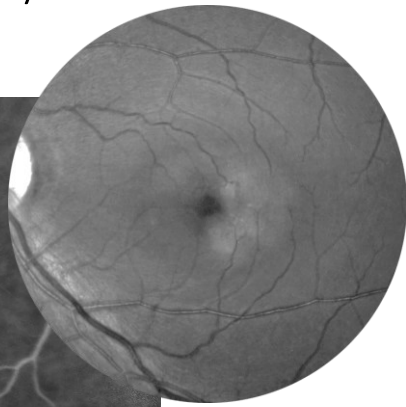
MacTel 2, cystoid cavities without dye pooling

- Despite leakage from telangiectasia, the cystoid cavities do not fill with dye

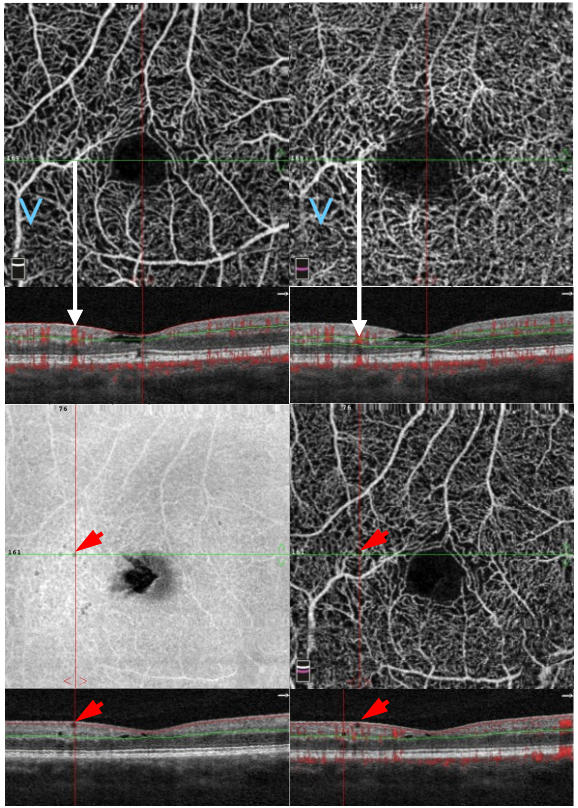


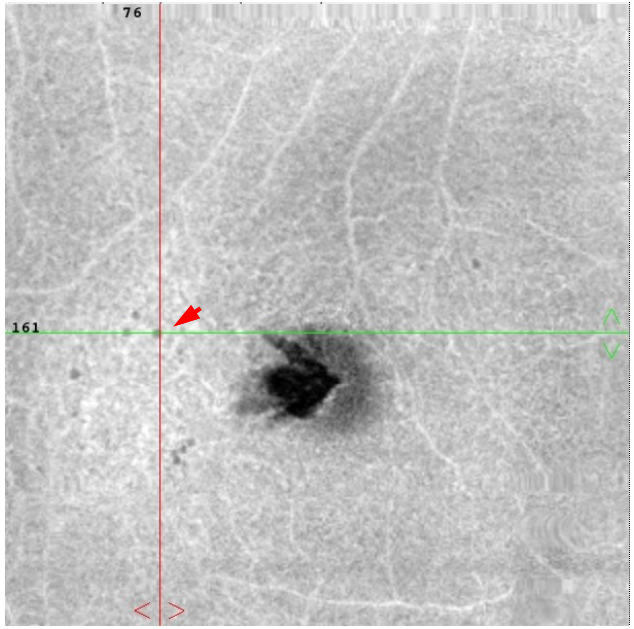






Mactel 2: microcysts





Gaudric A, Krivosic V. Optical coherence tomography angiography in macular telangiectasia type 2 , in OCT Angiography
DR Chow, PR Chaves de Oliveira ed , 2018, Thieme NY

- Microcysts are located in the MacTel area
- in the INL and the GCL
- inside and outside the area of fluorescein leakage
- They do not give any signal in FA

Okada M, Egan CA, Heeren TFC, Tufail A, Fruttiger M, Maloca PM. Macular telangiectasia type 2: Quantitative Analysis of a Novel Phenotype and Implications for the Pathobiology of the Disease. RETINA. 2018;38 Suppl 1:

Tractional cystoid maculopathies

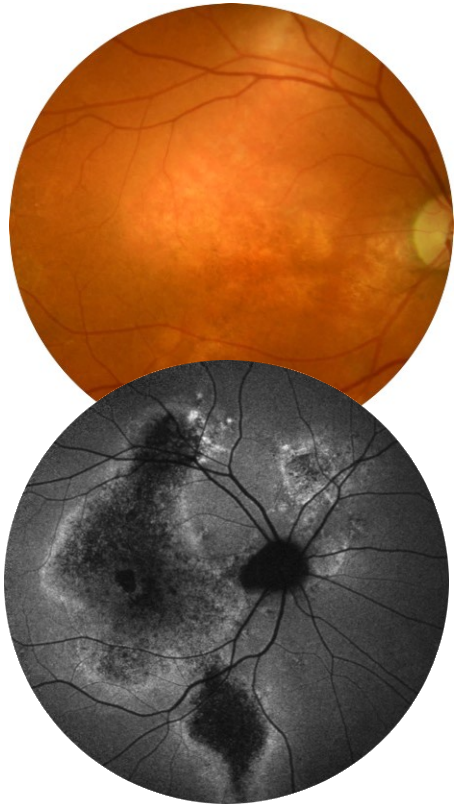
Retinal dystrophies and cystoid maculopathies

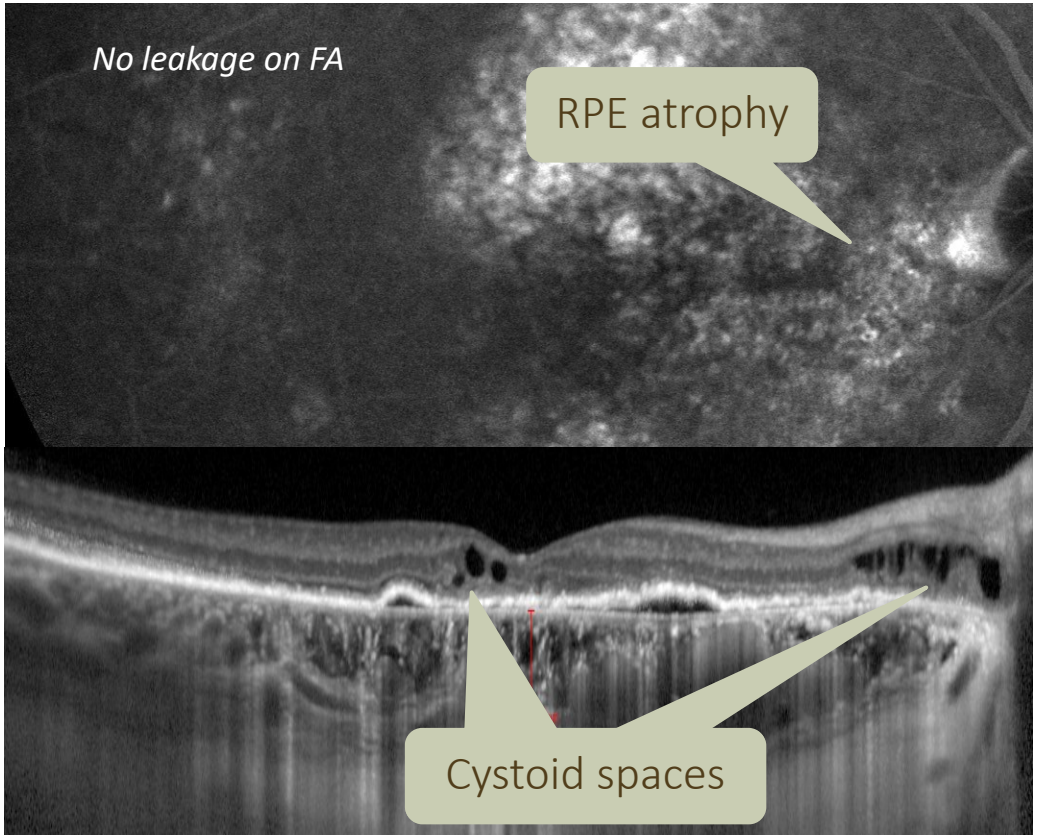
Chronic CSCR and cystoid maculopathy

Drug induced cystoid maculopathies

Miscellaneous

Chronic CSCR and cystoid cavities



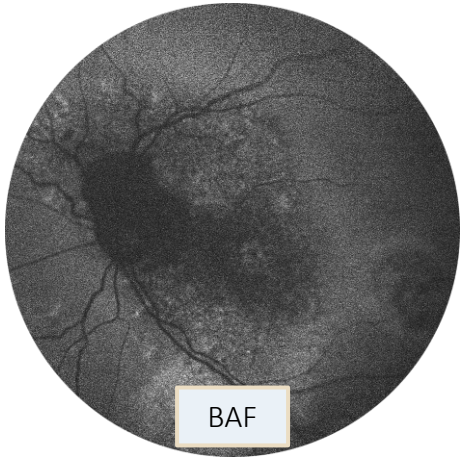


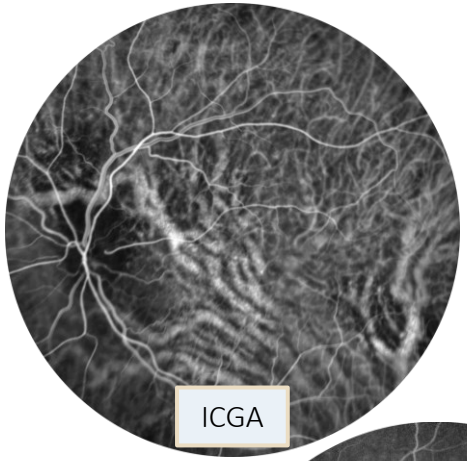
Yannuzzi, et al 1984. Ophthalmology 91, 1554-1572

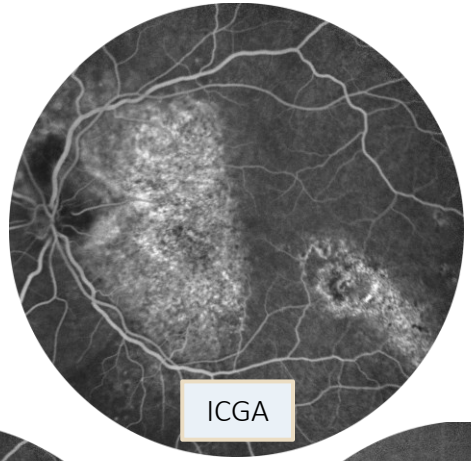
Mrejen S et al . Ophthalmology. 2019;126(4):576-588.

Université de Paris

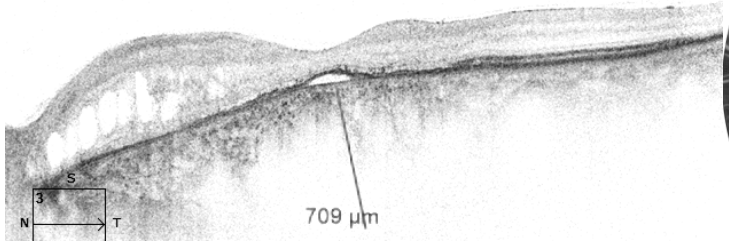
Chronic CSCR and cystoid cavities

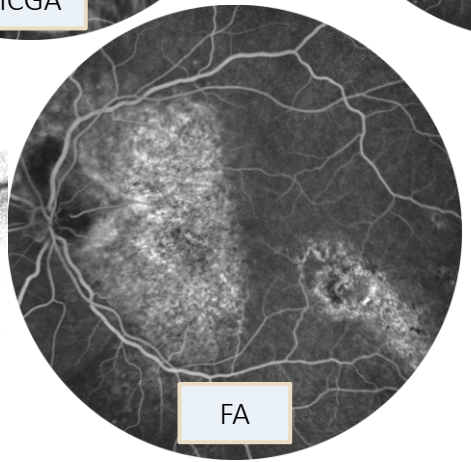


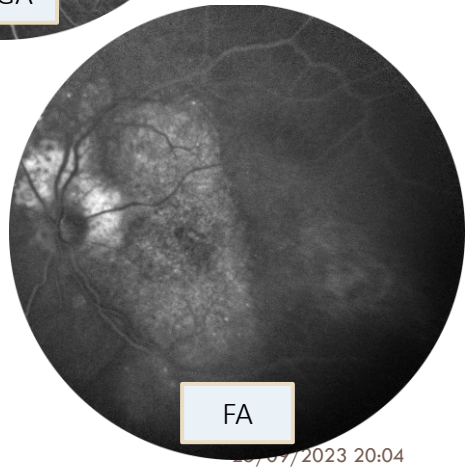




30 min

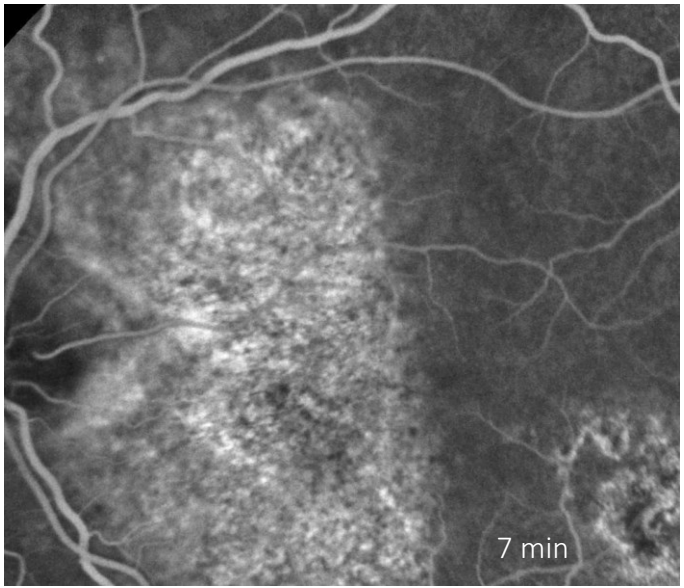


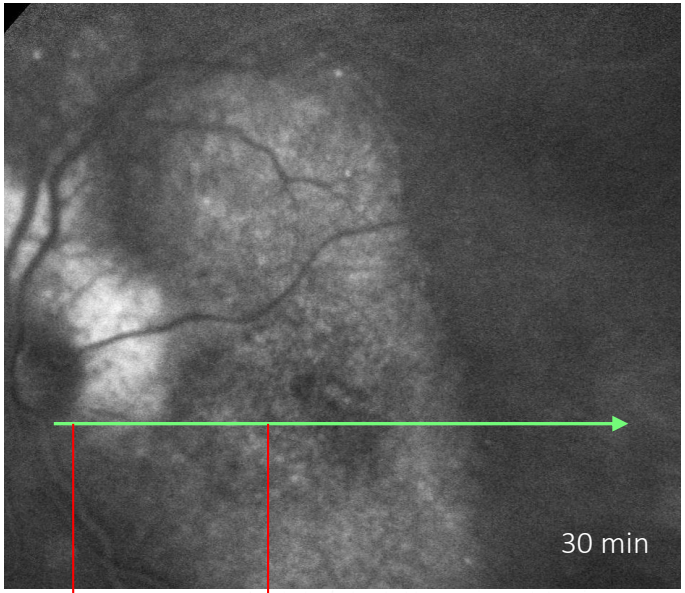


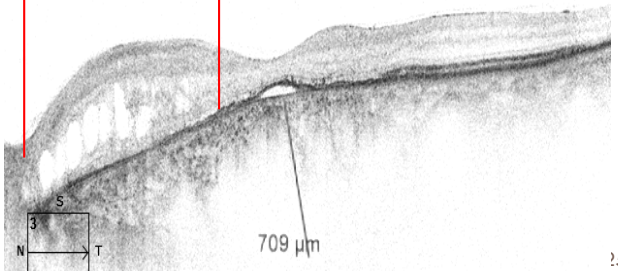


30 min

Chronic CSCR and cystoid cavities



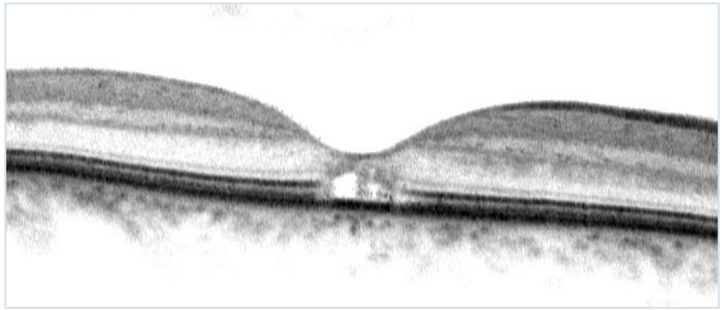


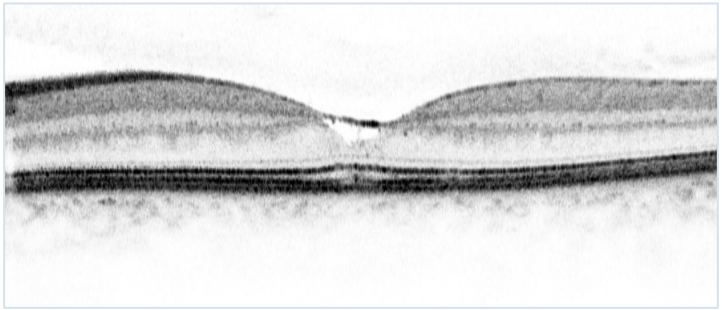


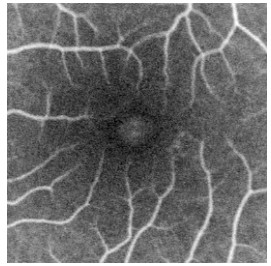
Drug induced cystoid maculopathies

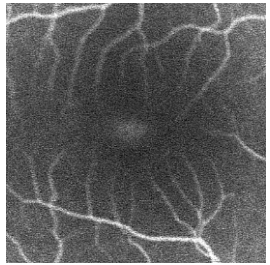
Drug induced cystoid maculopathy

- Tamoxifen retinopathy
  - high doses of tamoxifen have given CME with Fluorescein leakage
  - low doses may give inner and outer foveal cavitations
  - without any fluorescein leakage
    - resembling Mactel 2 lesions , with sometimes crystals in the inner retina







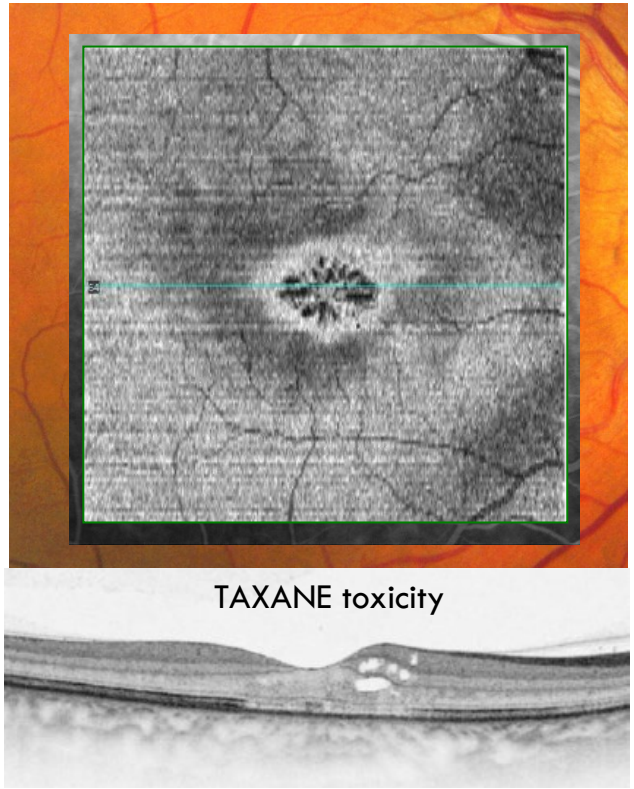


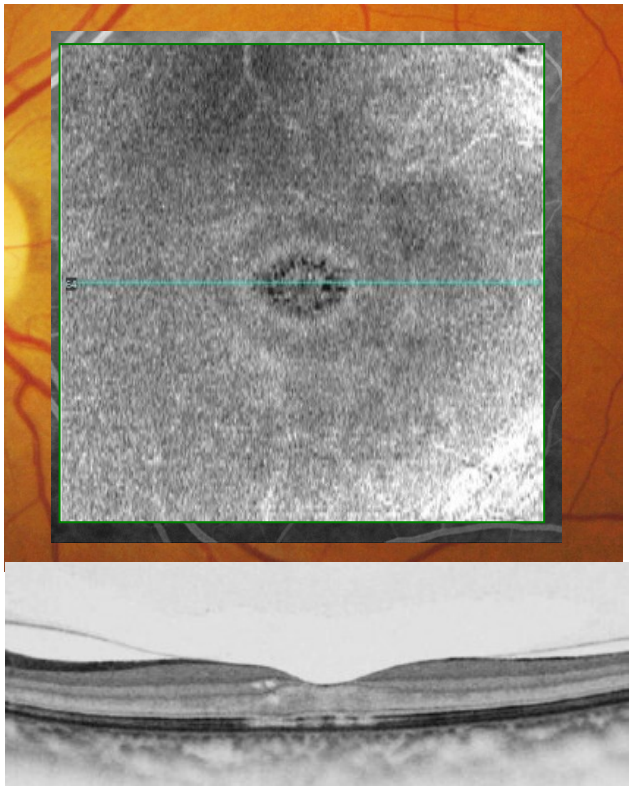
- Toxicity for Müller cells is suspected

Gualino V, Cohen SY, Delyfer MN, Sahel JA, Gaudric A. Optical coherence tomography findings in tamoxifen retinopathy. Am J Ophthalmol 2005;140(4):757–758.

Doshi RR, Fortun JA, Kim BT, Dubovy SR, Rosenfeld PJ. Pseudocystic Foveal Cavitation in Tamoxifen Retinopathy. Am J Ophthalmol. 2014;157(6):1291-1298.e3.

Drug induced cystoid maculopathy





Review by Makri OE, et al, Drug-Induced Macular Edema. Drugs. 2013;73(8):789-802.

Courtesy Dr S Nghiem-Buffet

Other drugs

- Nicotinic Acid
  - *Domanico, D., C. Carnevale, S. Fragiotta, F. Verboschi, S. Altimari and E. M. Vingolo (2013). "Cystoid macular edema induced by low doses of nicotinic Acid." Case Rep Ophthalmol Med 2013: 713061.*
- *Latanoprost*
- *Epinephrin*
- *Fingolimod*
  - *gives CME with fluorescein leakage*
    - *Afshar, A. R., J. K. Fernandes, R. D. Patel, S. M. Ksiazek, V. S. Sheth, A. T. Reder and S. M. Hariprasad (2013). "Cystoid macular edema associated with fingolimod use for multiple sclerosis." JAMA Ophthalmol 131(1): 103-107.*

Tractional cystoid maculopathies

Retinal dystrophies and cystoid maculopathies

Chronic CSCR and cystoid maculopathy

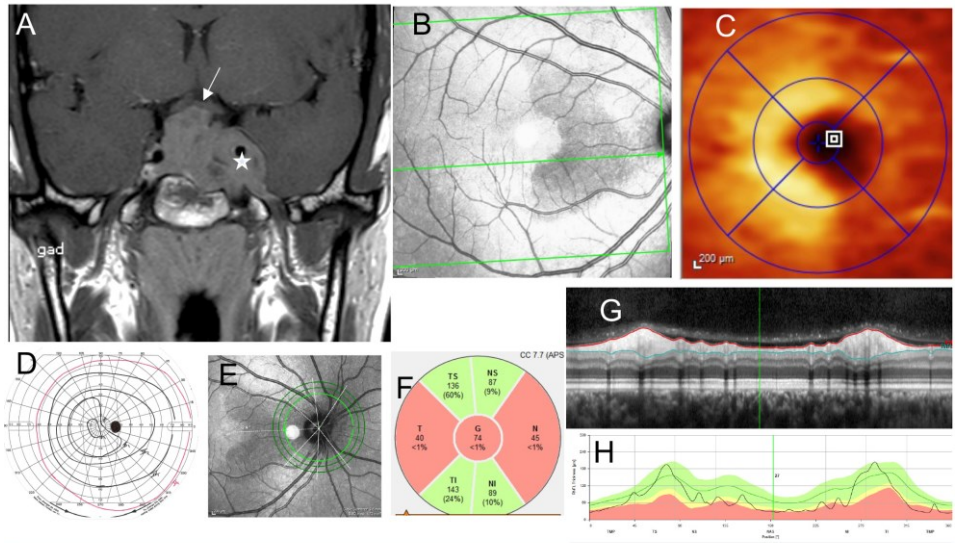
Drug induced cystoid maculopathies

Miscellaneous

Other causes of non vasogenic Cystoid Maculopathies

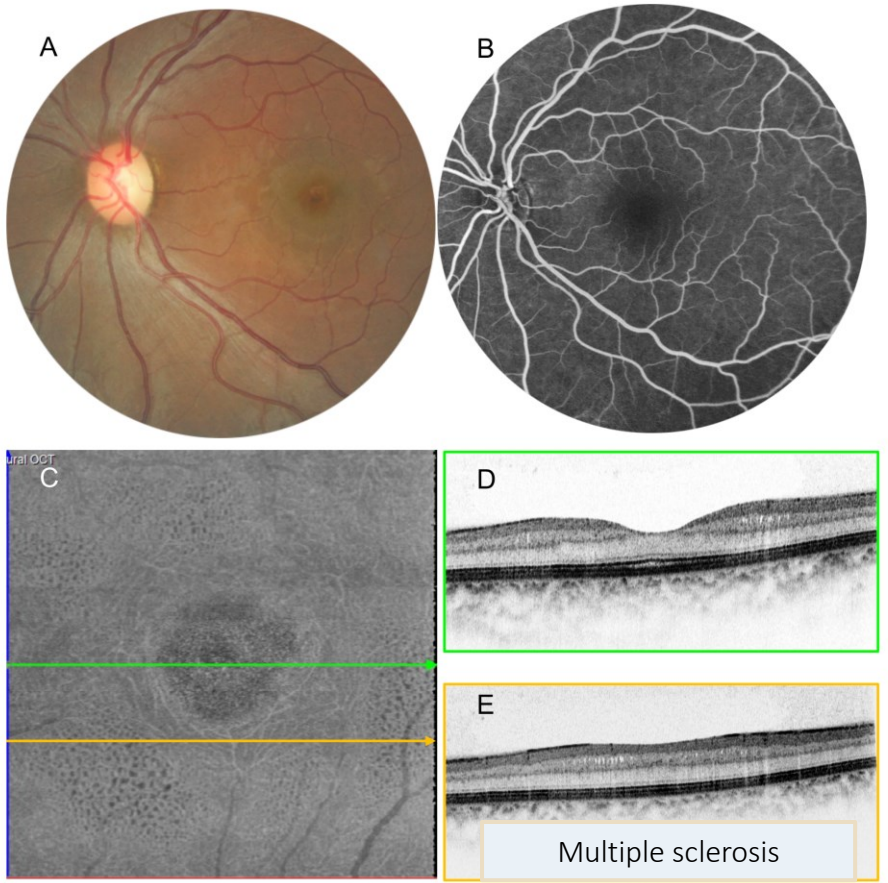
- Optic nerve pit
- Optic atrophy
  - *Abegg, M., M. Dysli, S. Wolf, J. Kowal, P. Dufour and M. Zinkernagel (2014). "Microcystic Macular Edema Retrograde Maculopathy Caused by Optic Neuropathy." Ophthalmology 121(1): 142-149.*
- Glaucoma
- Cancer Associated Retinopathy
  - Moyer, K., A. DeWilde and C. Law (2014). "Cystoid macular edema from cancer-associated retinopathy." Optom Vis Sci 91(4 Suppl 1): S66-70.

Optic neuropathies



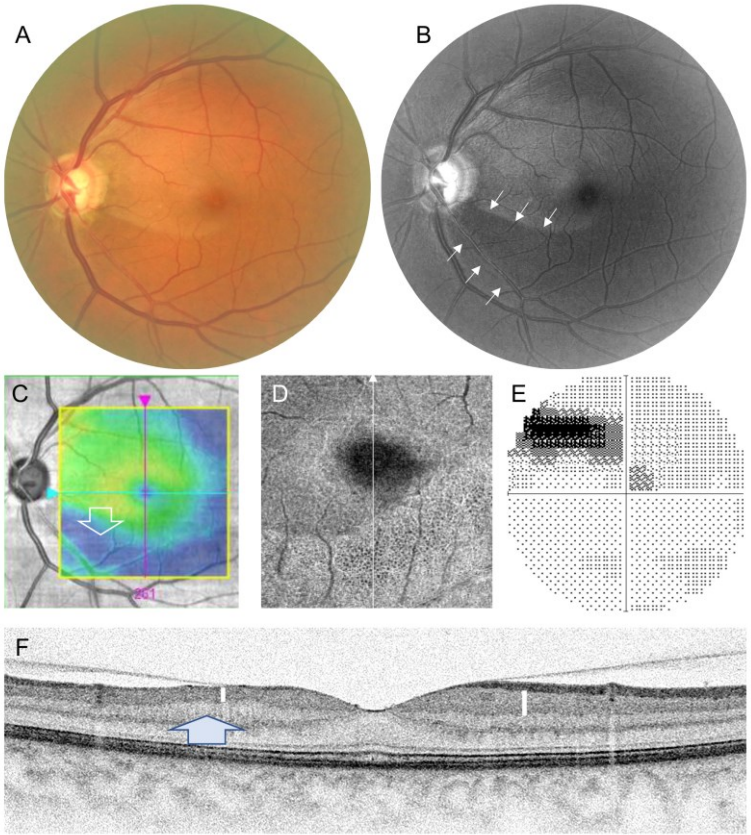
Chiasmatic compression

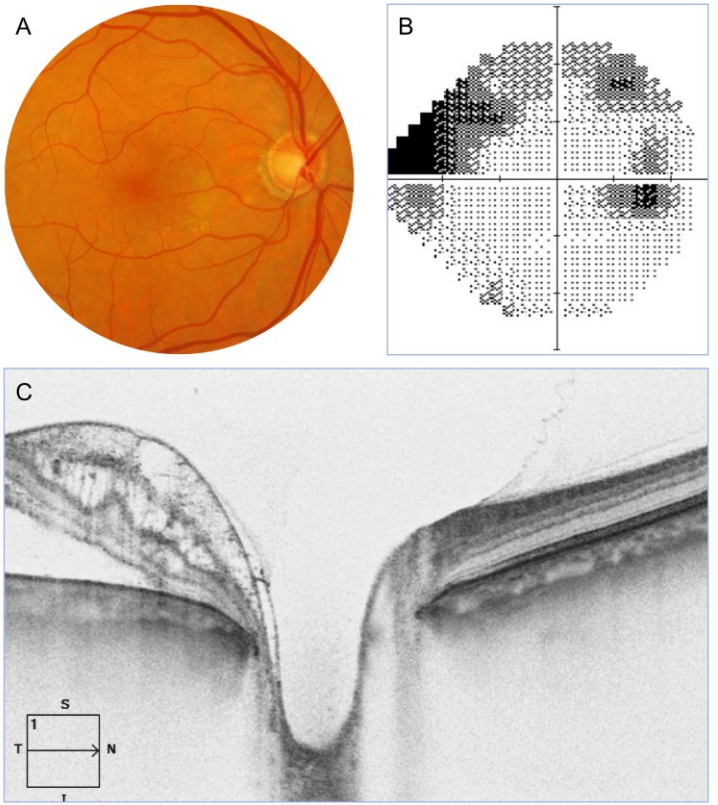
Courtesy Dr Catherine Vignal



Multiple sclerosis

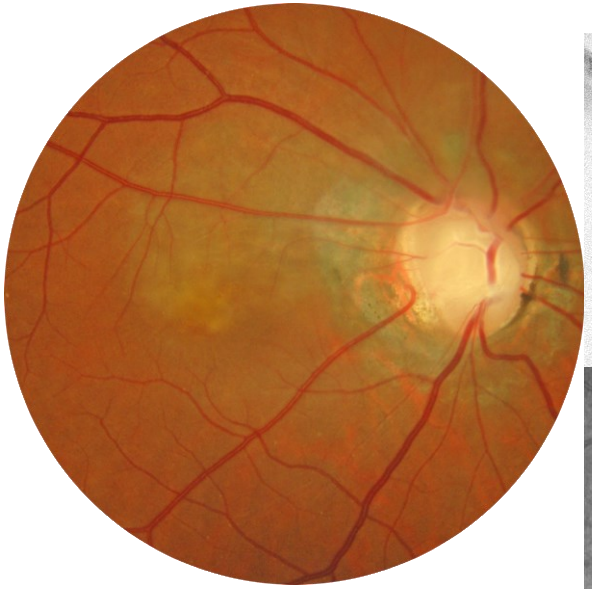
Primary Open Angle Glaucoma

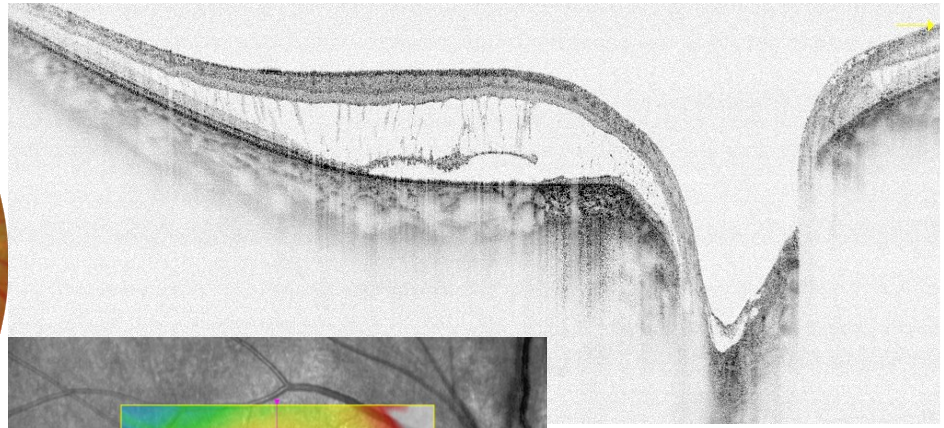


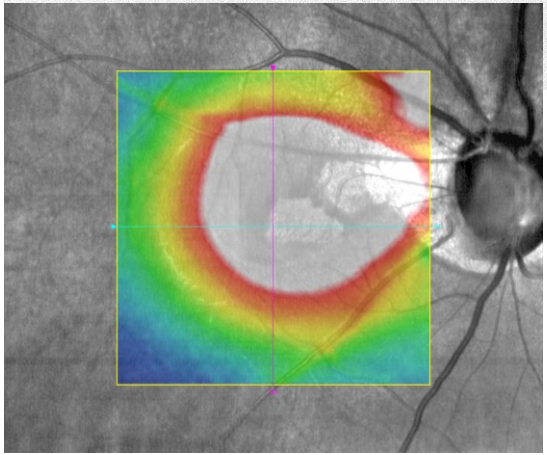


Courtesy Dr Catherine Vignal

Retinoschisis by optic disc pit







No leakage on FA

Maculopathies cystoides non-vasogéniques

Mechanical (tractional)	
	Vitreomacular traction
	Macular hole
	Epiretinal membrane
	Stellate non-hereditary idiopathic foveomacular retinoschisis
	Myopic foveoschisis
Inherited Retinal dystrophies	
	X-linked retinoschisis
	Enhanced S-cone Syndrome
	Bestrophinopathies
	Retinitis pigmentosa
	CRB1 associated retinal dystrophies
	Cohen Syndrome
	MFRP-related posterior microphthalmos, retinitis pigmentosa, optic nerve head drusen and foveoschisis
	Choroideremia
	Gyrate atrophy
	Crystalline dystrophies
Macular Telangiectasia Type 2	

Acquired RPE dysfunction	
	Central serous Chorioretinopathy
	Cancer associated retinopathy
	Bilateral diffuse uveal melanocytic proliferation
	Paraneoplastic vitelliform maculopathy
Non-exudative Age Macular degeneration	
Optic nerve diseases	
	Chiasmatic compression
	Multiple sclerosis
	Neuromyelitis optica
	Wolfram syndrome
	Leber hereditary optic neuropathy
	Autosomal dominant optic atrophy
	Primary open angle glaucoma
	Optic nerve drusen
	Optic pit maculopathy
Drug toxicity	
	Tamoxifen
	Taxane
	Nicotinic acid

In summary (1),

- In most cases CME is due to leakage from retinal capillaries or choroid through the RPE, and cavities fill with fluorescein.
- However, OCT has revealed many other Cystoid Maculopathies
  - in which there is no blood retinal barrier breakdown (no fluorescein leakage)
  - but which appear similar to CME on OCT
- Cystoid maculopathies may be
  - Tractional (ERM, VMT, Myopic foveoschisis, etc…)
  - Degenerative (chronic CSCR, Mactel2, Optic atrophy, etc…)
  - Genetic (X-linked retinoschisis, Bestrophinopathy, Enhanced S-cone syndrome, etc…)
  - Toxic (Taxanes, Tamoxifen, Nicotinic acid, etc…)

In summary (2),

- In Cystoid maculopathies, intra-retinal fluid may come from other sources of fluid than the vessels :
  - Vitreous body
  - Or endogenous H_2O produced by retinal cell metabolism
- The intra retinal accumulation of fluid may be due to :
  - Opening of retinal spaces (VMT, myopic foveoschisis, etc…)
  - Impairment of fluid reabsorption by the RPE or the Müller cells (CSCR., Bestrophinopathies etc…)
  - Abnormal communication with the vitreous cavity (optic disc pit…)

Take home message

- The diagnosis of cystoid swelling of the macula can be made on OCT alone.
- But only FA may differentiate
  - "Vasogenic" Cystoid Macular Edema, with dye leakage

  from
  - "Non vasogenic" Cystoid maculopathy " without leakage

This distinction is important in seeking the cause of the cystoid spaces

and prescribe the appropriate treatment

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Invited Review Article

Non-vasogenic cystoid maculopathies

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ABSTRACT

Besides cystoid macular edema due to a blood-retinal barrier breakdown, another type of macular cystoid spaces referred to as non-vasogenic cystoid maculopathies (NVCM) may be detected on optical coherence tomography but not on fluorescein angiography. Various causes may disrupt retinal cell cohesion or impair retinal pigment epithelium (RPE) and Müller cell functions in the maintenance of retinal dehydration, resulting in cystoid spaces formation. Tractional causes include vitreomacular traction, epiretinal membranes and myopic foveoschisis. Surgical treatment does not always allow cystoid space resorption. In inherited retinal dystrophies, cystoid spaces may be part of the disease as in X-linked retinoschisis or enhanced S-cone syndrome, or occur occasionally as in bestrophinopathies, retinitis pigmentosa and allied diseases, congenital microphthalmia, choroideremia, gyrate atrophy and Bietti crystalline dystrophy. In macular telangiectasia type 2, cystoid spaces and cavitations do not depend on the fluid leakage from telangiectasia. Various causes affecting RPE function may result in NVCM such as chronic central serous chorioretinopathy and paraneoplastic syndromes. Non-exudative age macular degeneration may also be complicated by intraretinal cystoid spaces in the absence of fluorescein leakage. In these diseases, cystoid spaces occur in a context of retinal cell loss. Various causes of optic atrophy, including open-angle glaucoma, result in microcystoid spaces in the inner nuclear layer due to a retrograde transsynaptic degeneration. Lastly, drug toxicity may also induce cystoid maculopathy. Identifying NVCM on multimodal imaging, including fluorescein angiography if needed, allows guiding the diagnosis of the causative disease and choosing adequate treatment when available.

1. Introduction

Edema is an abnormal accumulation of fluid in the interstitium. Macular edema can be simply defined as an excess of fluid within the retinal tissue (Henkind, 1978). The retina is protected from the circulating blood by the Blood-Retinal Barrier (BRB) at the retinal capillary endothelium and at the Retinal Pigment Epithelium (RPE) where intercellular tight junctions prevent the leakage of small and large molecules into the retinal neuroglia (Ashton and Cunha-Vaz, 1965; Cunha-Vaz et al., 1975; Cunha-Vaz and Maurice, 1967). However, the water coming from the vitreous cavity percolates through the retina pushed by the intraocular pressure and the retinal cellular metabolism

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