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Significance of late-phase hypofluorescence on ICGA in various retinal diseases *

Alain Gaudric



Service d'Ophtalmologie
Hôpital Lariboisière

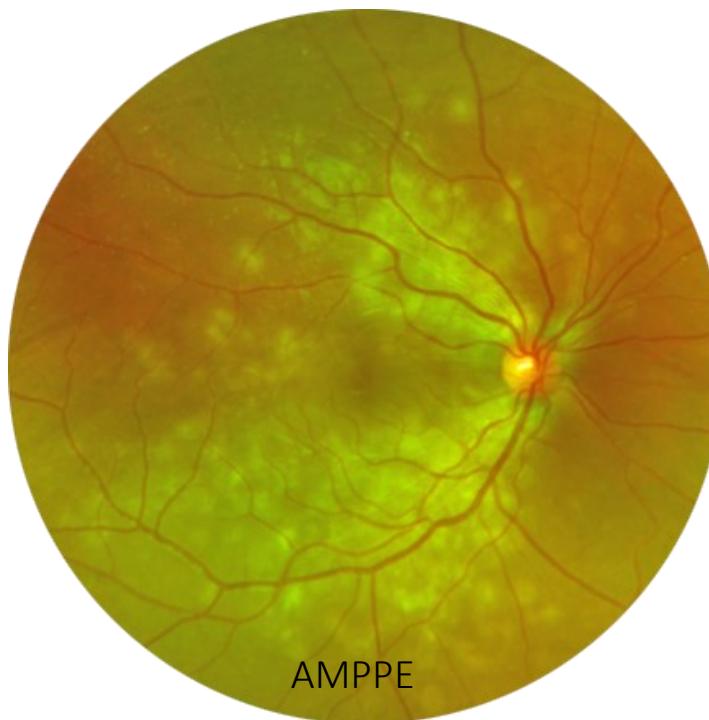
*Value and significance of hypofluorescent lesions seen on late phase indocyanine green angiography. Accepted in *Ophthalmology Science* 2023

Financial Disclosure :

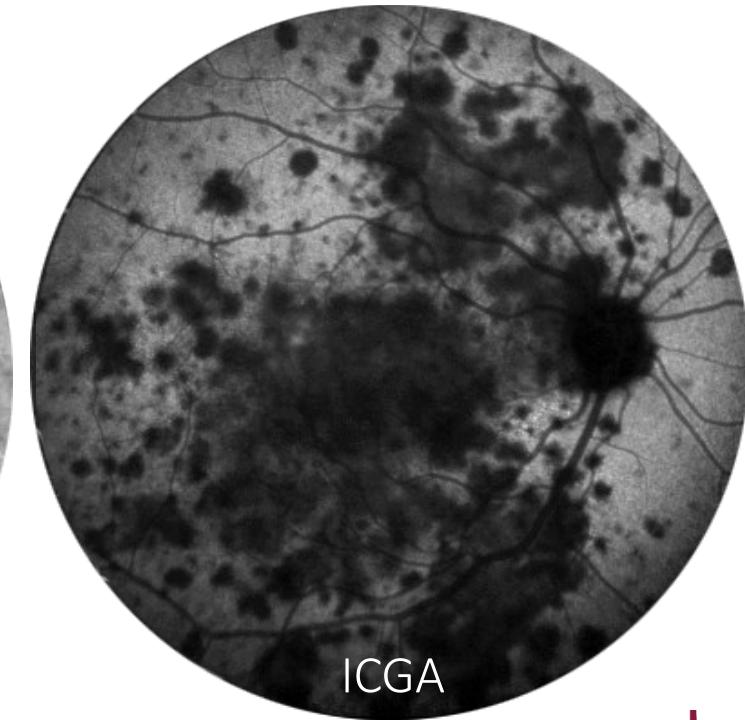
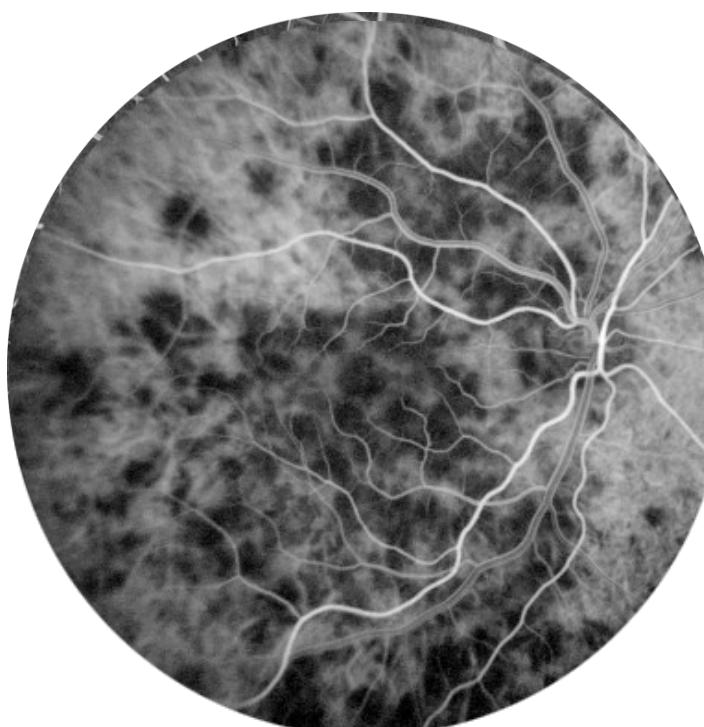
NONE

ICGA hypofluorescence

- Hypofluorescence in the late phase of ICGA is easy to interpret when it corresponds to a choriocapillaris hypoperfusion evidenced on the early phase of FA and ICGA



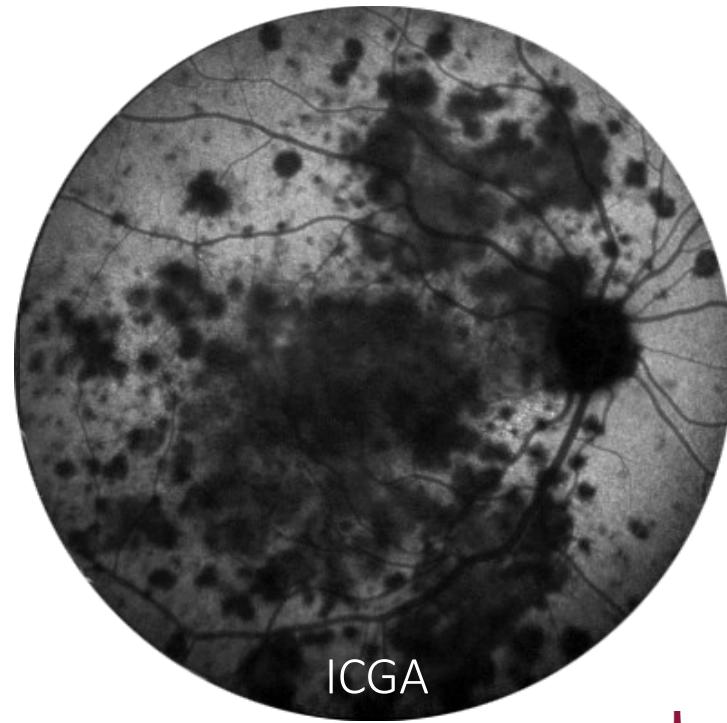
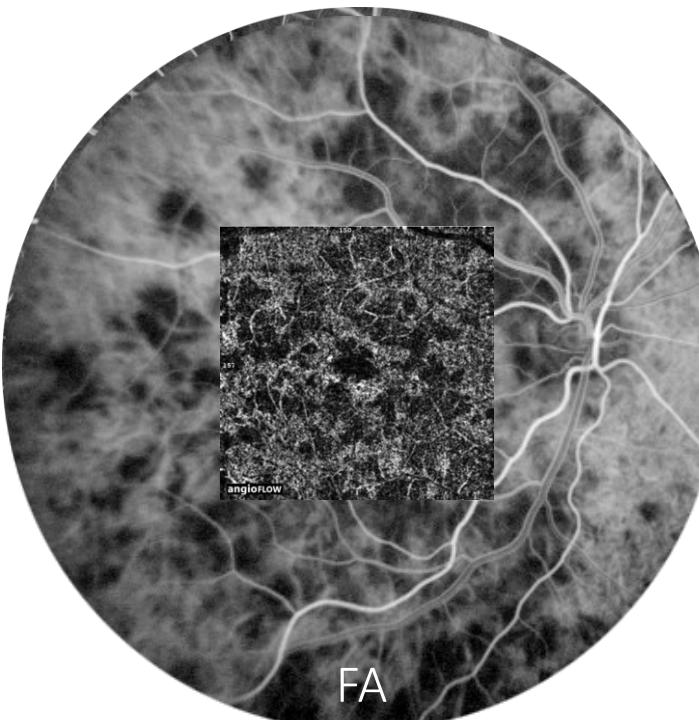
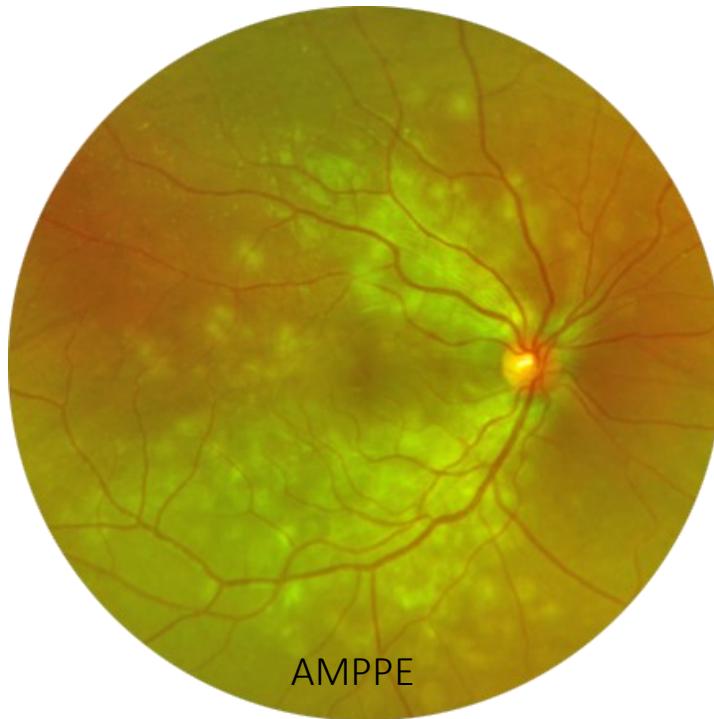
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ICGA

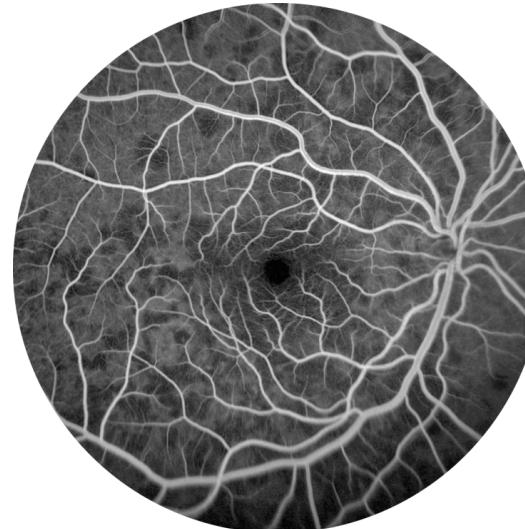
ICGA hypofluorescence

- Hypofluorescence in the late phase of ICGA is easy to interpret when it corresponds to a choriocapillaris hypoperfusion evidenced on the early phase of FA and ICGA , and confirmed by OCTA



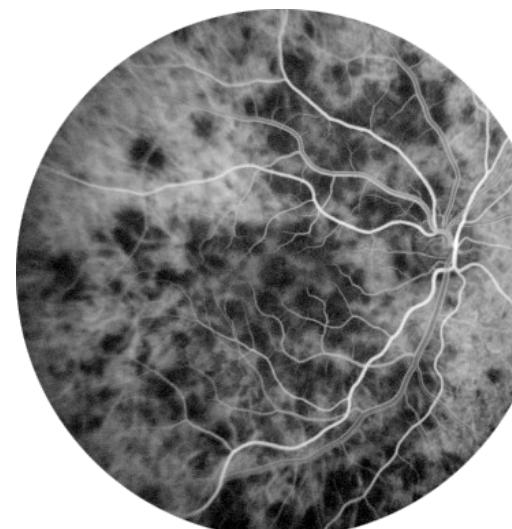
Common interpretation of differences between late phase FA and ICGA

FA

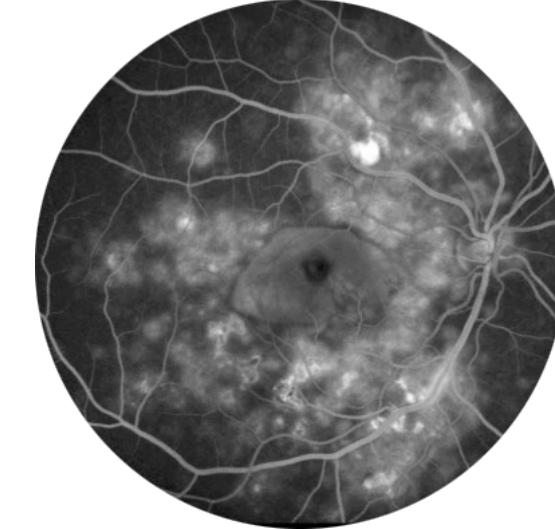


choriocapillaris hypoperfusion

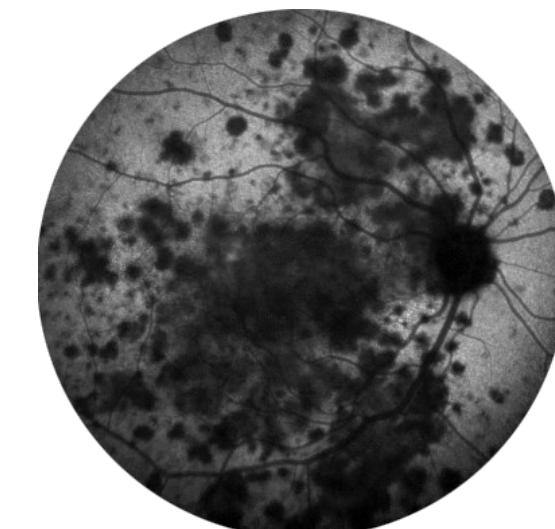
ICGA



choriocapillaris hypoperfusion



leakage through impaired RPE

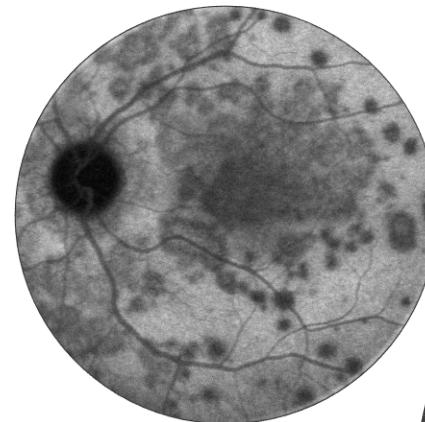


no leakage through impaired RPE due to ICG MW or binding to proteins

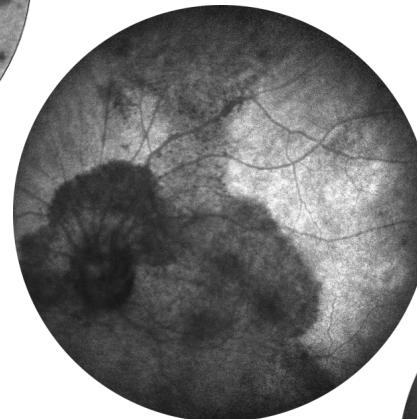
Hypofluorescence in late phase ICGA only

- We studied 3 diseases in which hypofluorescent lesions appeared only at the late phase (20 to 30min) of ICGA and extended these observations to other diseases.

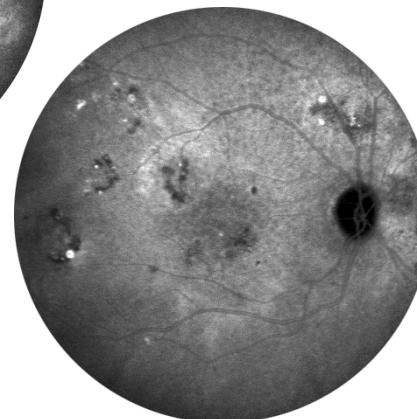
- MEWDS



- Syphilitic Placoid



- Chronic CSCR



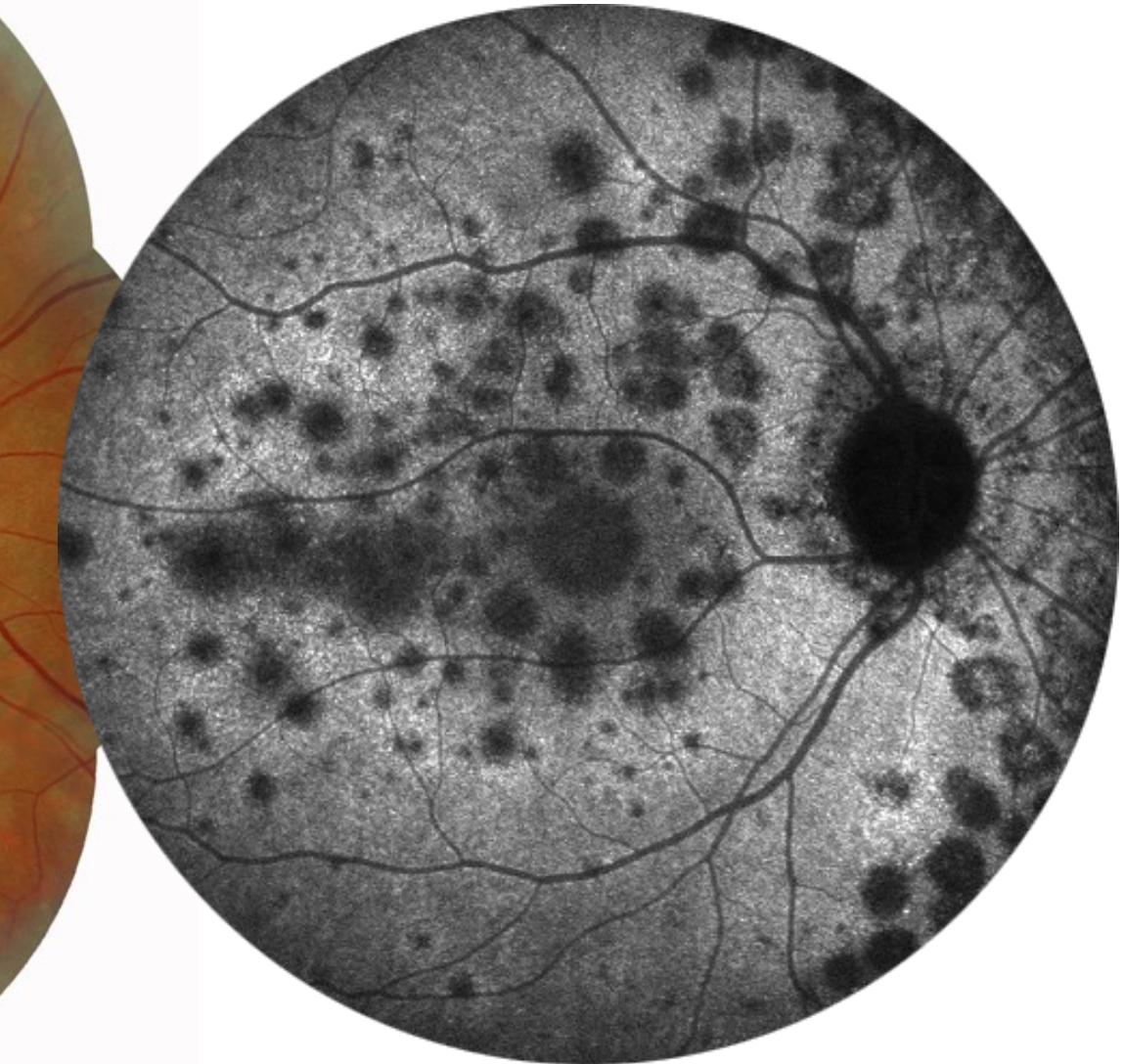
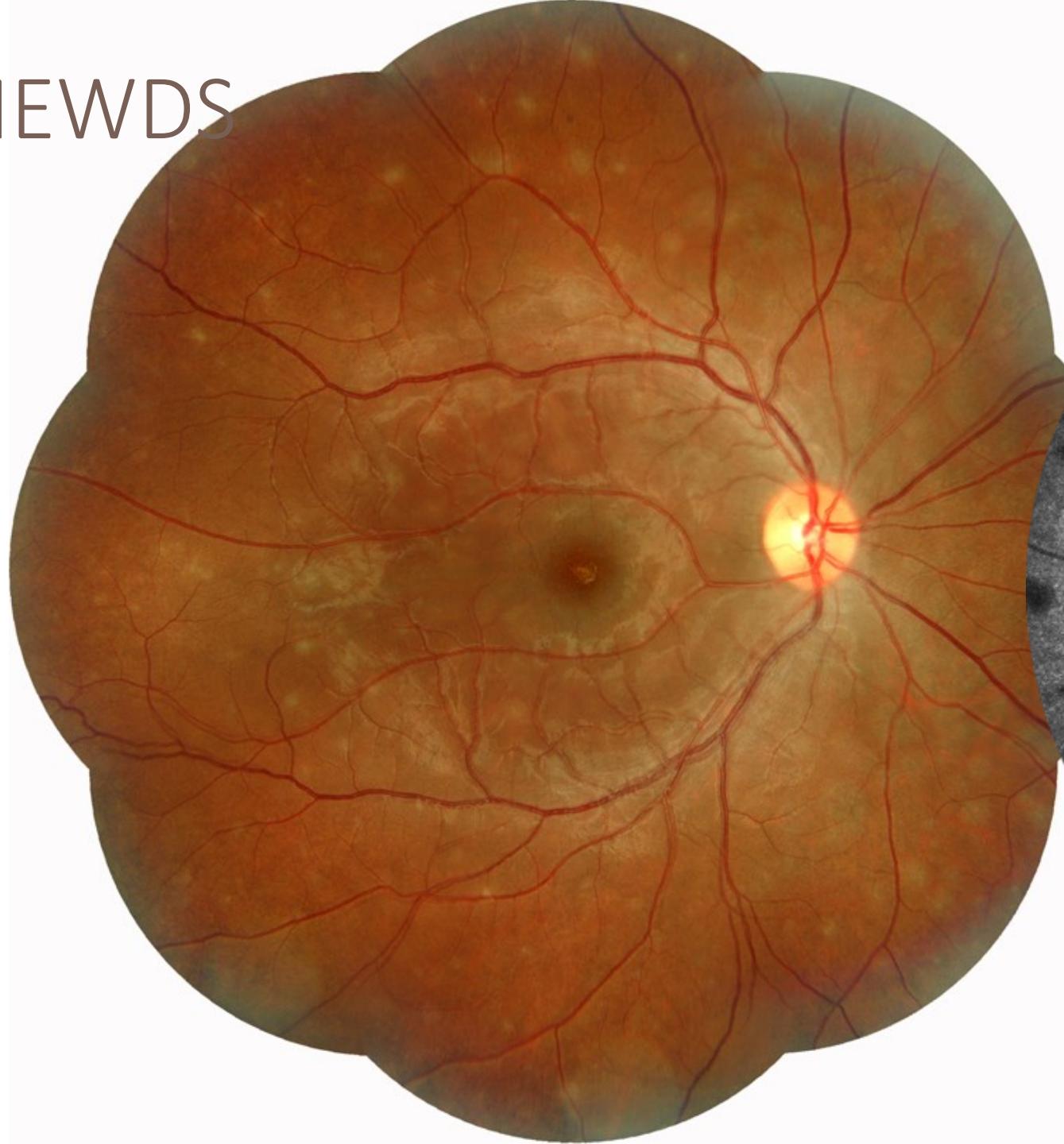
MEWDS

- We studied 15 eyes (15 patients)
 - aged 18 to 34 (3 M, 12 F)
 - color photo, FA, ICGA, OCT
- All had the same sequence on ICGA
 - normal early phase , progressive hypofluorescence of white dots
 - best contrasted at 30 min

**WHY THE DOTS ARE BLACK ONLY
IN THE LATE PHASE OF THE
INDOCYANINE GREEN ANGIOGRAPHY
IN MULTIPLE EVANESCENT WHITE DOT
SYNDROME** Ret Cases Brief Rep 2017 11: S81-S85

Alain Gaudric, MD,* Sarah Mrejen, MD†

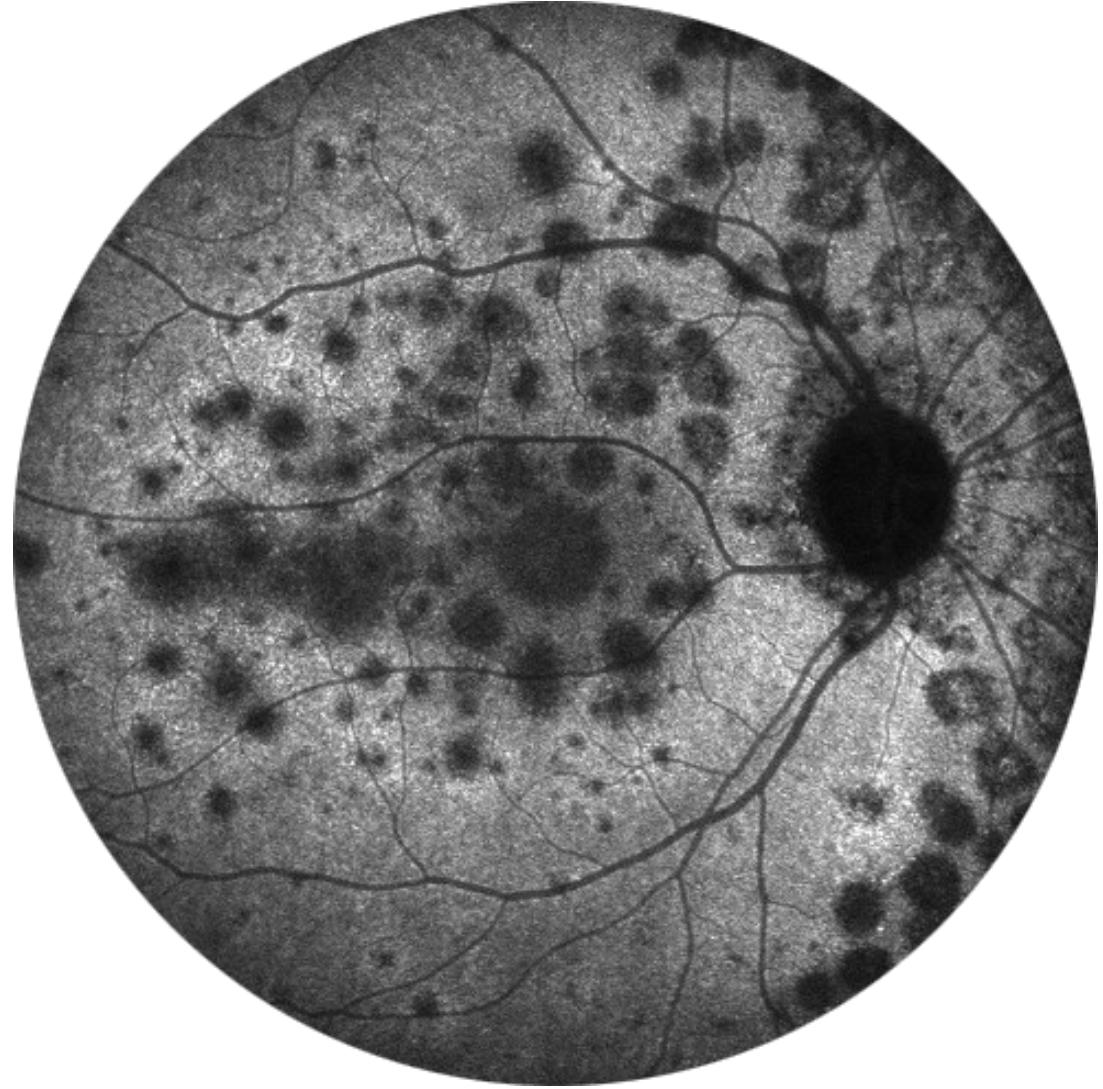
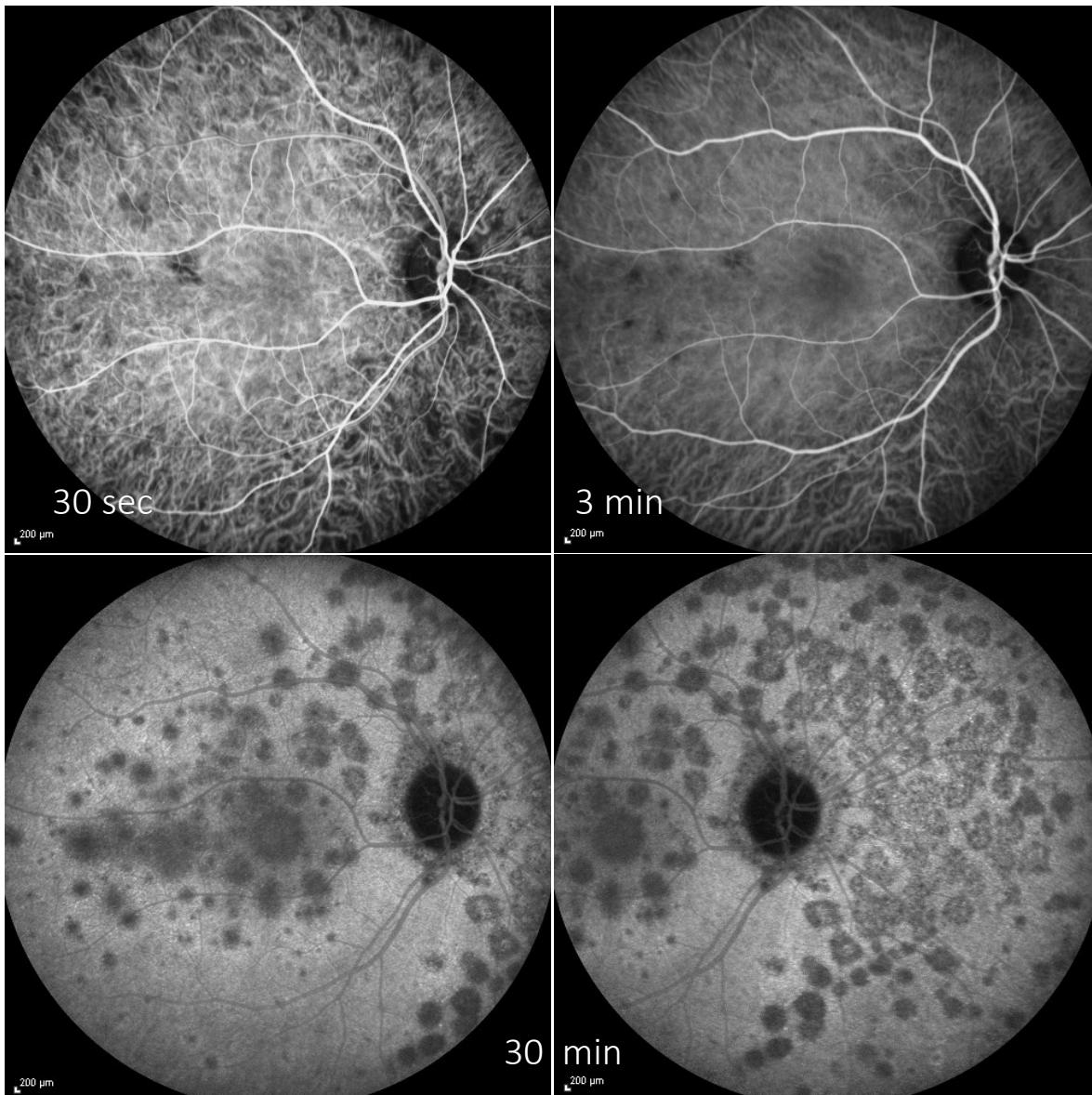
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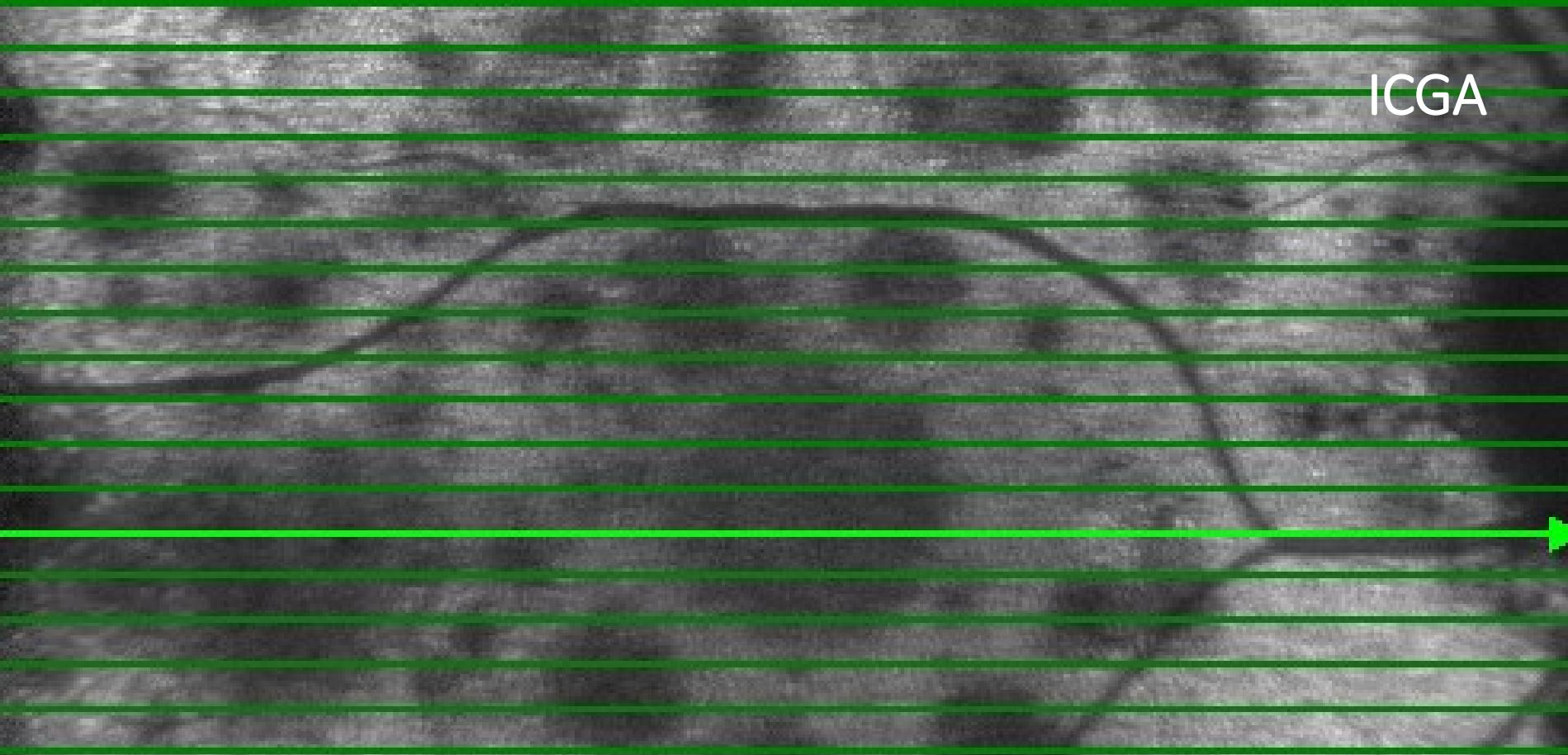


30 min

25/09/2023 20:03

MEWDS

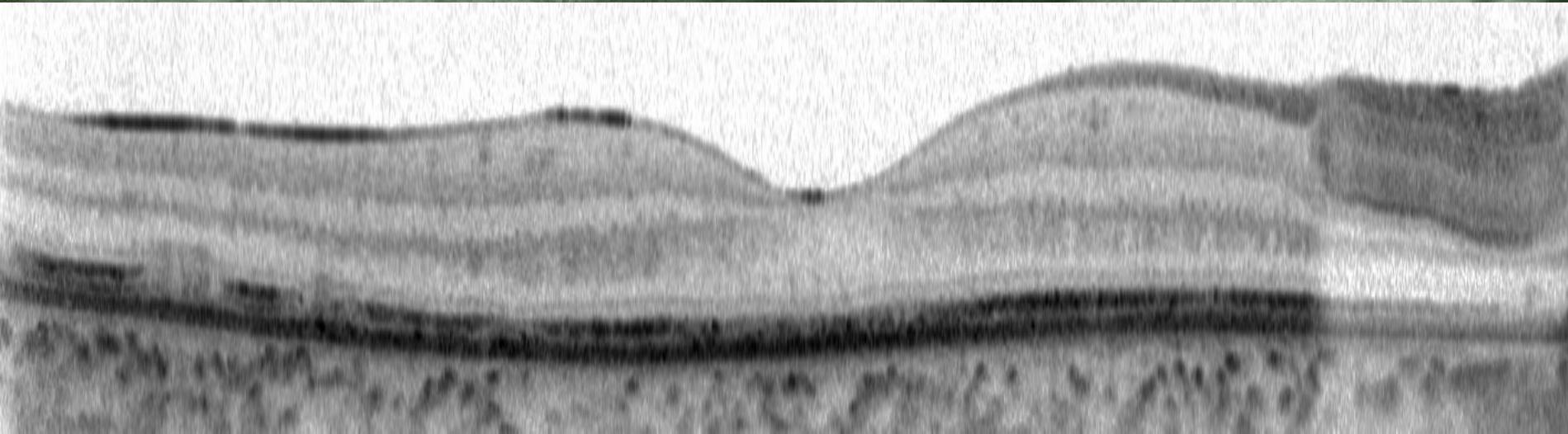




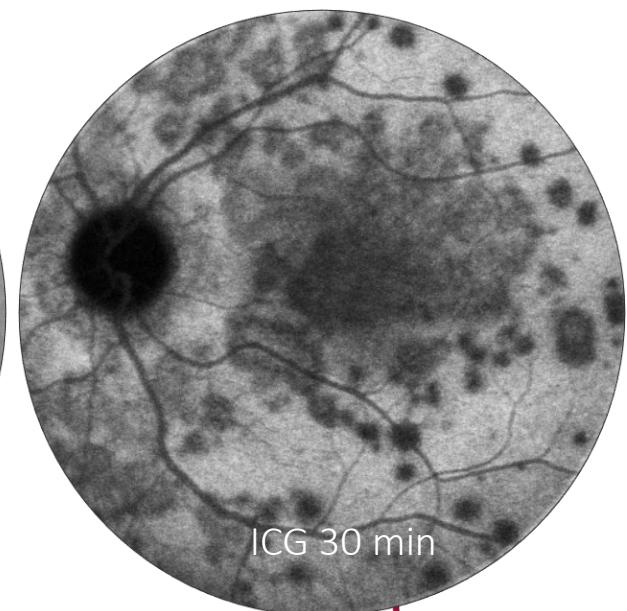
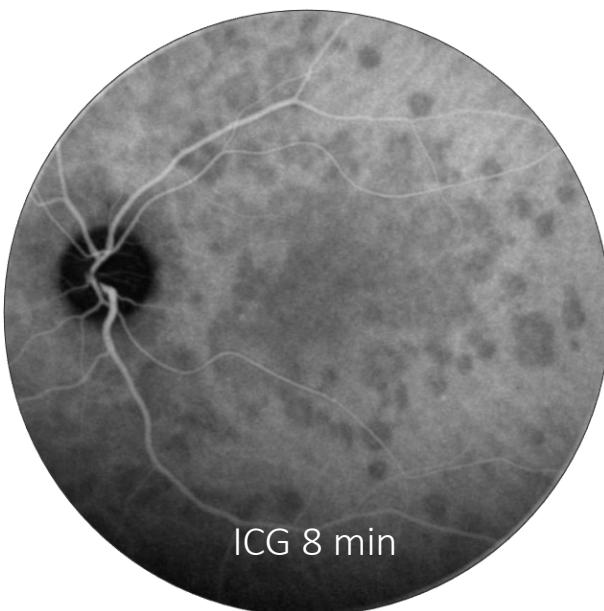
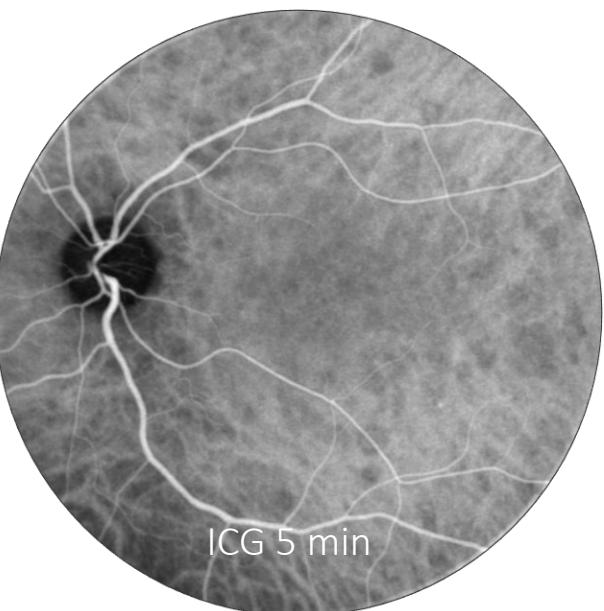
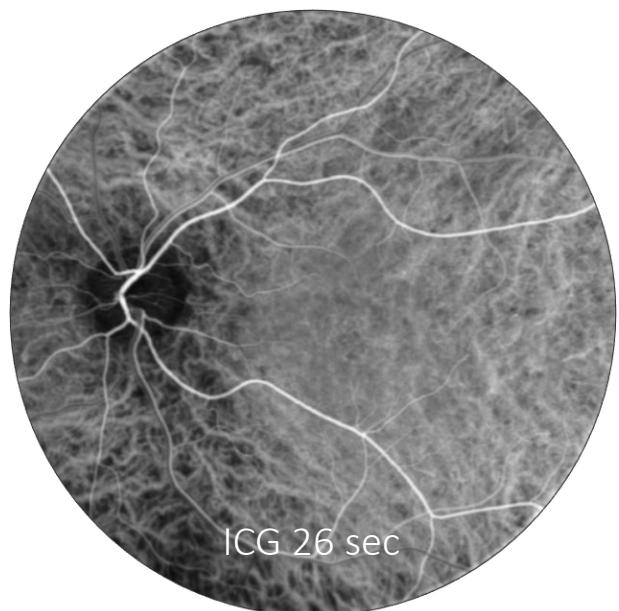
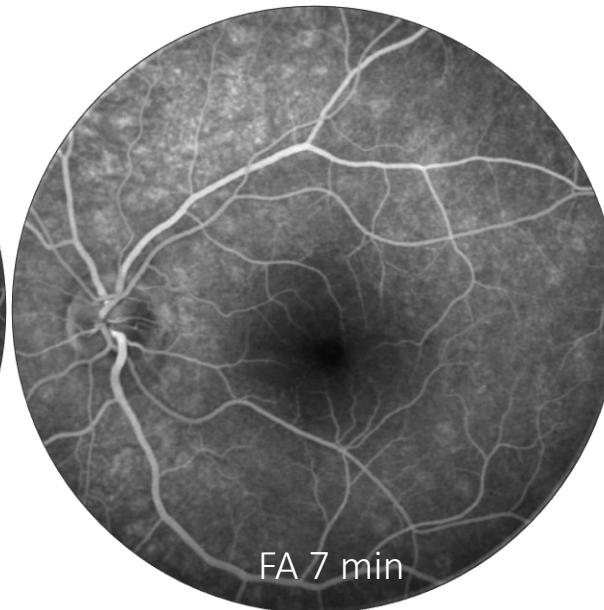
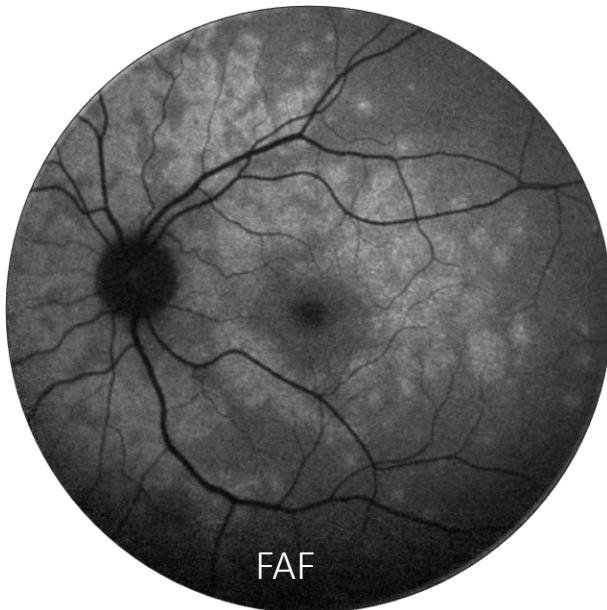
ICGA

MEWDS

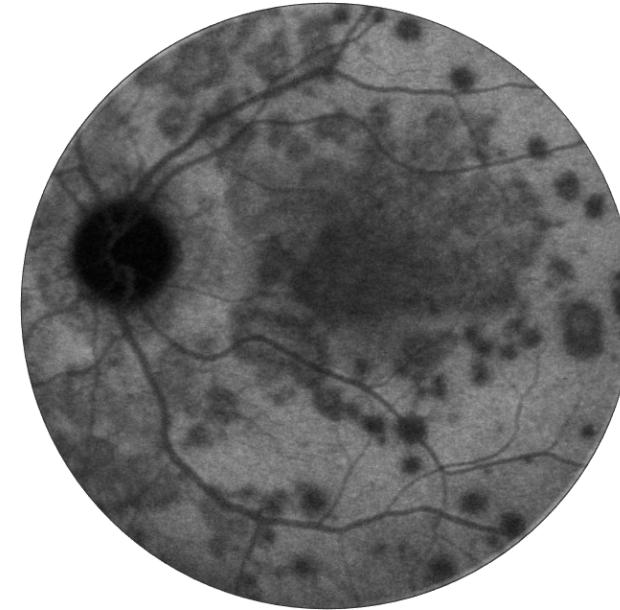
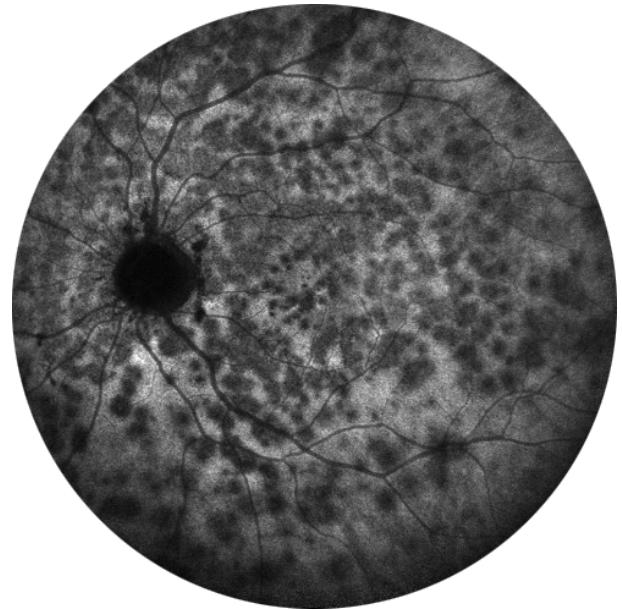
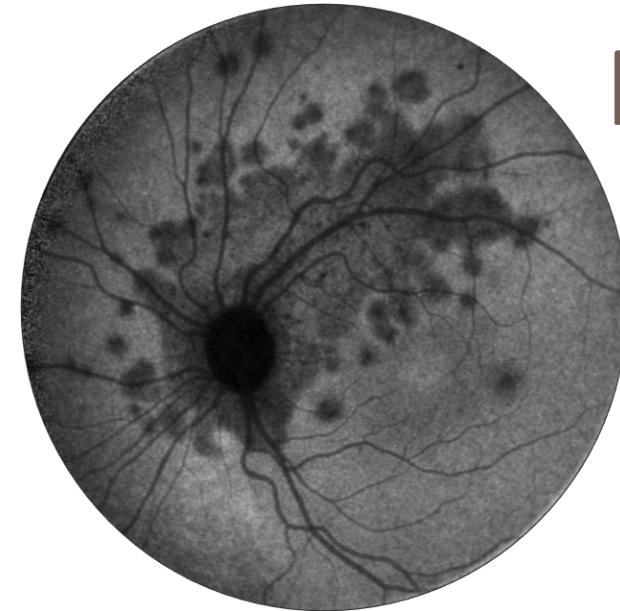
EZ irregularity or
disruption in front
of dark spots on
late phase ICGA



MEWDS



MEWDS



Syphilitic placoid

- We studied 15 eyes (12 patients)
 - aged 34- 58 (11 M, 1 F)
 - color photo, FA, ICGA, OCT
- All had the same sequence in ICGA
 - normal early phase ,
 - except for black spots due to RPE granulations
 - progressive hypofluorescence of the plaque
 - best contrasted at 30 min



Indocyanine Green Angiography Features in Acute Syphilitic Posterior Placoid Chorioretinitis



JÉRÉMIE VILLARET, MARIE-HÉLÈNE ERRERA, JOSÉ-ALAIN SAHEL, ALAIN GAUDRIC, SARAH MREJEN, AND MICHEL PAQUES

J Ophthalmol 2022;241: 40–46. © 2022 Elsevier Inc. All rights reserved.

• PURPOSE: Acute syphilitic posterior placoid chorioretinitis (ASPPC) is a rare clinical manifestation of ocular syphilis. The cause of the placoid lesion is still up for debate but could be caused by an impaired choriocapillaris perfusion. However, less attention has been paid to the hypofluorescence of the plaque on late-phase indocyanine green angiography (ICGA). The aim of this study was to comprehensively analyze multimodal imaging findings in patients with ASPPC and to highlight the value of ICGA for the diagnosis of ASPPC.

• DESIGN: Retrospective observational case study.

• METHODS: The medical records of patients with uveitis who consulted our tertiary center between 2012 and December 2015 were reviewed. Patients who were diagnosed with uveitis related to syphilis infection with posterior placoid lesions seen on multimodal imaging were included. We compared the aspect of ASPPC on fundus color photography, blue autofluorescence, fluorescein angiography, optical coherence tomography, and early-, mid- and late-phase ICGA.

• RESULTS: Fifteen eyes of 12 patients were included in the study. Hypofluorescent plaques were seen on late-phase ICGA in all eyes, corresponding to the placoid lesions visible on blue autofluorescence, while the choriocapillaris filling was normal on fluorescein angiography and ICGA. Within the plaques, optical coherence tomography showed ellipsoid zone disruptions, outer retinal disruptions, and retinal pigment epithelium granulations.

• CONCLUSION: ASPPC could be caused by retinal pigment epithelium dysfunction secondary to an infectious or inflammatory disorder, characterized by a hypofluorescence visible only on late-phase ICGA, and resulting in photoreceptor disruptions. The RPE impairment was reversible after prompt antibiotic treatment. (Am J Ophthalmol 2022;241: 40–46.)

Accepted for publication February 4, 2022.

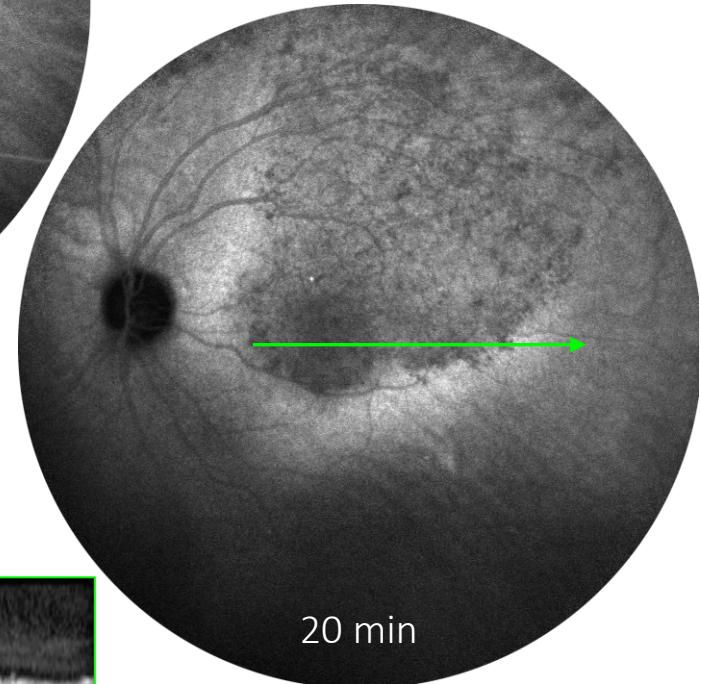
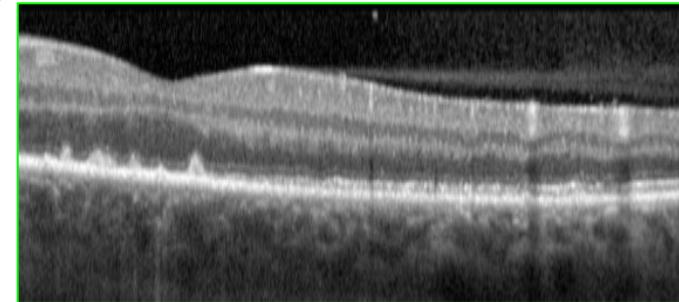
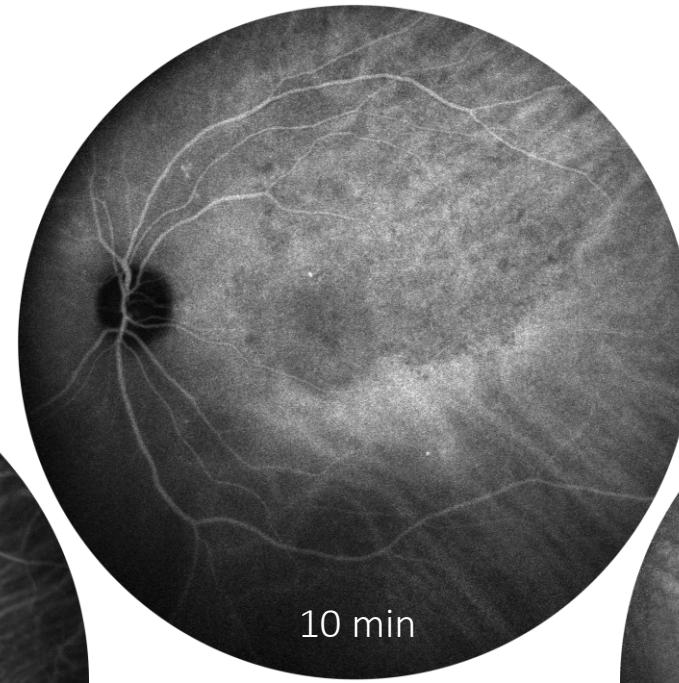
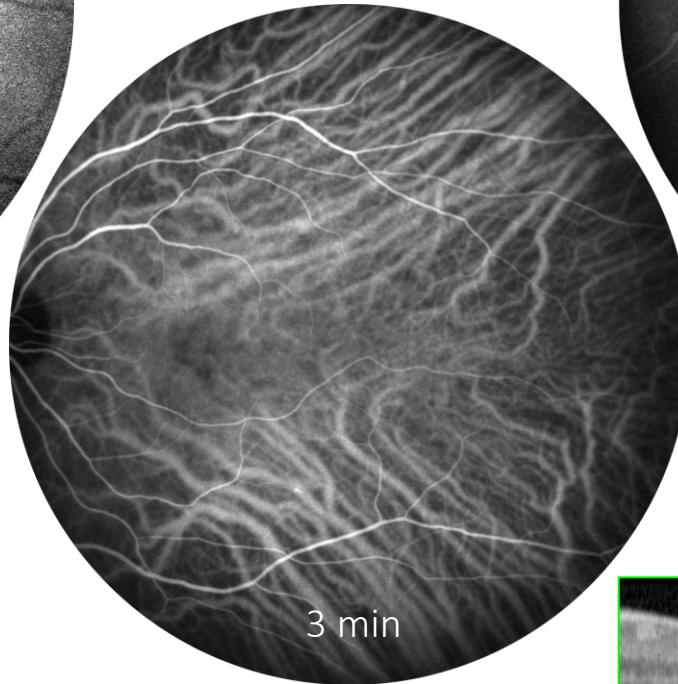
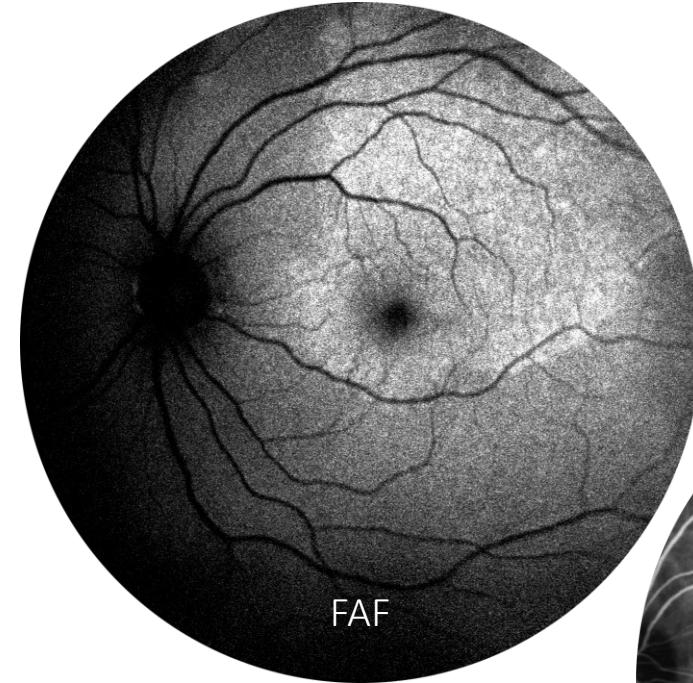
From the Centre Hospitalier National des Quinze-Vingts (J.V., M.-H.E., J.-A.S., S.M.), DHU Sight Restore, Paris; Ophthalmology Department (A.G.), Université de Paris, APHP Hôpital Lariboisière, Paris, France; Department of Ophthalmology (M.-H.E., J.-A.S.), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

Inquiries to Sarah Mrejen, Centre Hospitalier National des Quinze-Vingts, 28 rue de Charenton, 75012 Paris, France; e-mail: s.mrejen@15v.fr.

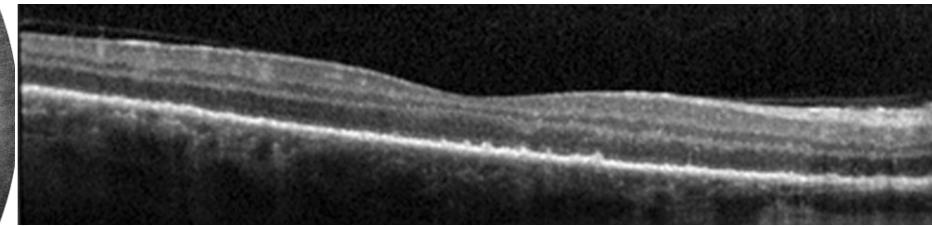
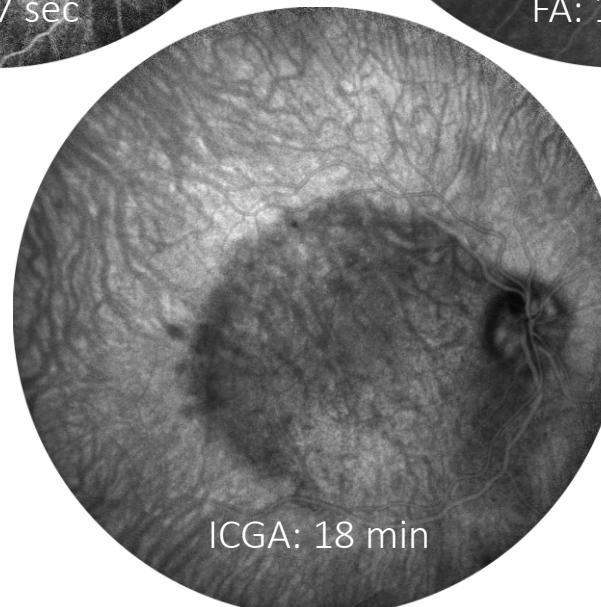
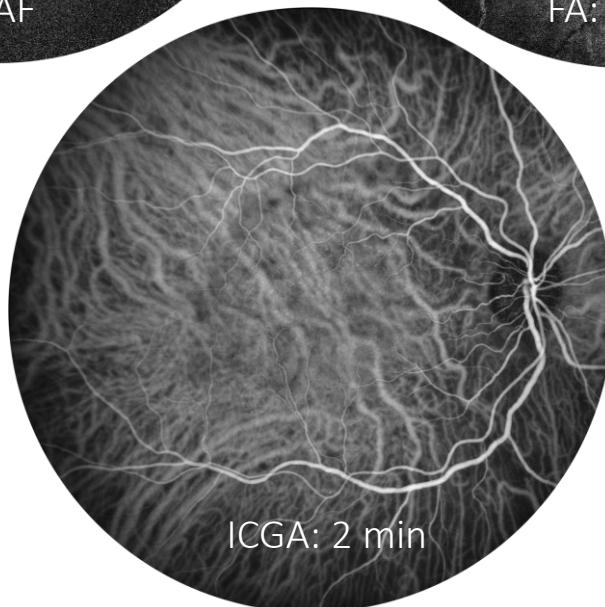
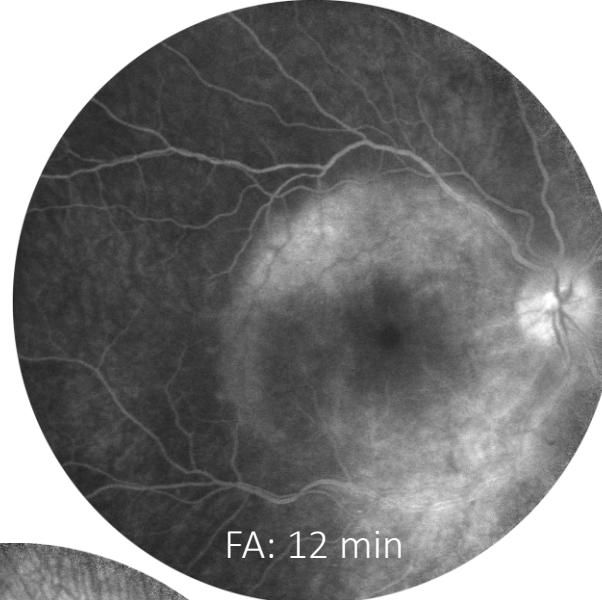
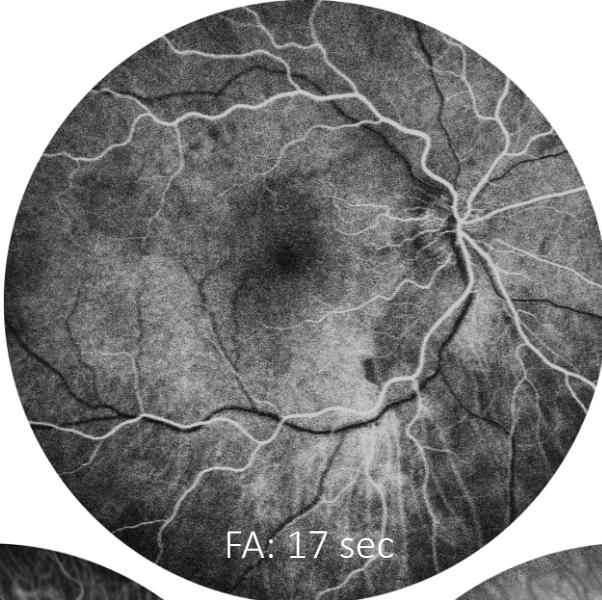
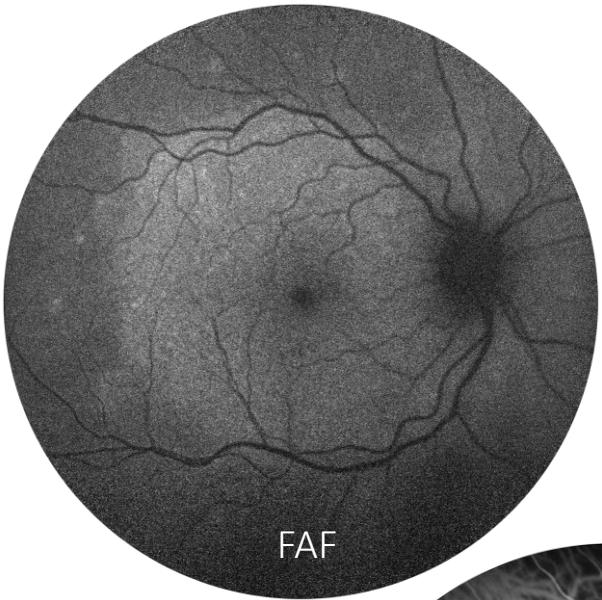
PATIENTS AND METHODS

The charts of 1493 patients diagnosed with uveitis who consulted our tertiary ophthalmological center (Centre Hospitalier National d'Ophthalmologie des Quinze-Vingts, Paris, France) between January 2012 and December 2015

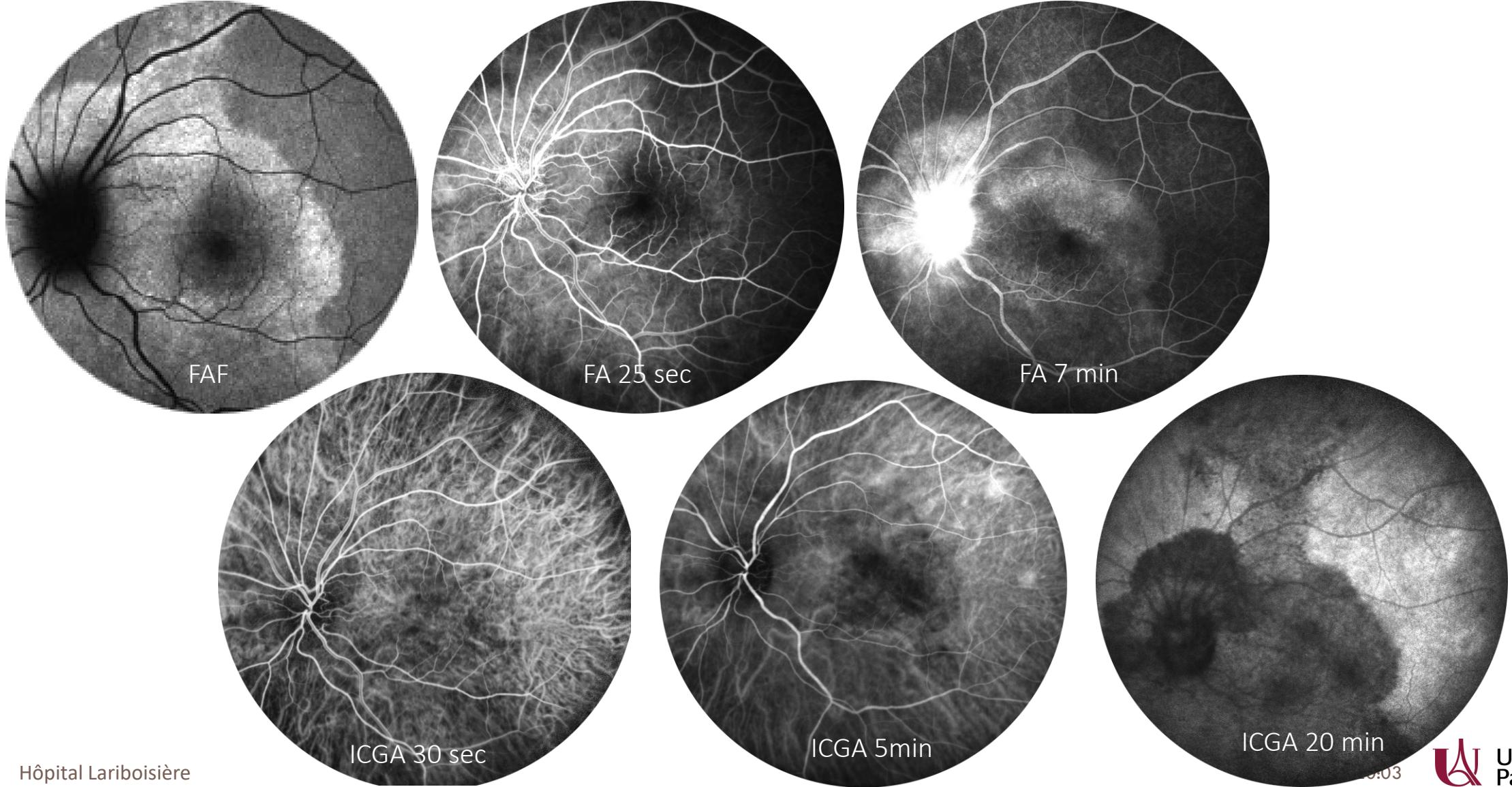
Syphilitic placoid



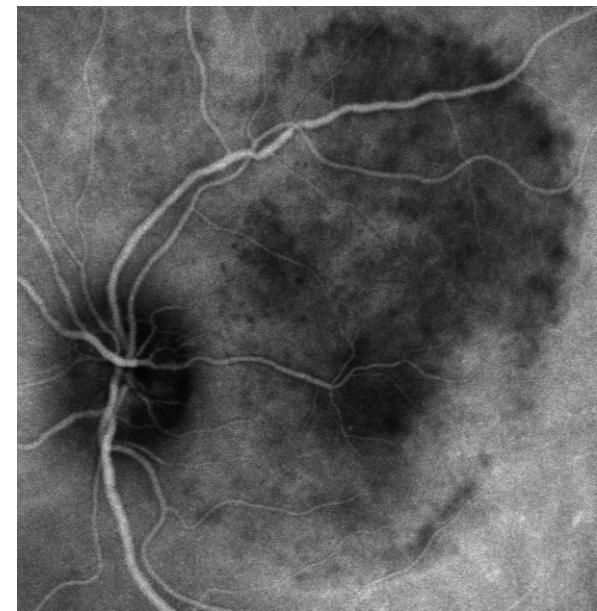
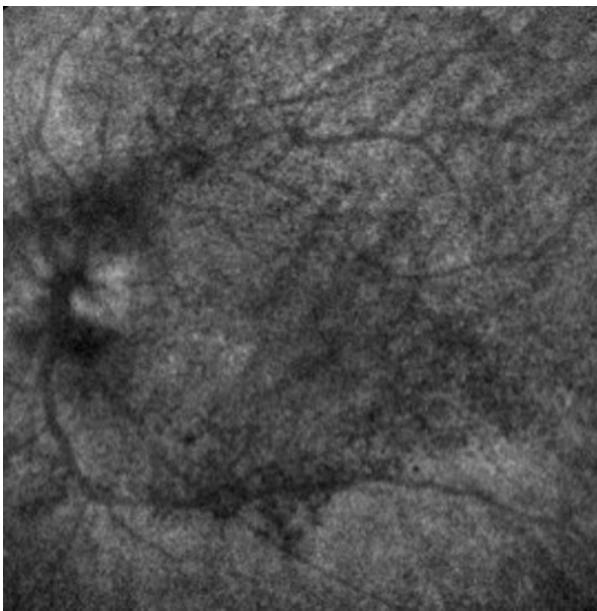
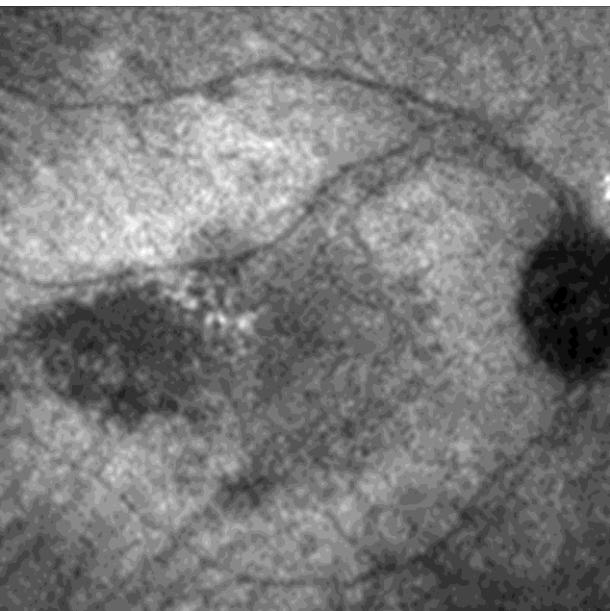
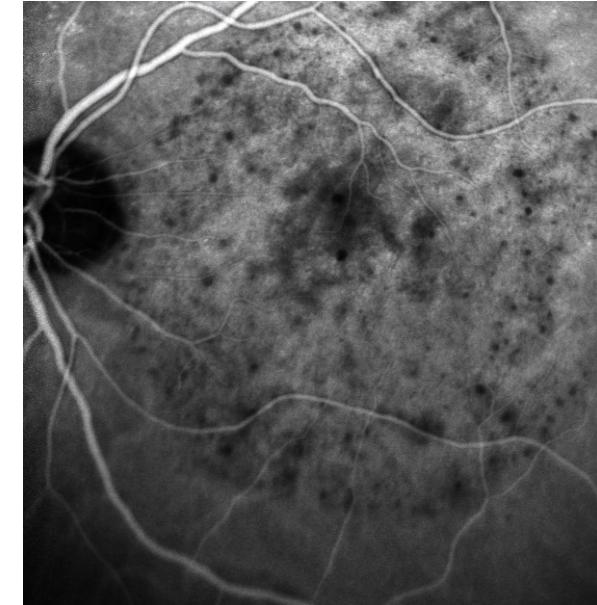
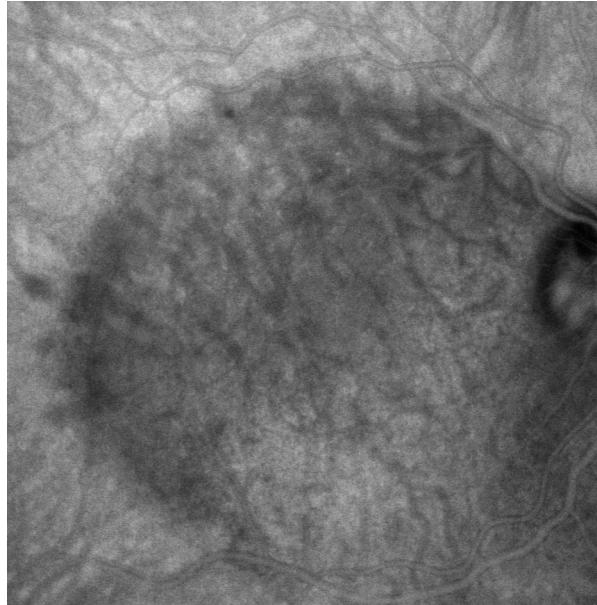
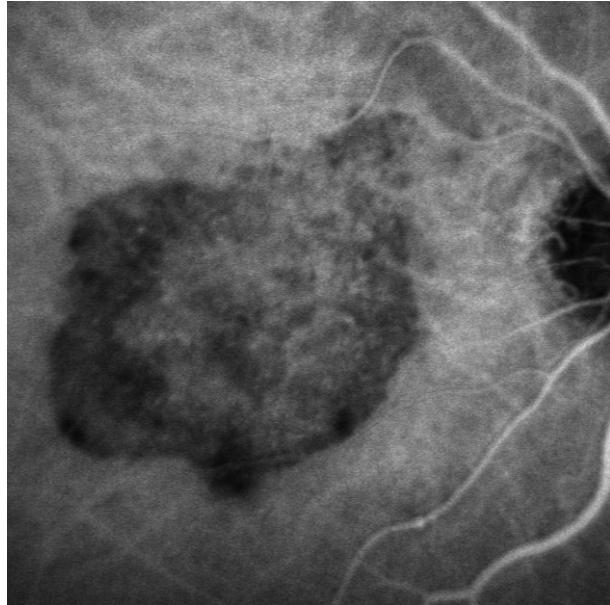
Syphilitic placoid



Syphilitic placoid



Syphilitic placoid



- All the cases had the same dynamics of fluorescence in ICGA
 - Progressive heterogeneous hypofluorescence in the area of the autofluorescent plaque
 - corresponding to a loss or fragmentation of the EZ on OCT

Chronic CSCR

- We studied 20 eyes (19 patients)
 - aged 52- 69 (16 M, 4 F)
 - color photo, FA, ICGA, OCT
- With hypofluorescent lesions appearing ONLY on the late phase of ICGA
- All had the same sequence in ICGA:
 - dilated choroidal veins in early phase ICGA
 - progressive **hyper**-fluorescent plaques at the mid-phase of ICGA
 - becoming progressively **hypo**-fluorescent at the late phase

Central serous chorioretinopathy: risk factors for serous retinal detachment in fellow eyes

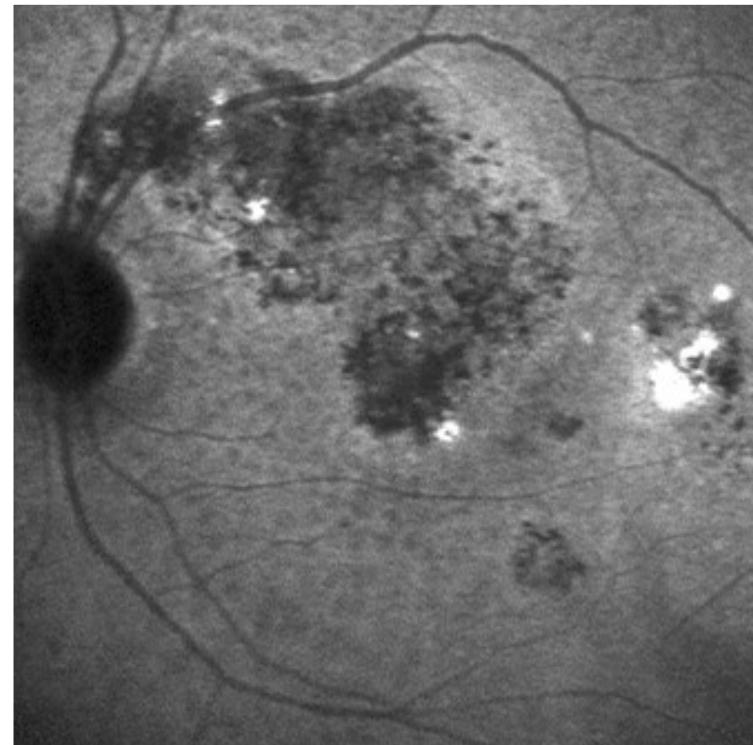
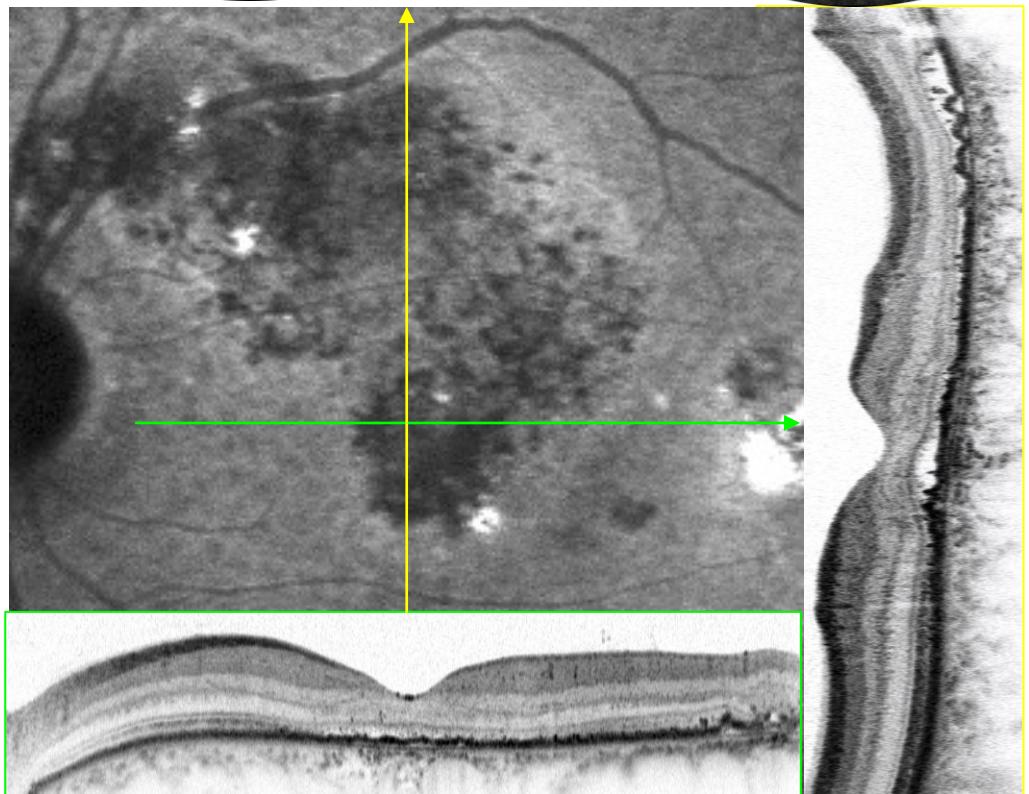
Ari Shinojima  ^{1,2}, Chadi Mehanna ^{3,4}, Carlo Alessandro Lavia, ¹ Alain Gaudric, ¹ Ramin Tadayoni, ^{1,4} Elodie Bousquet ^{4,5}

Brit J Ophthalmol. 2020;104(6):852-856.

Mid-Phase Hyperfluorescent Plaques Seen on Indocyanine Green Angiography in Patients with Central Serous Chorioretinopathy

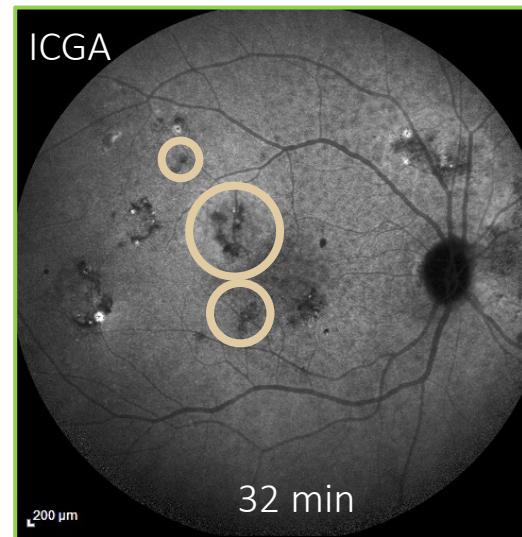
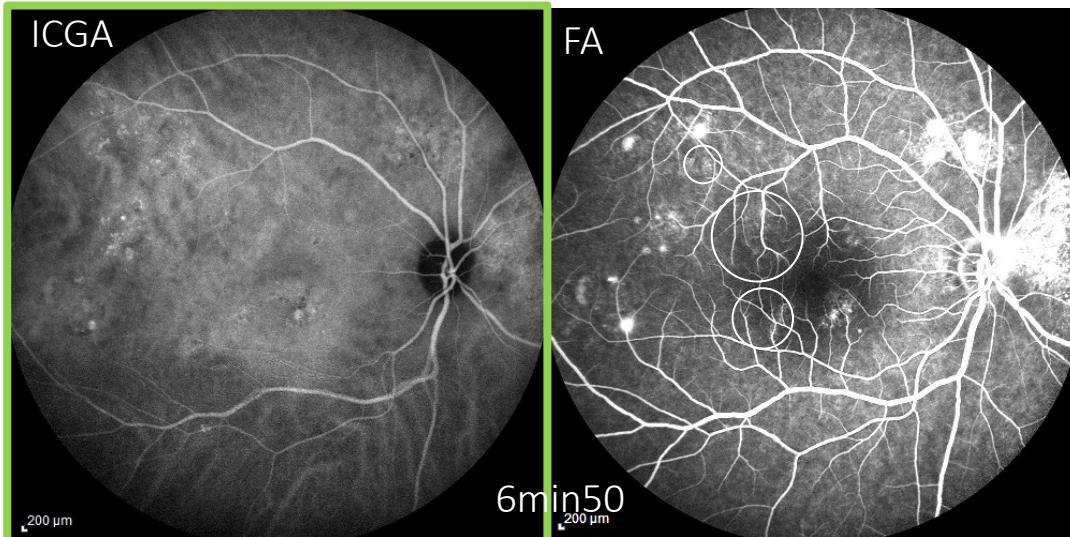
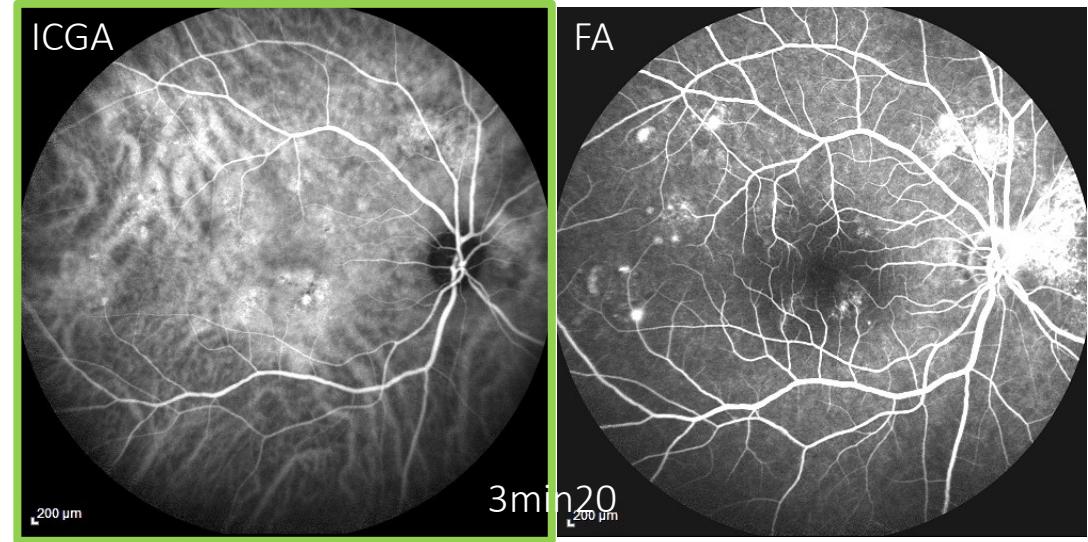
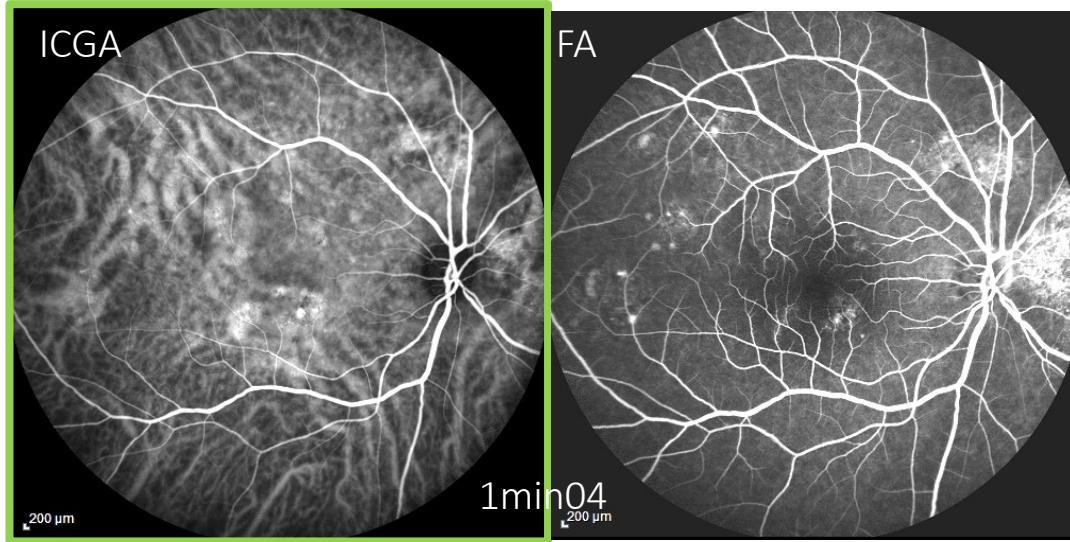
Elodie Bousquet ^{1,2,*}, Julien Provost ^{1,*}, Marta Zola ¹, Richard F. Spaide ³, Chadi Mehanna ^{1,4,5} and Francine Behar-Cohen ^{1,2,*}

J Clin Medicine. 2021;10(19):4525.



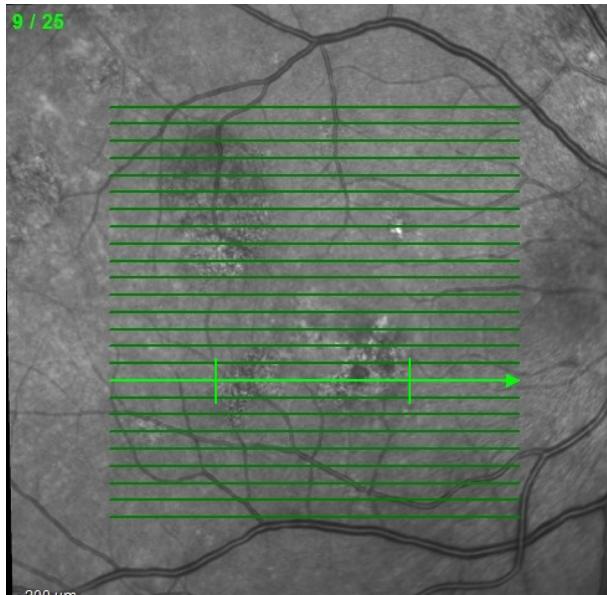
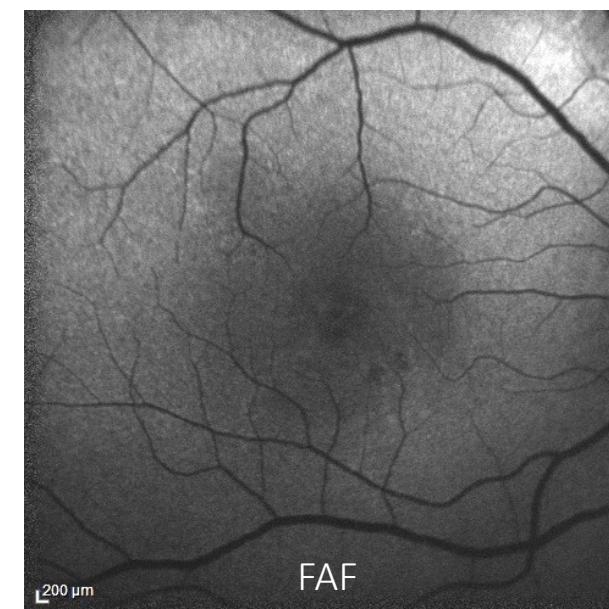
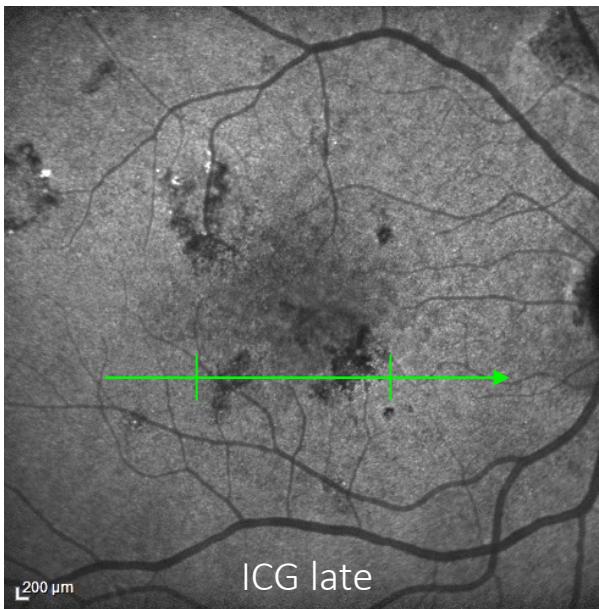
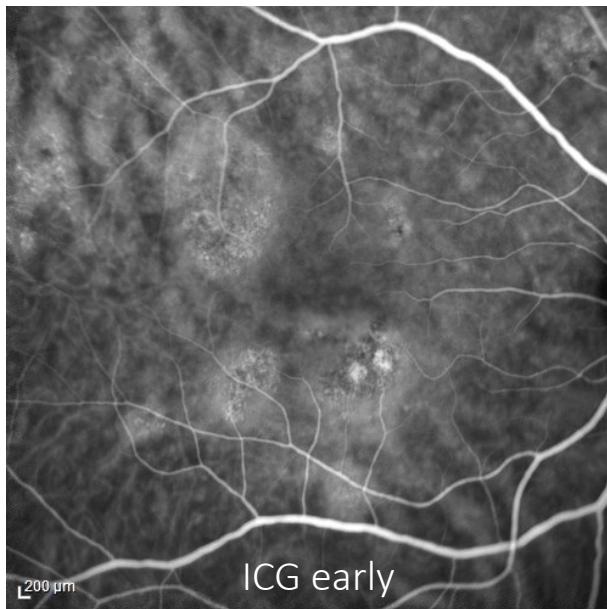
- dilated choroidal veins
- hyperfluorescent plaques
- late hypofluorescence
- corresponding to hyper autofluorescence area

Chronic CSCR

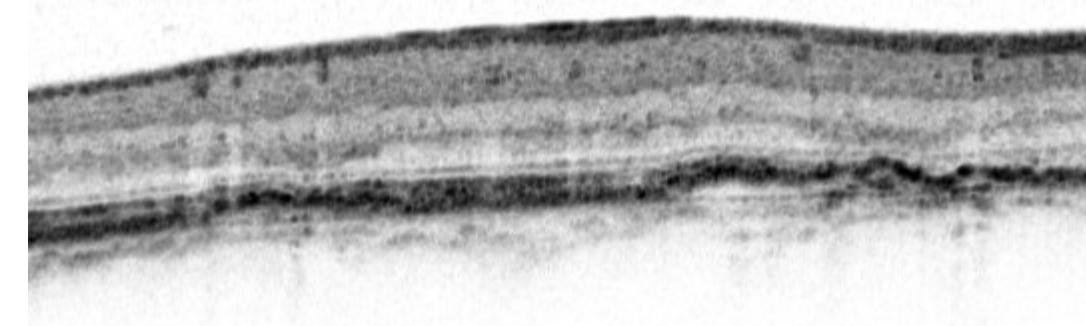


- Some, late dark spots did not correspond to leakage on FA

Chronic CSCR

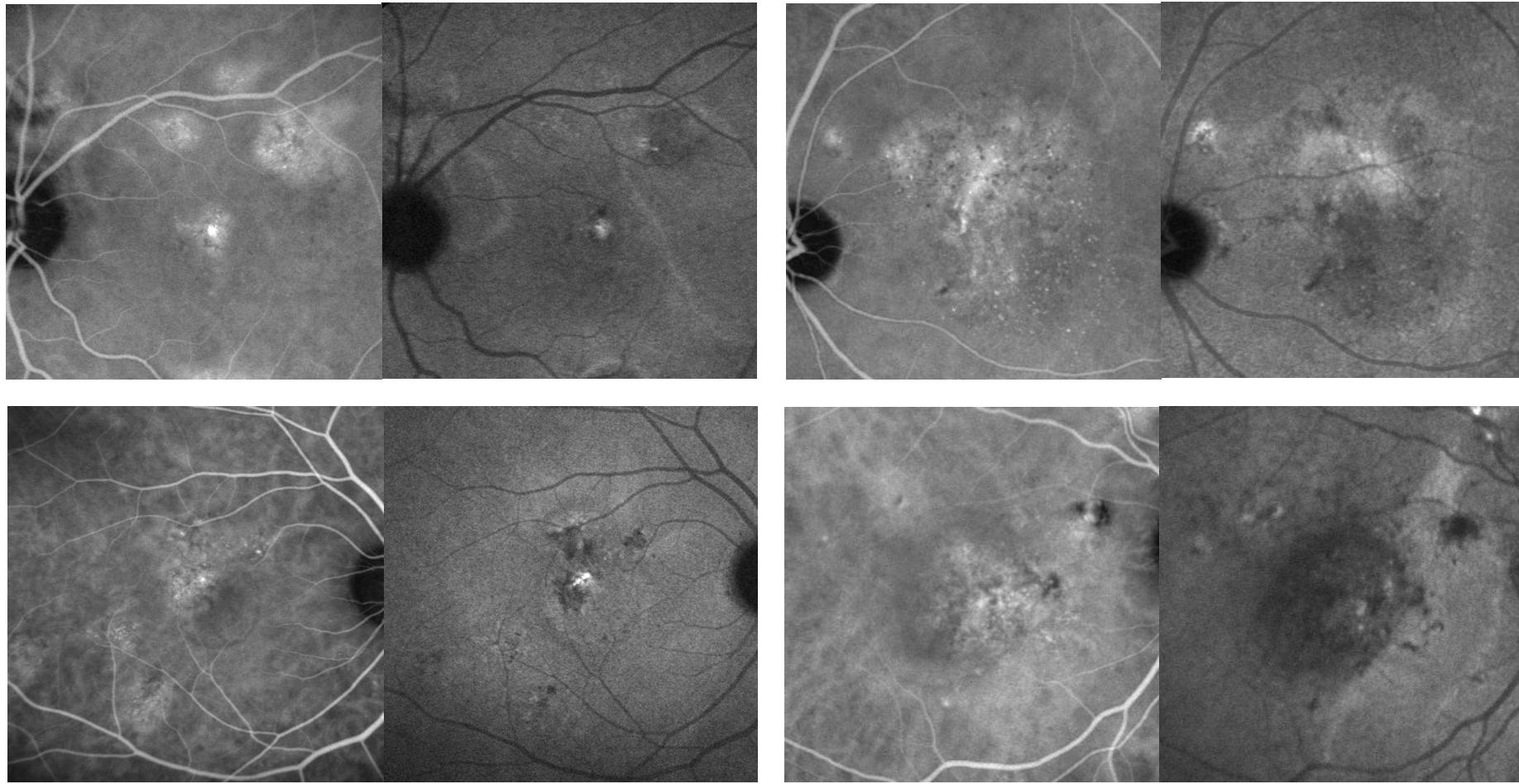


- Dark spots in late ICGA did not correspond to hypo-autofluorescence in blue light.



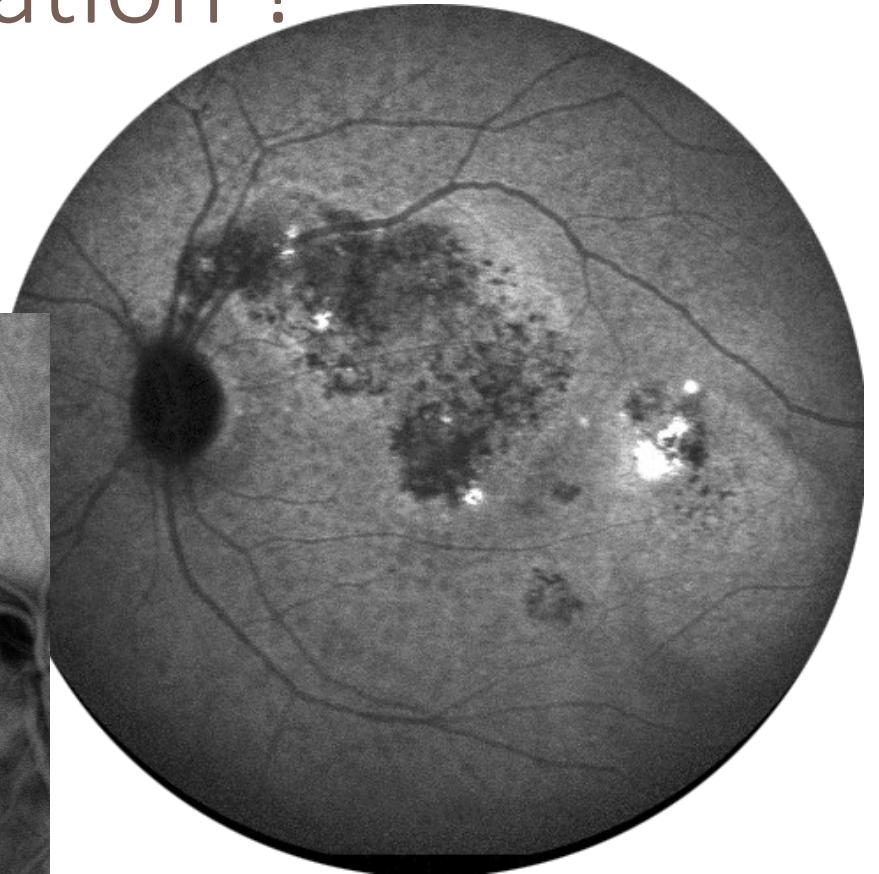
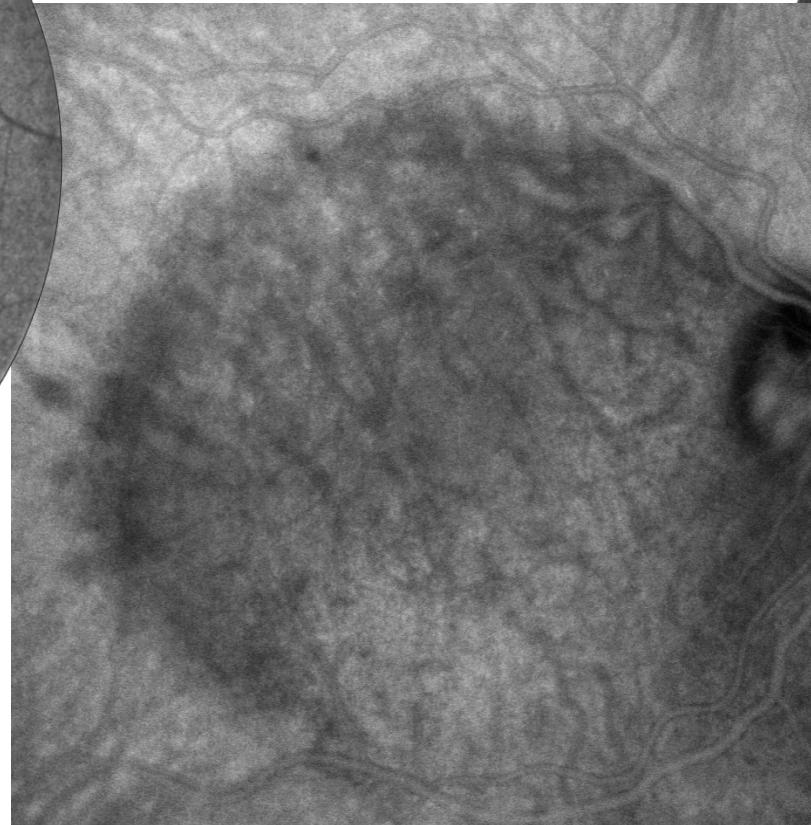
- They most often corresponded to FIPED on OCT

Chronic CSCR



- All the cases had the same dynamics of fluorescence in ICGA
 - Hyperfluorescent area at the mid-phase of ICGA
 - becoming hypofluorescent at the late phase (30min)

How to find a common explanation ?



ICG and the fluorescence of the fundus

- ICG is a large amphiphil molecule
 - which is linked to
 - water¹
 - albumin¹
 - and to lipoproteins, especially phospholipids^{2,3}
- These characteristics prevent its passage through the retinal vascular endothelium
 - but not through the choriocapillaris endothelium
- ICG diffuses into the choroidal stroma¹
 - but does not enter the subretinal space

1. Flower RW. Evolution of ICG choroidal angiography. *Opt Eng.* 1995;34(3):727-736.

2. Mordon S, et al. Indocyanine Green: Physicochemical factors affecting its fluorescence in Vivo. *Microvasc Res.* 1998;55(2):146-152

3. Yoneya S, Saito T, Komatsu Y, Koyama I, Takahashi K, Duvoll-Young J. Binding properties of indocyanine green in human blood. *Invest Sci.* 1998;39(7):1286-1290.

Ophth Vis

ICG and the fluorescence of the fundus

- ICG penetrates progressively into the RPE cells
 - findings often neglected in the interpretation of late phase of the ICGA (30 min or more)

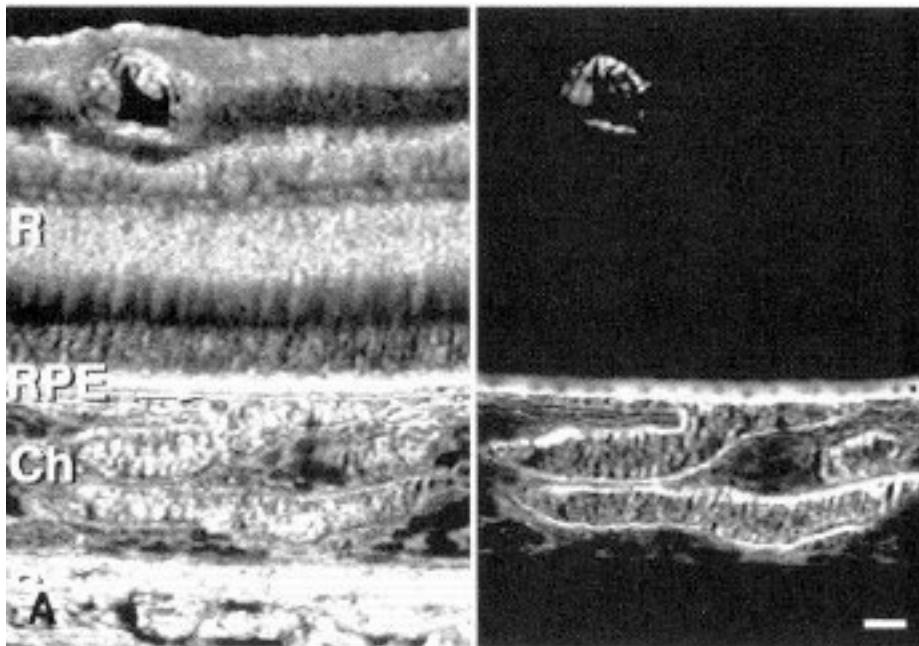
Histologic Localization of Indocyanine Green Dye in Aging Primate and Human Ocular Tissues with Clinical Angiographic Correlation

Andrew A. Chang, FRACO,¹ Laurence S. Morse, MD, PhD,¹ James T. Handa, MD,¹ Ronald B. Morales,¹ Richard Tucker, PhD,² Leonard Hjelmeland, PhD,¹ Lawrence A. Yannuzzi, MD³

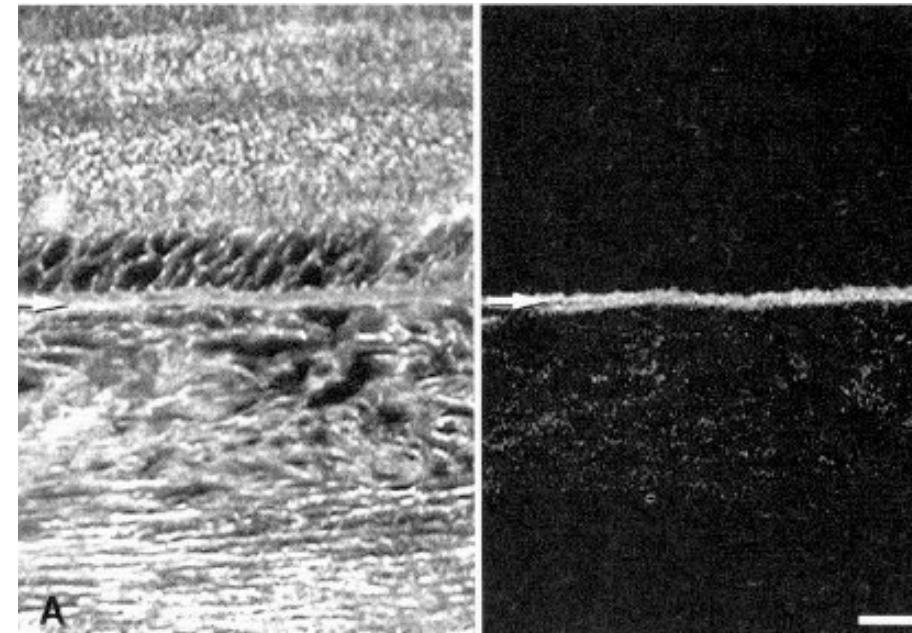
Ophthalmology 1998;105:1060-1068

The ICG dye does not remain solely within the choroidal intravascular space but extravasates into the choroidal stroma and **accumulates within the RPE**. These findings will enhance the interpretation of clinical ICG angiography.

ICG and the fluorescence of the fundus



Monkey eye 7 min after IV ICG injection



Human eye 40 min after IV ICG injection

- At 7 min, ICG starts to enter the basal portion of the RPE
- At 40 min, there is no longer ICG in the vessels, its presence in the choroid is negligible
 - RPE is markedly stained by ICG

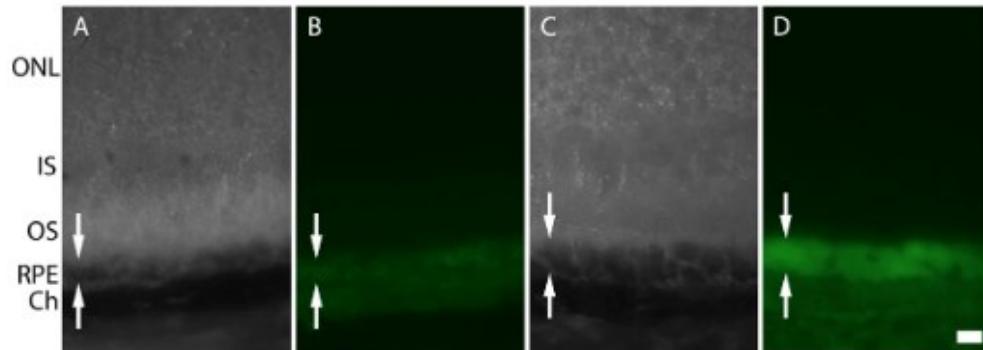
Chang AA, et al. Histologic localization of indocyanine green dye in aging primate and human ocular tissues, clinical angiographic correlation. Ophthalmology. 1998.

ICG et fluorescence du fond d'œil

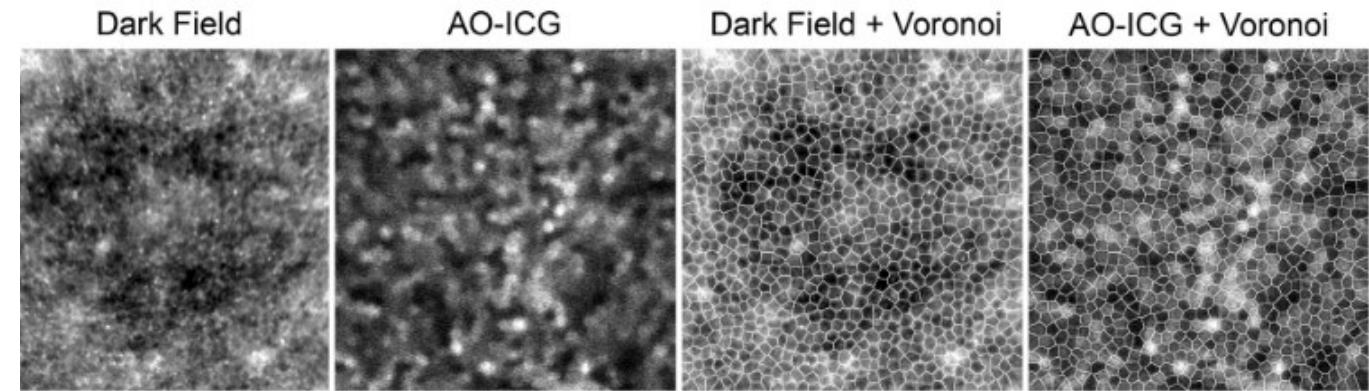
In Vivo Imaging of the Human Retinal Pigment Epithelial Mosaic Using Adaptive Optics Enhanced Indocyanine Green Ophthalmoscopy *Invest Ophth Vis Sci 57, 4376–4384 (2016).*

Johnny Tam,¹ Jianfei Liu,¹ Alfredo Dubra,^{2–4} and Robert Fariss⁵

Dans l'œil humain



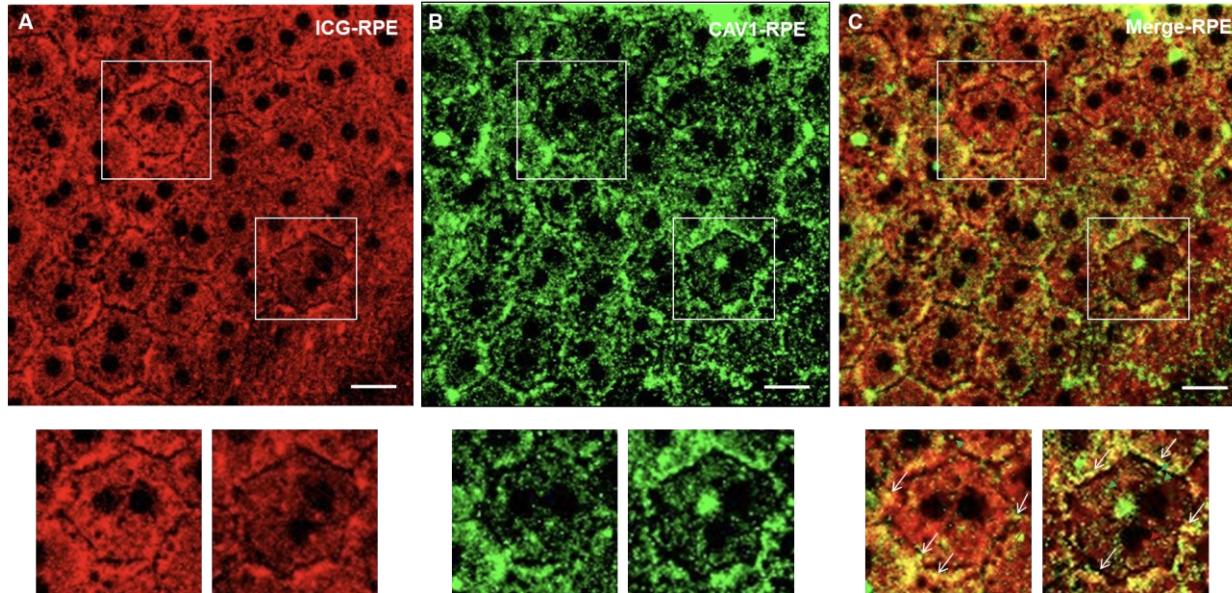
Confirmation de la localisation spécifique de l'ICG aux cellules de l'EP chez la souris



L'OA-ICG est une nouvelle méthode d'imagerie à haute résolution des cellules de l'EP. Elle a révélé la présence d'un signal stable qui a persisté entre 20 et 120 minutes après l'injection IV d'ICG à une dose clinique standard.

ICG et fluorescence du fond d'œil

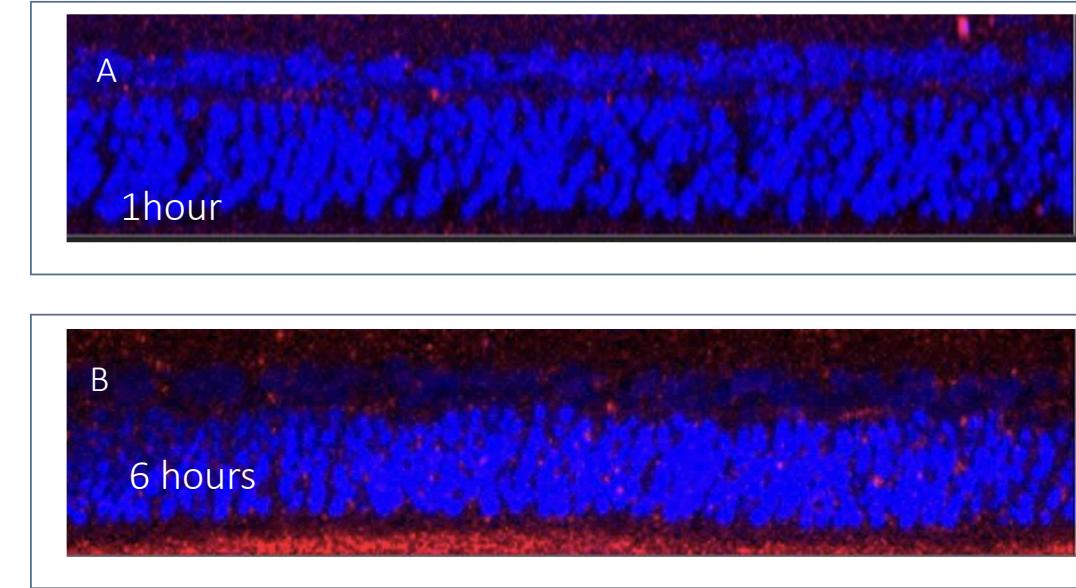
Identification of structures labeled by indocyanine green (ICG) in the rat choroid and retina can guide interpretation of ICG angiography.
D Mejłachowicz, PaLassiaz, M Zola, B Leclercq, E Gélizé, S Achiedo, M Zhao, A Rousseau, F Behar-Cohen . Soumis à IOVS



Deep infrared confocal imaging of RPE flat-mounts and caveolin immunohistochemistry

A: Deep infrared imaging of RPE flat mount one hour after ICG intravenous injection, insets show magnification. B: Caveolin-1 immunohistochemistry on RPE flat mount one hour after ICG injection, insets show magnification.

C: Merge of image A and B, inset shows magnification with yellow co-stained vesicles (white arrows), caveolin-1 vesicles (green arrows) and ICG-stained vesicles (red arrows). Scale bar: 20µm



Transverse pictures showing ICG staining (red) from photoreceptor outer segments to inner nuclear layer 1h (A) and 6h (B) after IV ICG injection

ICG and the fluorescence of the fundus

■ Other indices of the affinity of ICG for the RPE

The Interaction of Indocyanine Green with Human Retinal Pigment Epithelium

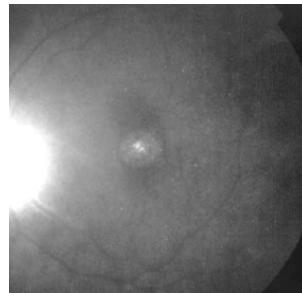
Andrew A. Chang,^{1,2,3} Meidong Zhu,^{1,2} and Frank Billson^{1,2} IOVS 2005

This study demonstrates the in vitro uptake of ICG by cultured human RPE cells. Ouabain reduced the uptake of ICG into RPE cells, which suggests that ICG uptake by the RPE is likely to involve the Na⁺,K⁺-ATPase pump.

Persistence of Fundus Fluorescence after Use of Indocyanine Green for Macular Surgery

Ophthalmology 2003

Ramin Tadayoni, MD, Michel Paques, MD, PhD, Jean François Girmens, MD, Pascale Massin, MD, Alain Gaudric, MD

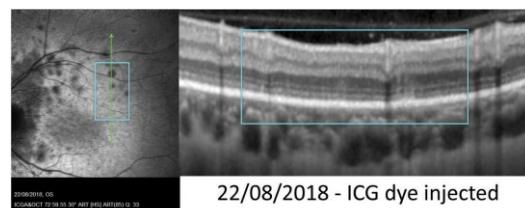


Persistence of RPE staining in the macular center , 3 months, after ILM peeling using ICG in the surgery of MH . the MH is closed.

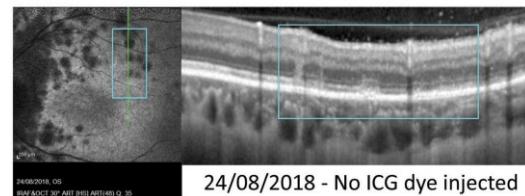
Multimodal Imaging of Multiple Evanescent White Dot Syndrome: A New Interpretation

Federico Zicarelli, MD¹, Alessandro Mantovani, MD², Chiara Preziosa, MD¹, and Giovanni Staurenghi, MD¹

Multimodal imaging allowed us to suggest the RPE to be the key tissue involved in the inflammatory process. The photoreceptors alterations may be consequent to the RPE dysfunction rather than the expression of a direct damage induced to the cells by the disease.



22/08/2018 - ICG dye injected

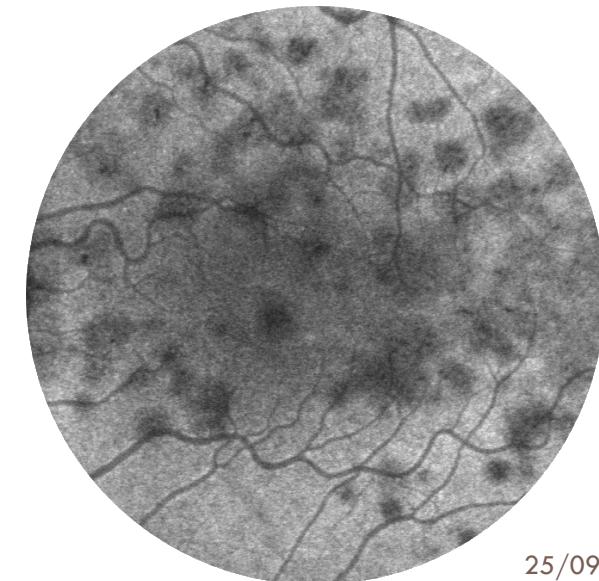
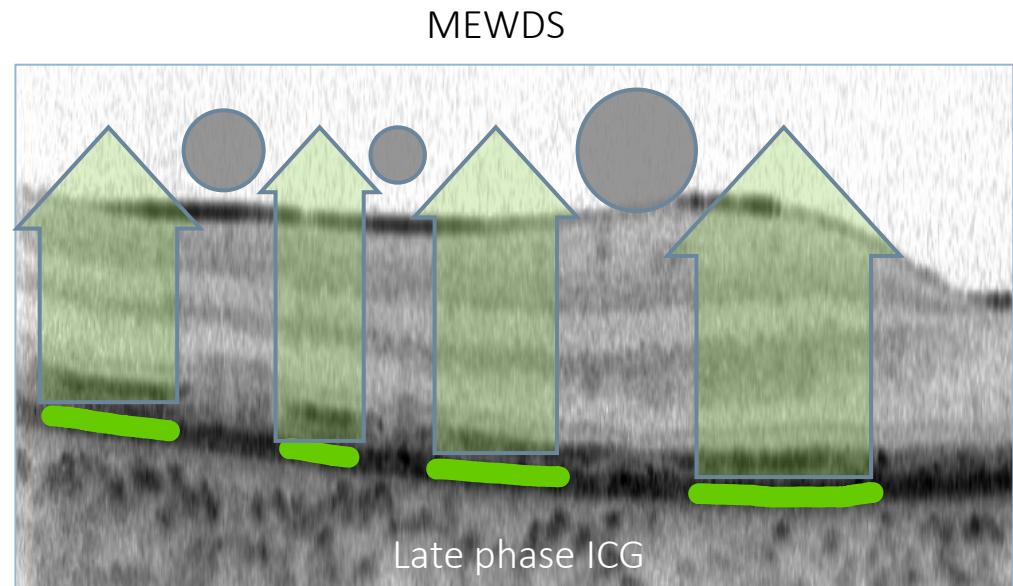


24/08/2018 - No ICG dye injected 3 20:03

Schematic late ICG hypofluorescence in various diseases

In MEWDS

- RPE fails to internalize ICG at the level of white dots.
- by contrast with the surrounding RPE the white dots appear progressively dark.
- This RPE dysfunction does not imply cellular death, but disturbs, transiently, photoreceptor cells function and anatomy



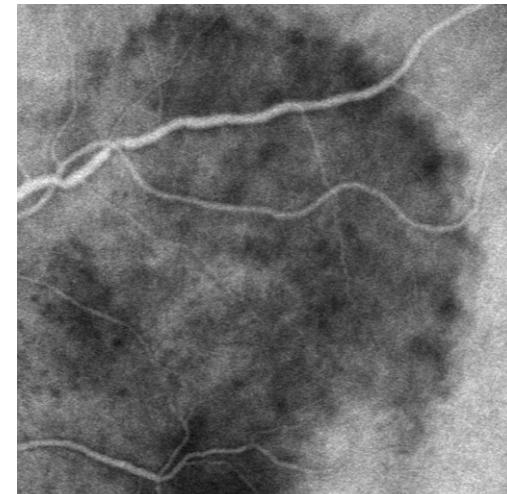
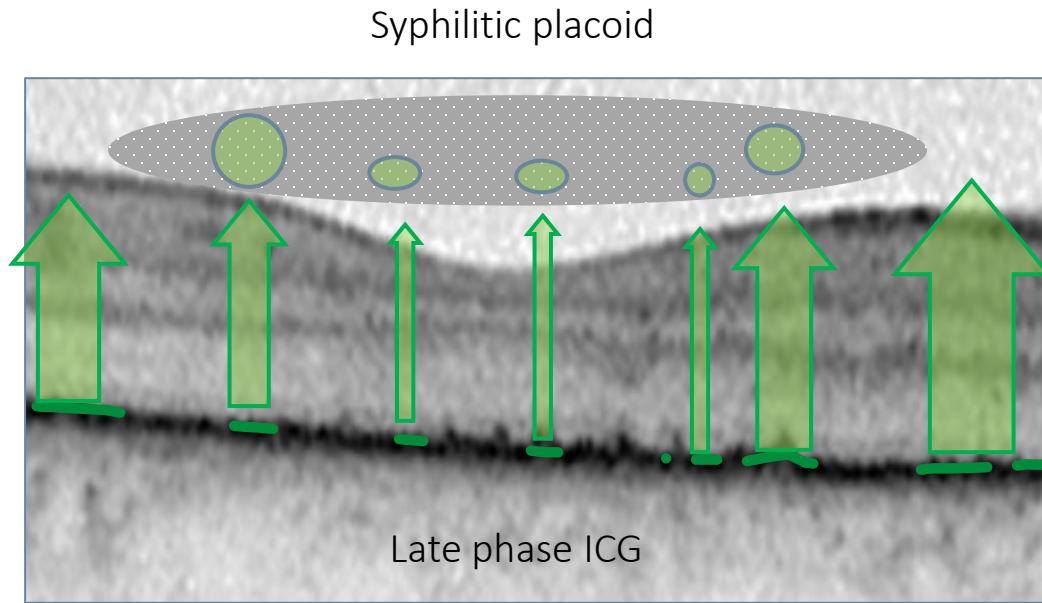
Owens SL. *Brit J Ophthalmol.* 1996;80(3):263

Gaudric A, Mrejen S. *Retin Cases Brief Reports.* 2016;11

Zicarelli F. *Ocular immunology and inflammation.* 2019;1-7

Schematic late ICG hypofluorescence in various diseases

- In acute syphilitic placoid
 - RPE fails to internalize ICG at the level of the plaque .
 - by contrast with the surrounding RPE the plaque becomes progressively dark.
 - However, the RPE dysfunction is not as homogeneous as in the MEWDS.
 - It may also be transient without scarring if the treatment is started early.

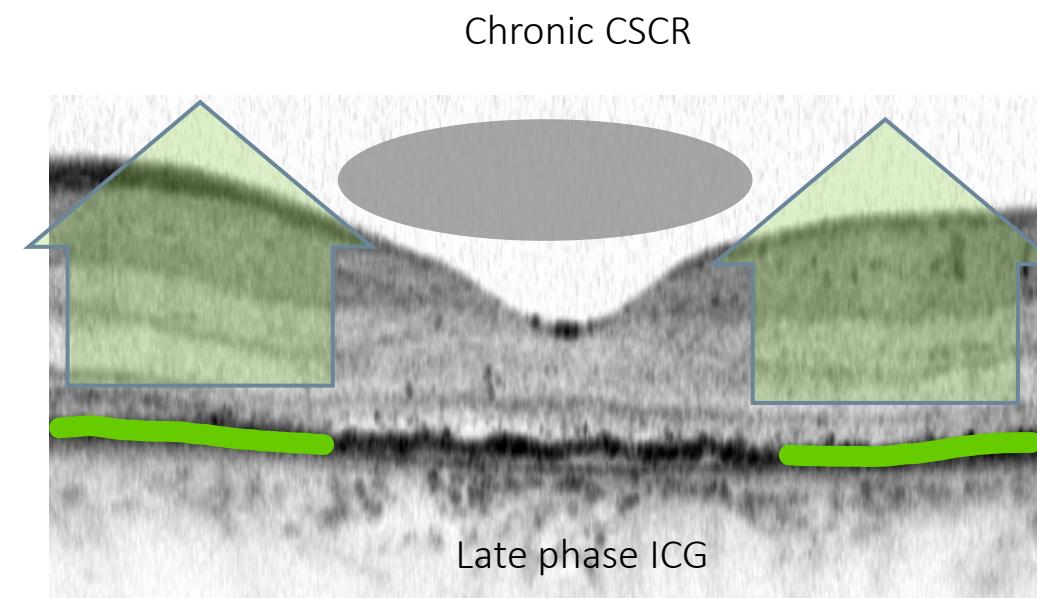
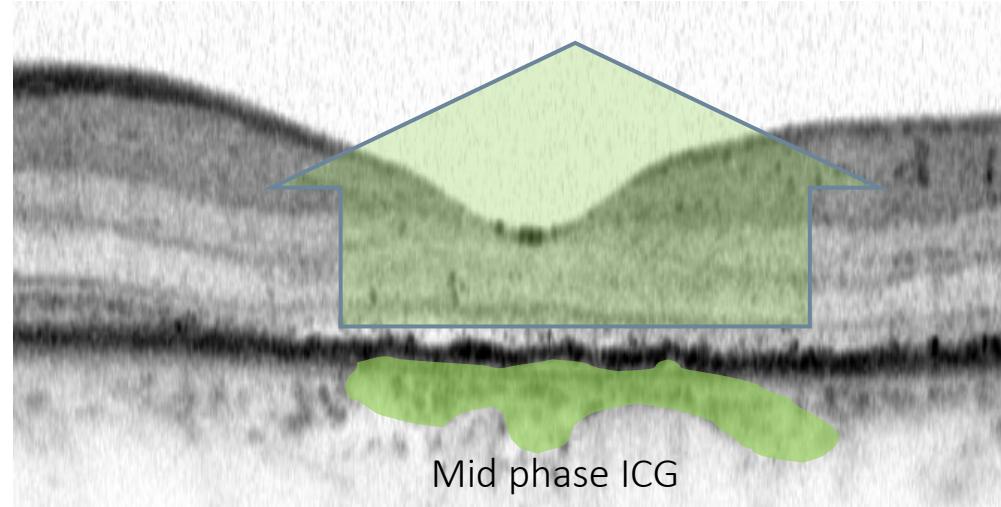
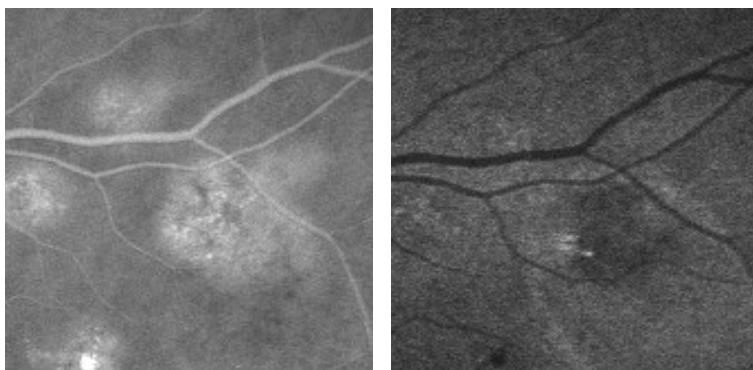


Schematic late ICG hypofluorescence in various diseases

- In chronic CSCR

- The early/mid phase hyperfluorescence of the lesions can be explained by choriocapillaris hyperpermeability and staining of the sub RPE space.

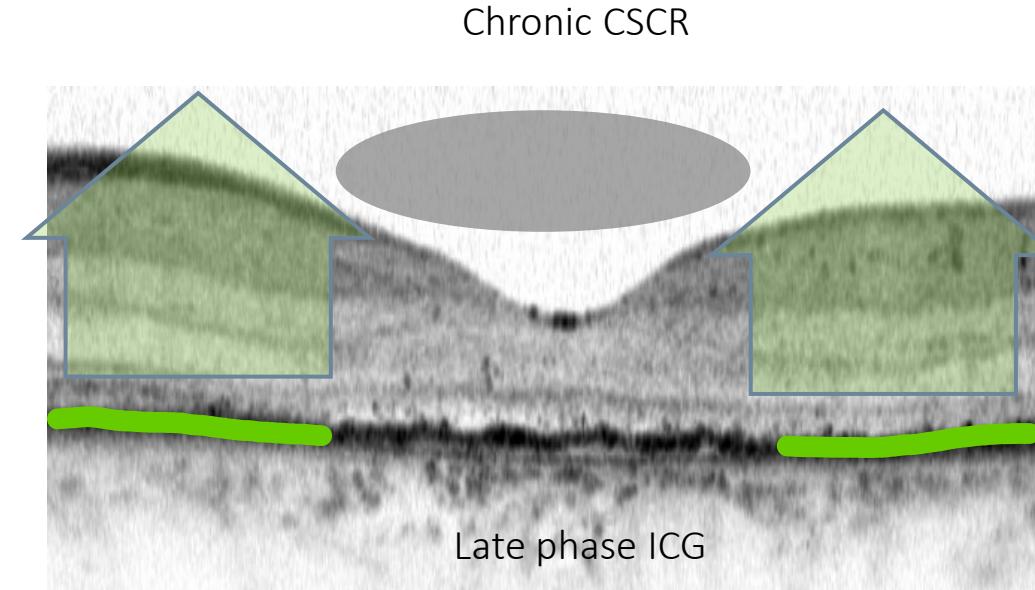
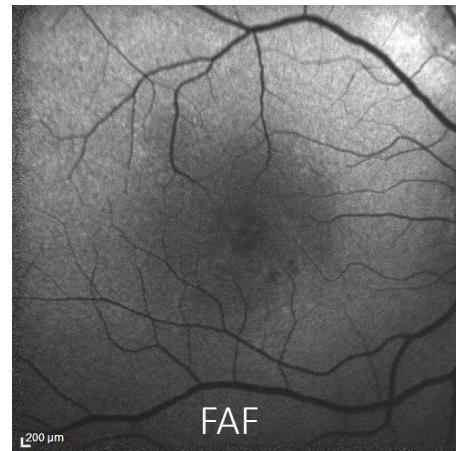
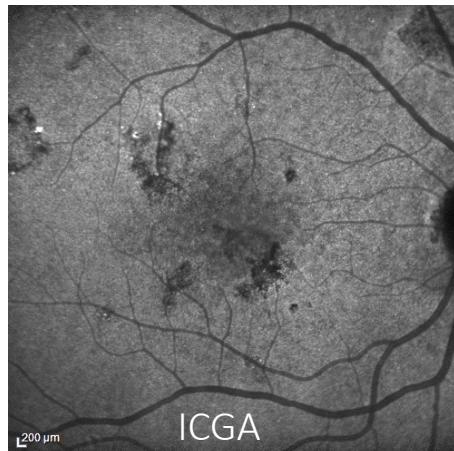
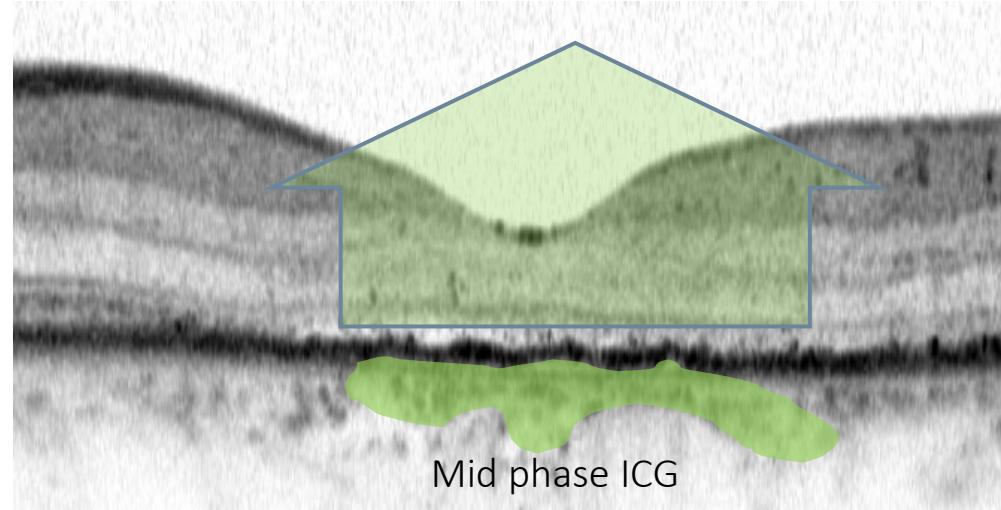
- In the late phase hypofluorescence reveals the inability of the RPE to uptake ICG



Schematic late ICG hypofluorescence in various diseases

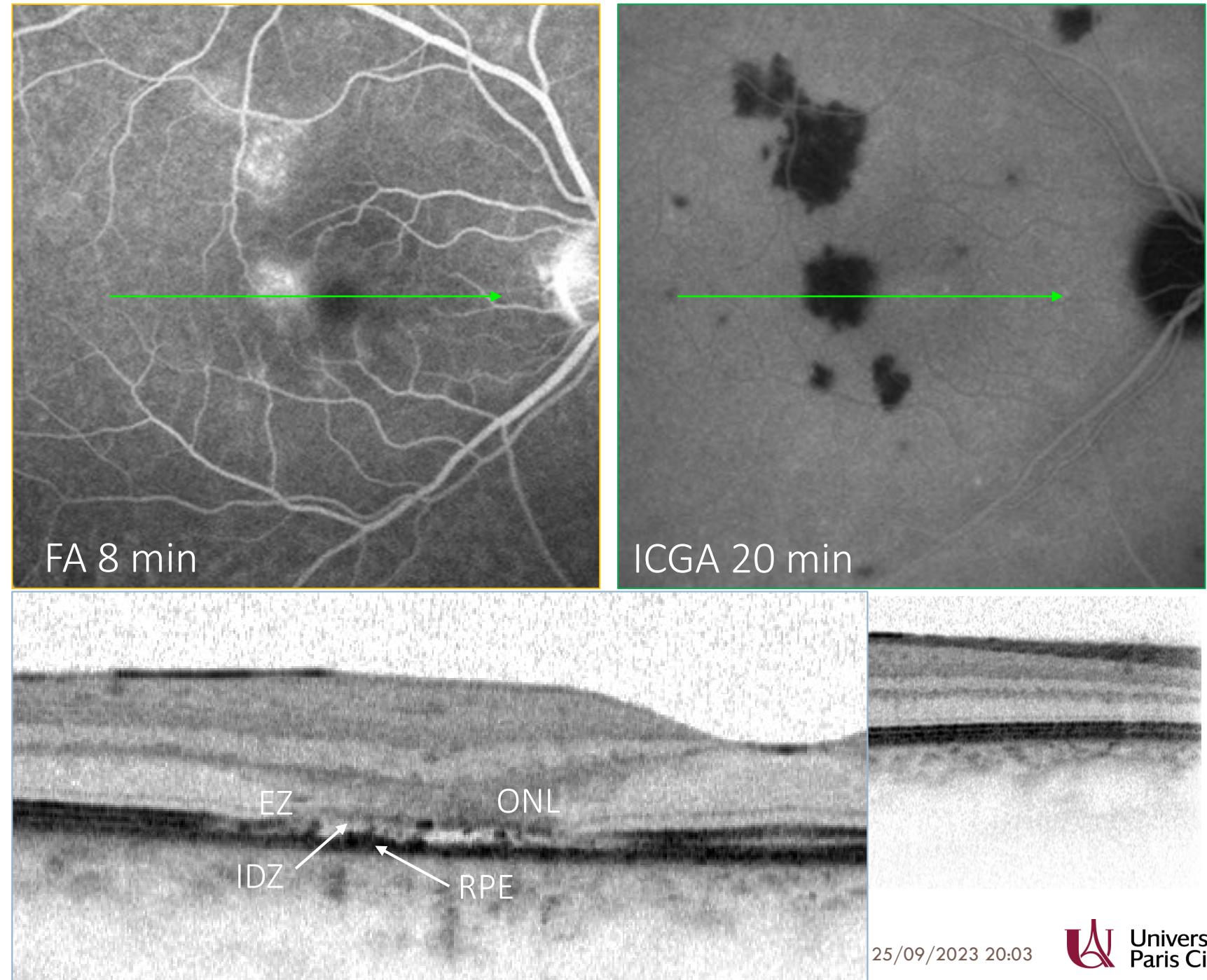
In chronic CSCR

- This late hypofluorescence does not correspond to RPE atrophy at this stage



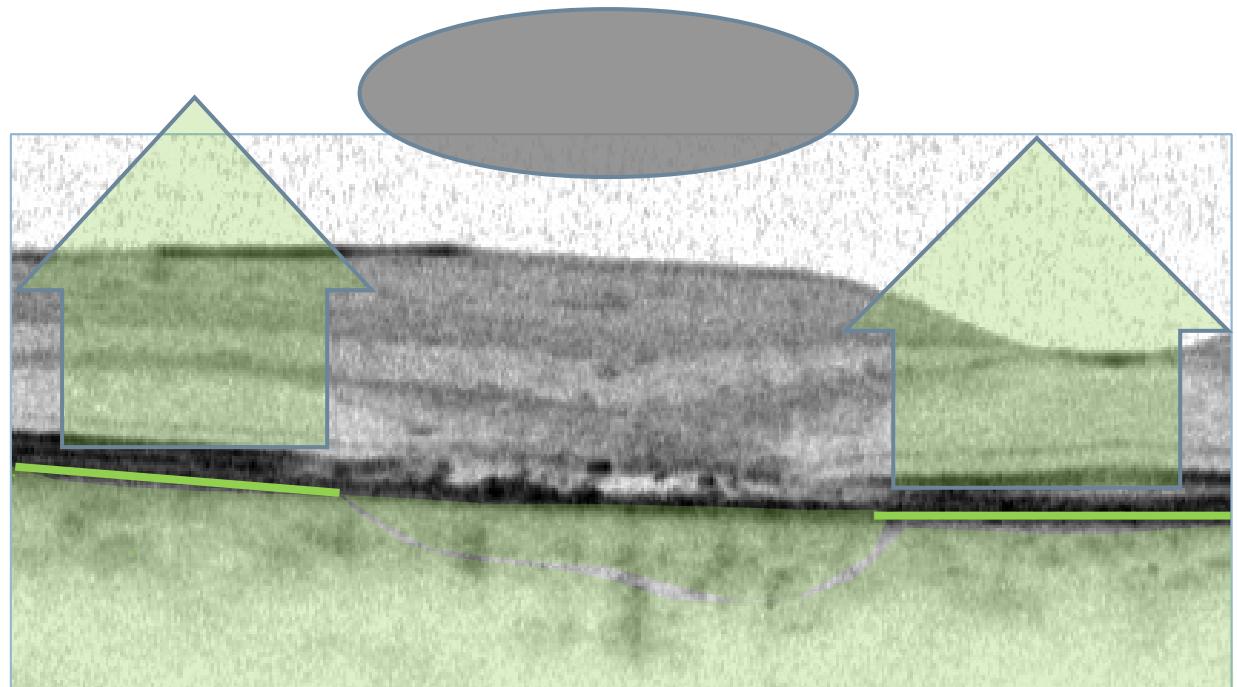
Other cases EEP/APMPPE

- Plaques visibles en AF et ICG correspondant à
 - hyperreflectivité ONL
 - disruption EZ
 - fragmentation IDZ
 - granulations EP



EEP (APMPPE)

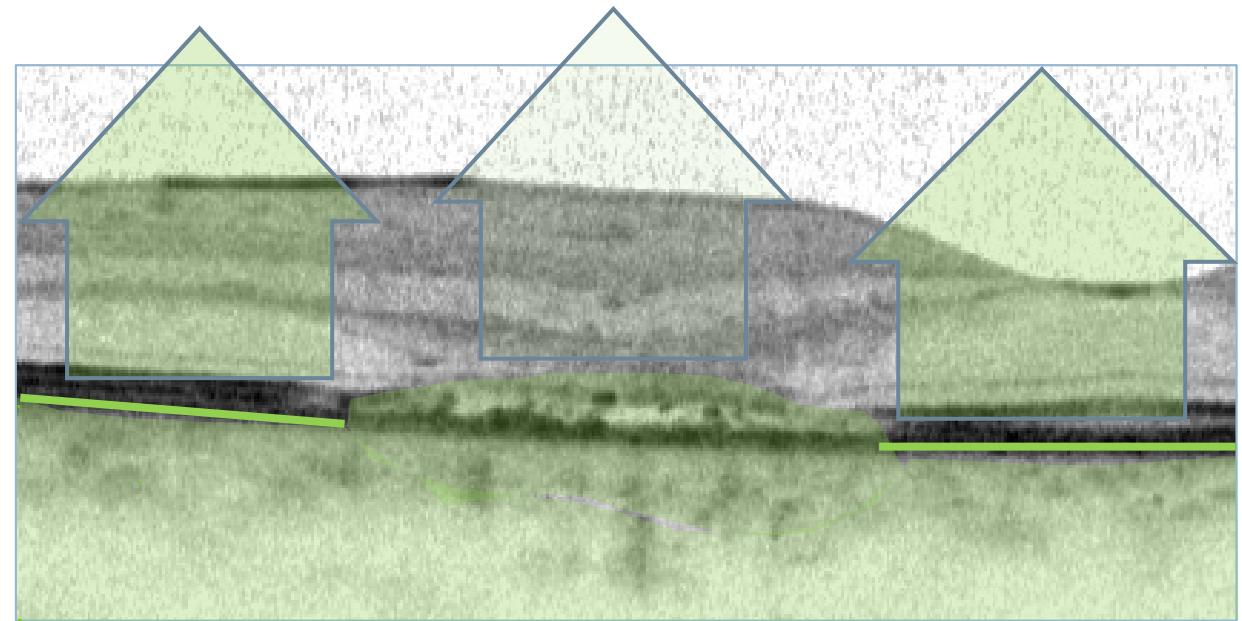
- Hypoperfusion localisée de la choroïde interne
 - pas de coloration tardive
 - malgré la diffusion de colorant dans la choroïde
 - pas de passage, dans, ni à travers l'EP



ICG

EEP (APMPPE)

- Hypoperfusion localisée de la choroïde interne
 - faible coloration tardive en fluo
 - par diffusion de colorant dans la choroïde
 - puis à travers l'EP altéré



FLUORESCÉINE

Other cases : choroidal hemangioma

■ "Washout" phenomenon

" In the middle portion of the study (6 to 10 minutes), the hyperfluorescence can persist or begin to wane. At the end of the study at 30 minutes there is almost routinely a "washout" hypofluorescence where the low-resistance, high-flow properties of this tumor allow rapid flow of the dye into and out of the tumor (Fig. 21-11). Therefore the tumor empties sooner than the normal surrounding choroid and thus appears hypofluorescent in comparison. "

INDOCYANINE GREEN Angiography

Lawrence A. Yannuzzi, M.D. Vice Chairman and Director of Retinal Services
Manhattan Eye, Ear, and Throat Hospital;
Professor of Clinical Ophthalmology
College of Physicians and Surgeons
Columbia University
New York, New York

Robert W. Flower, D.Sc. (hon) Senior Scientist
Retina Institute of Maryland;
Associate Professor of Ophthalmology
University of Maryland School of Medicine
Baltimore, Maryland

Jason S. Slakter, M.D. Attending Surgeon, Vitreoretinal Service
Manhattan Eye, Ear, and Throat Hospital;
Assistant Clinical Professor of Ophthalmology
College of Physicians and Surgeons
Columbia University
New York, New York

Mosby, 1997

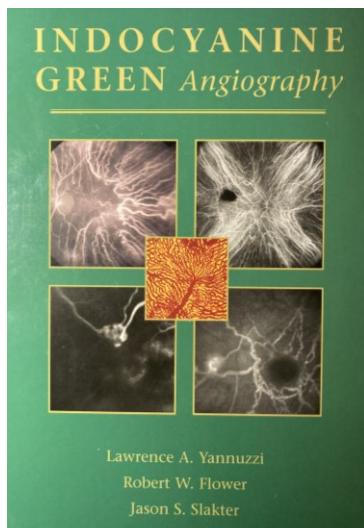
25/09/2023 20:03

Other cases : choroidal hemangioma

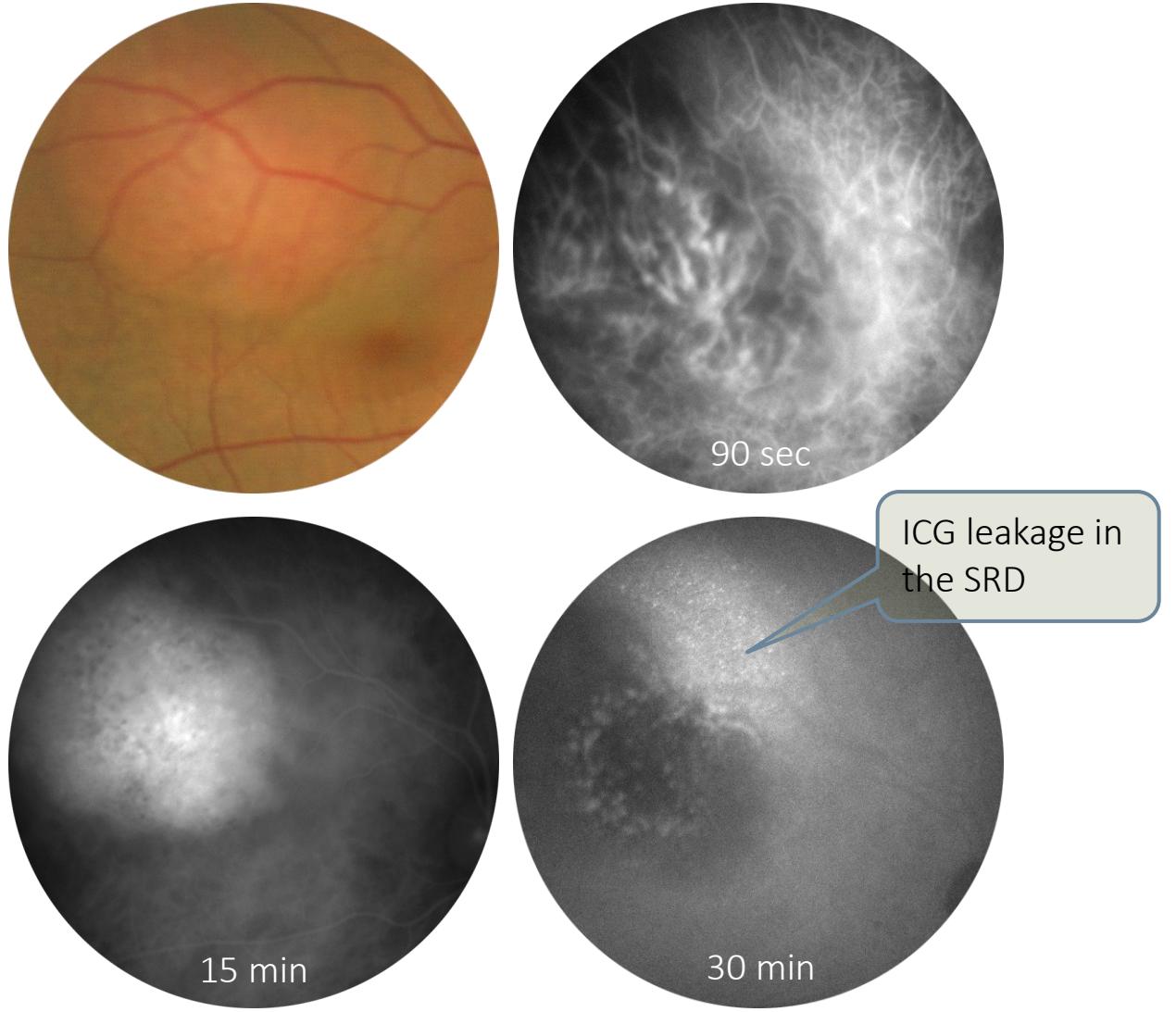
■ "Washout" phenomenon

This 1-minute stage of intense hyperfluorescence seen with choroidal hemangiomas is brighter than any other tumor, At the end of the study at 30 minutes there is almost routinely a **"washout"** hypofluorescence where the low-resistance, high-flow properties of this tumor allow rapid flow of the dye into and out of the tumor.

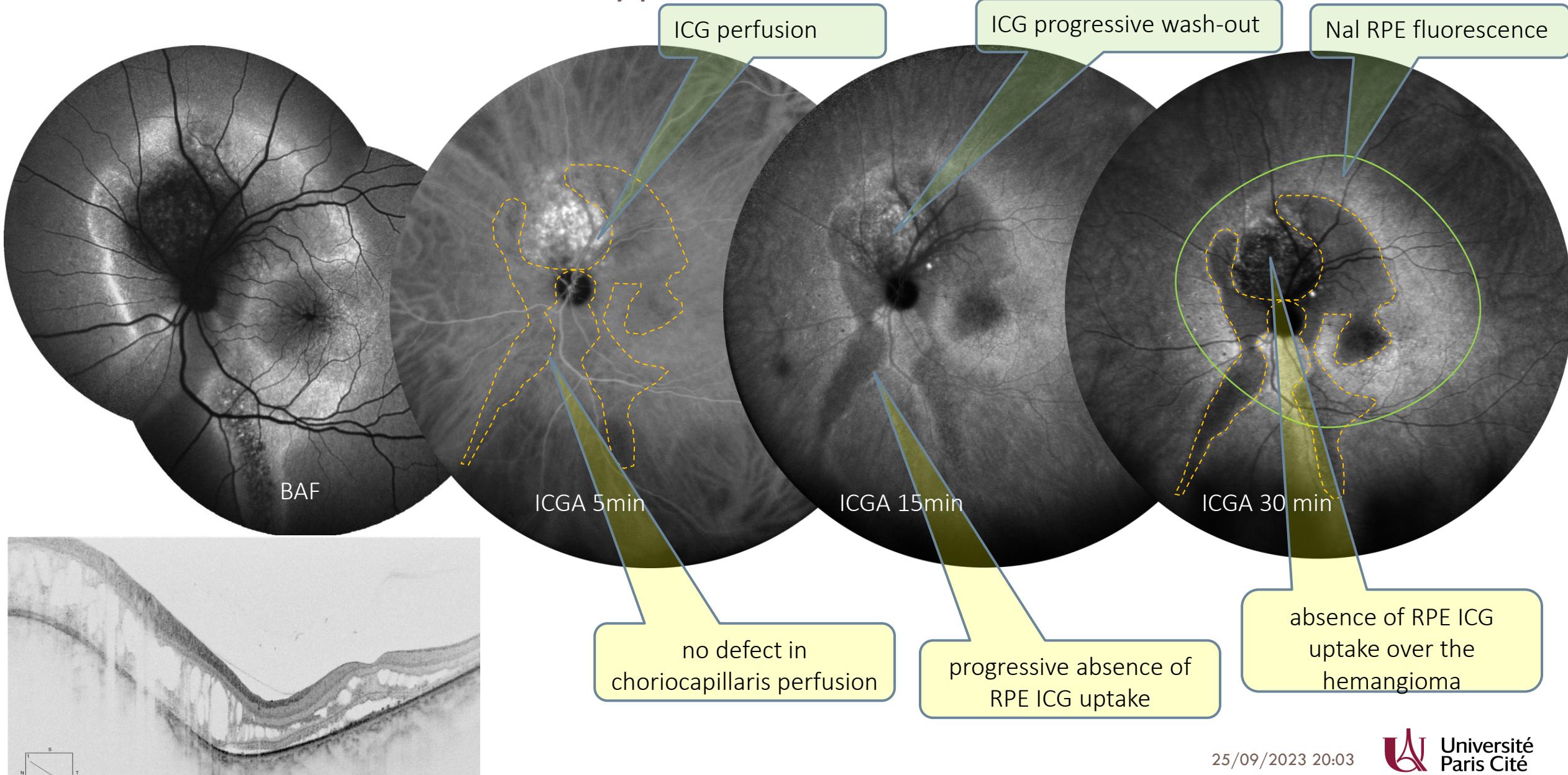
Therefore the tumor empties sooner than the normal surrounding choroid and thus appears hypofluorescent in comparison



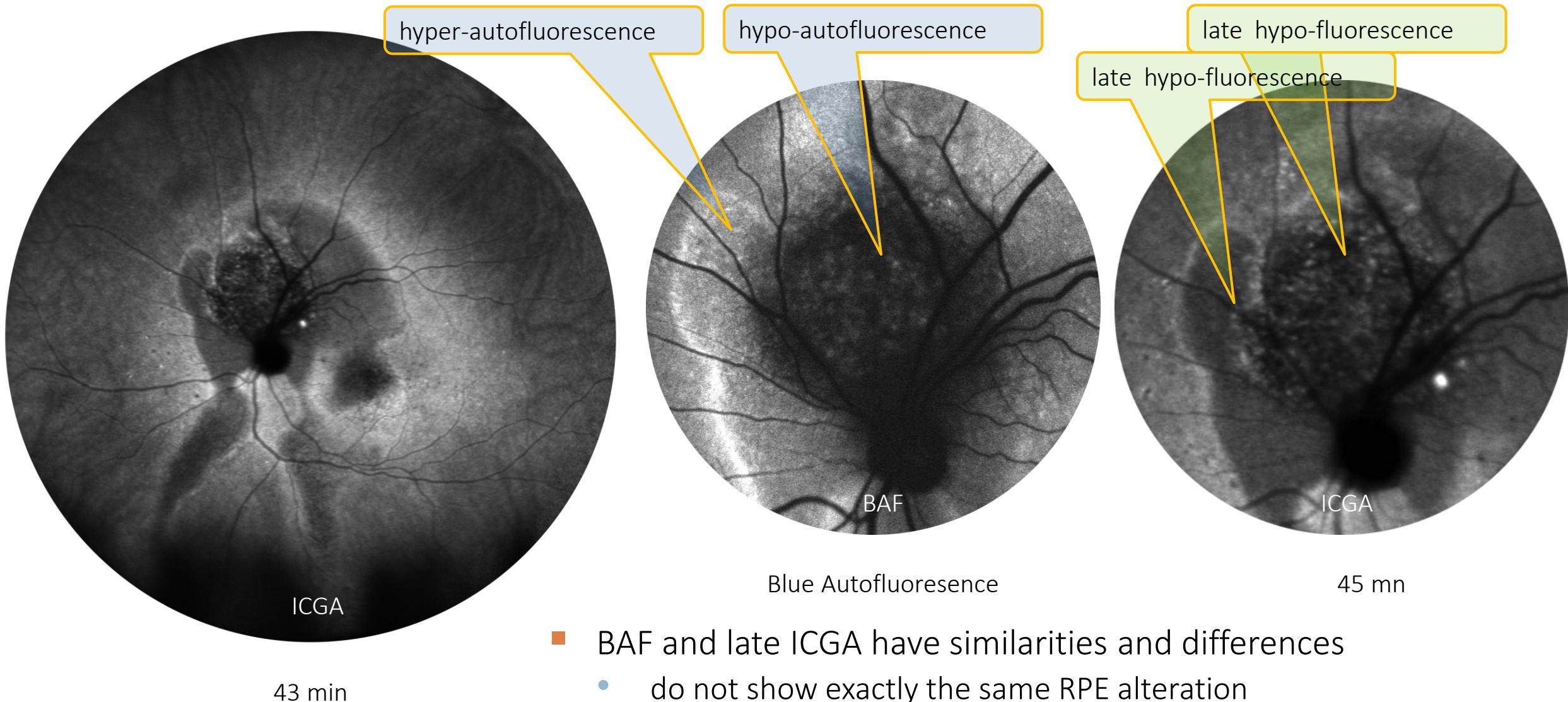
C Shields, in *Indocyanine Green Angiography*



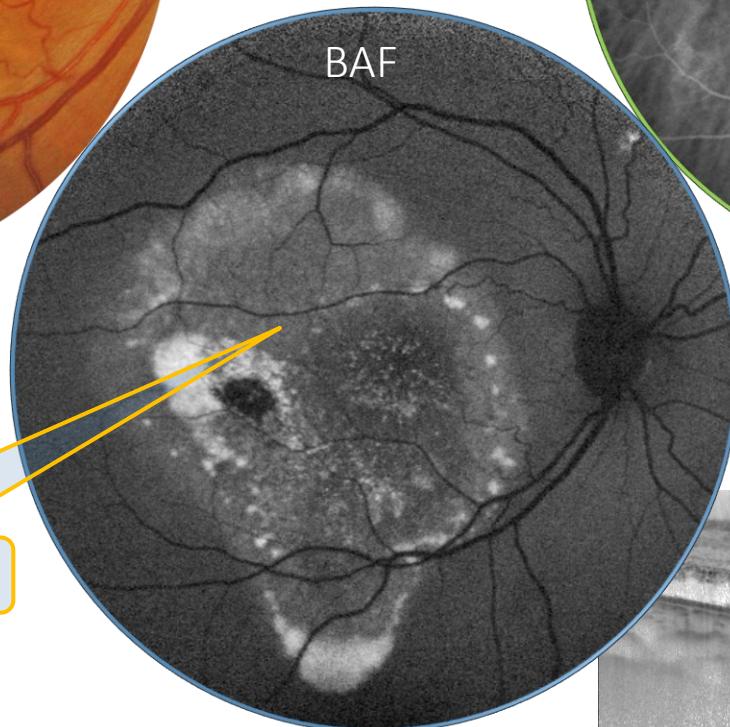
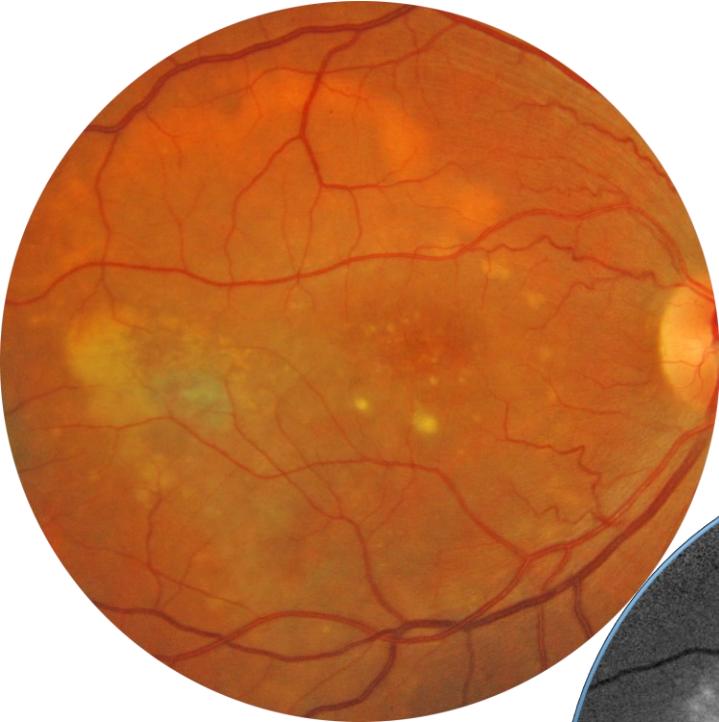
Schematic late ICG hypofluorescence in various diseases



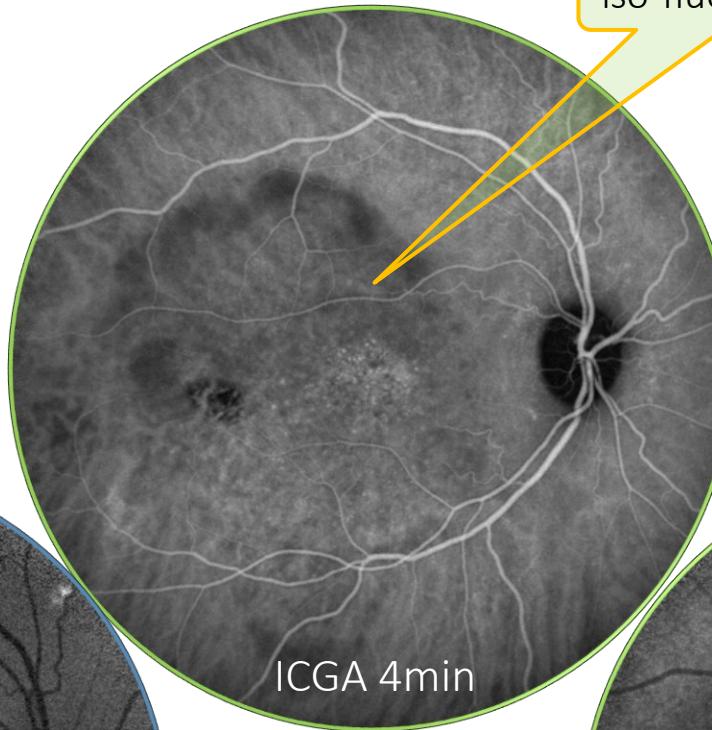
Choroidal hemangioma



Best's disease

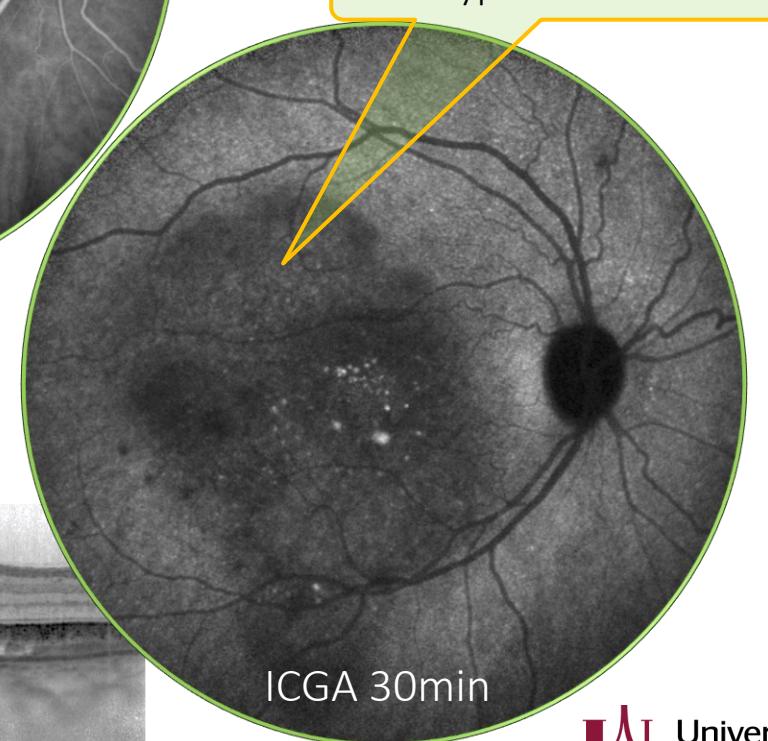


hyper-autofluorescence



ICGA 4min

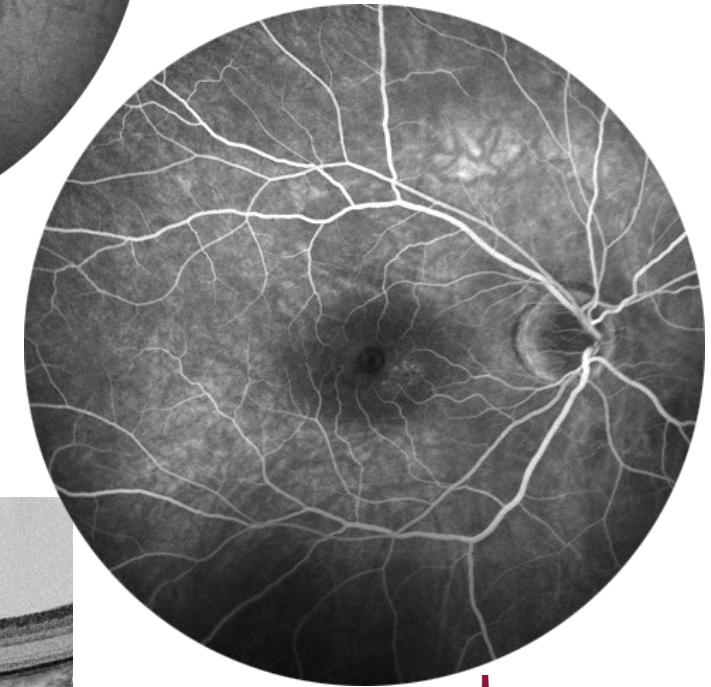
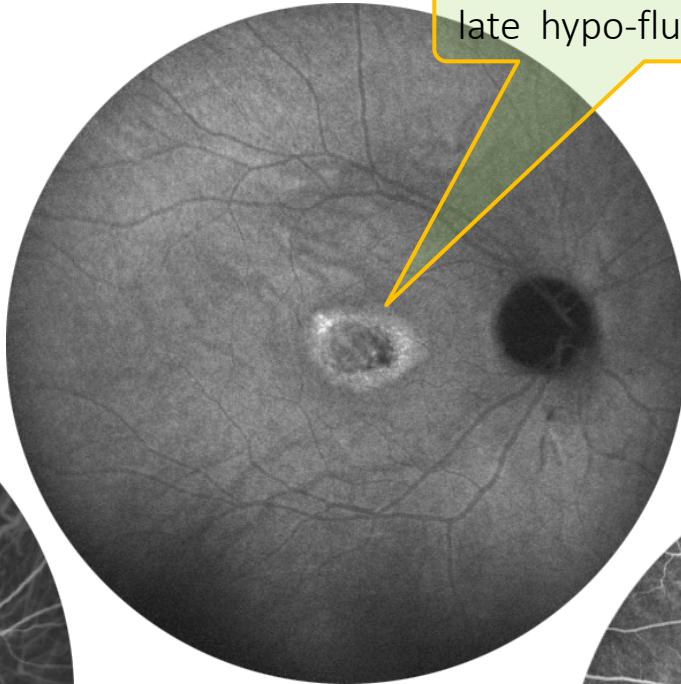
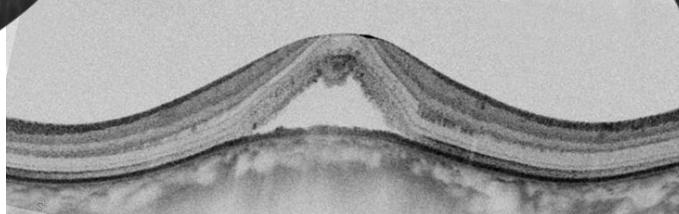
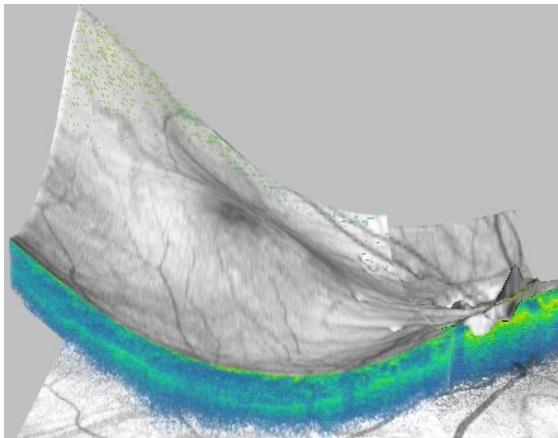
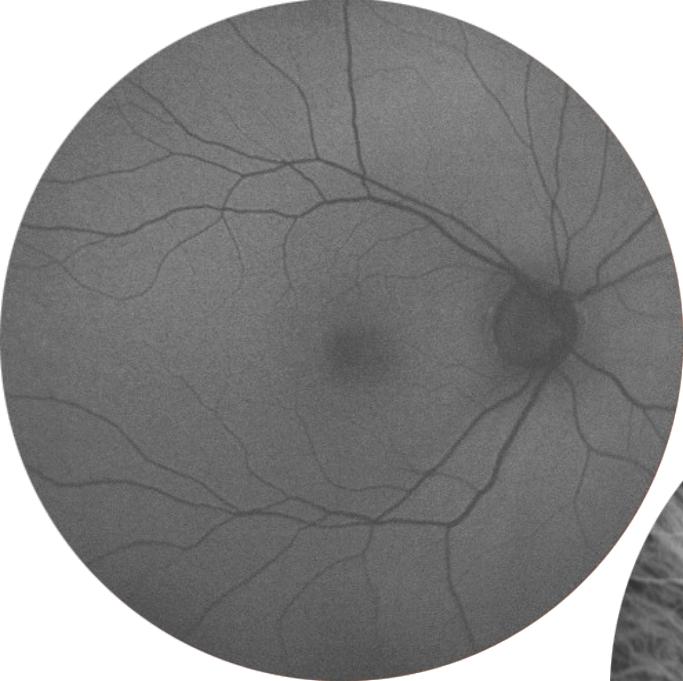
iso-fluorescence



ICGA 30min

25/09/2023 20:03

Dome shaped macula



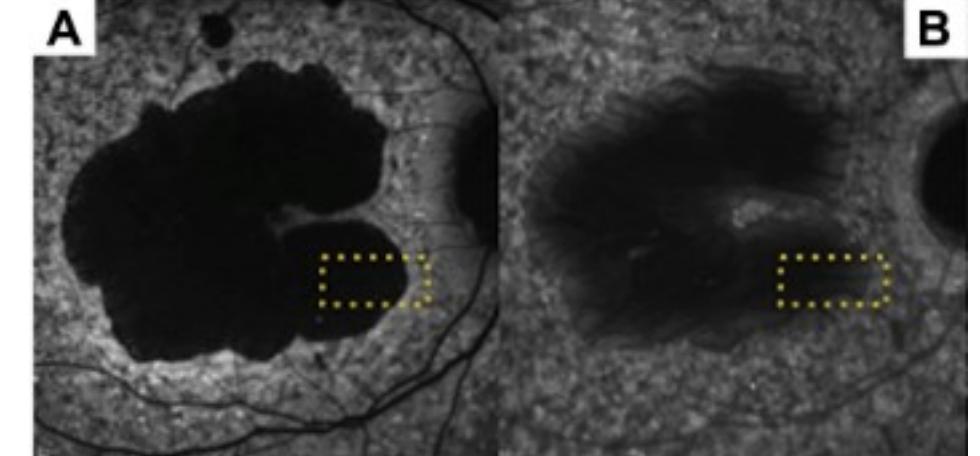
Dark Atrophy: An Optical Coherence Tomography Angiography Study

Marco Pellegrini, MD, Alessandra Acquistapace, MD, Marta Oldani, MD, Matteo Giuseppe Cereda, MD, Andrea Giani, MD, Mariano Cozzi, BS, Giovanni Staurenghi, MD, FARVO

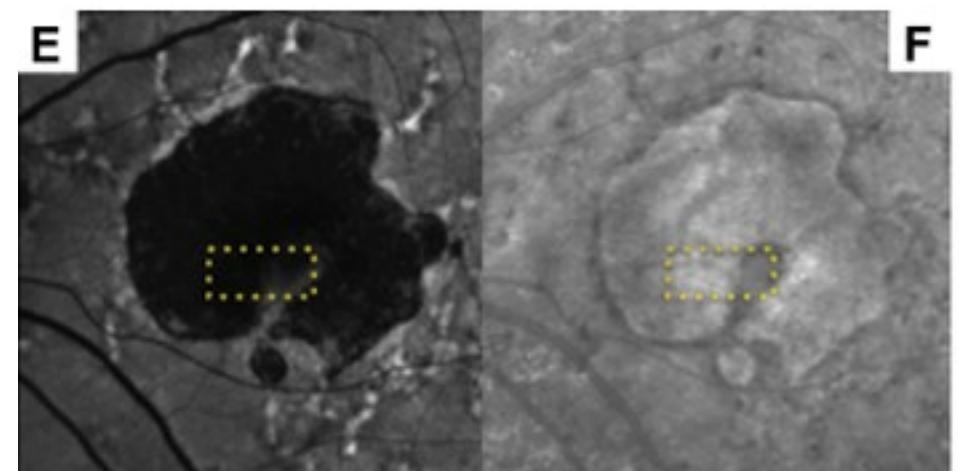
Ophthalmology. 2016;123(9):1879-1886.

- In Stargardt's disease
 - Macular atrophy was totally dark on late phase ICGA
- In GA
 - some late fluorescence was usually present on late ICGA

Stargardt



GA



This difference was thought to be due to differences in choriocapillary perfusion

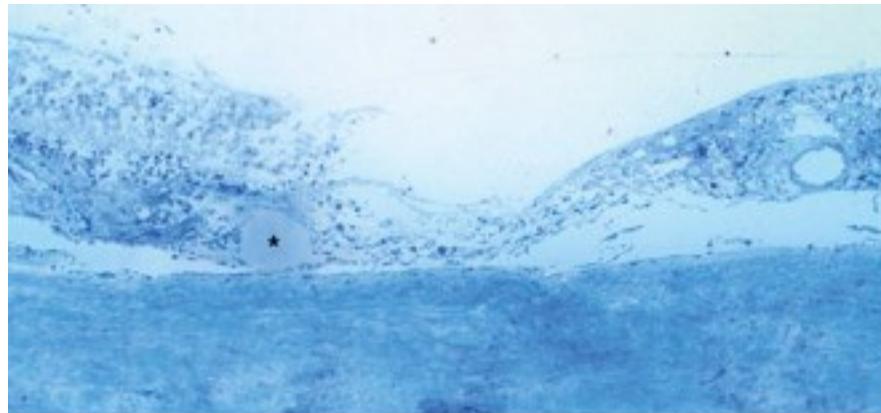
Complete and incomplete RPE atrophy

Retinal Histopathology in Eyes from a Patient with Stargardt disease caused by Compound Heterozygous ABCA4 Mutations*

Vera L. Bonilha¹, Mary E. Rayborn¹, Brent A. Bell¹, Meghan J. Marino¹, Gerald A. Fishman², and Joe G. Hollyfield¹

Ophthalmic Genet. 2014;37(2):1-11.

The fovea was severely degenerated, with little evidence of any retinal cell layer, including the RPE



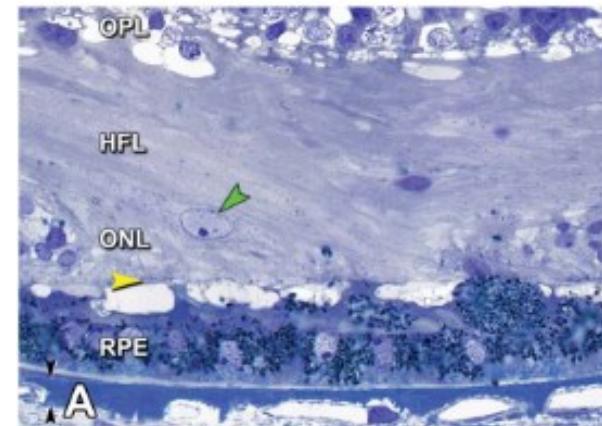
HISTOLOGY OF GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION

A Multilayer Approach

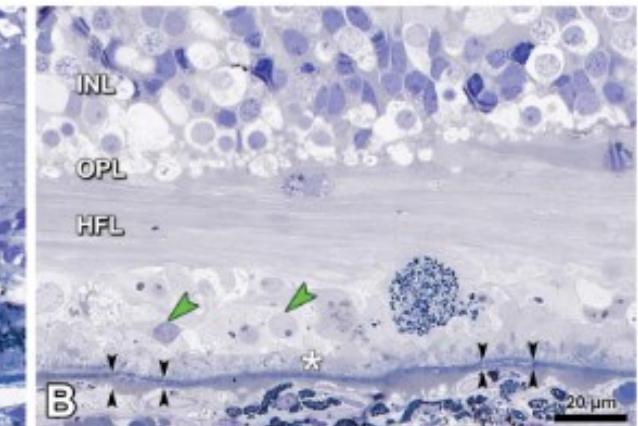
MIAOLING LI, MD, PhD,*† CARRIE HUISINGH, MSPH,* JEFFREY MESSINGER, DC,* ROSA DOLZ-MARCO, MD, PhD,‡§¶ DANIELA FERRARA, MD, PhD,** K. BAILEY FREUND, MD,‡§†† CHRISTINE A. CURCIO, PhD*

Retina. 2018;38(10):1937-1953.

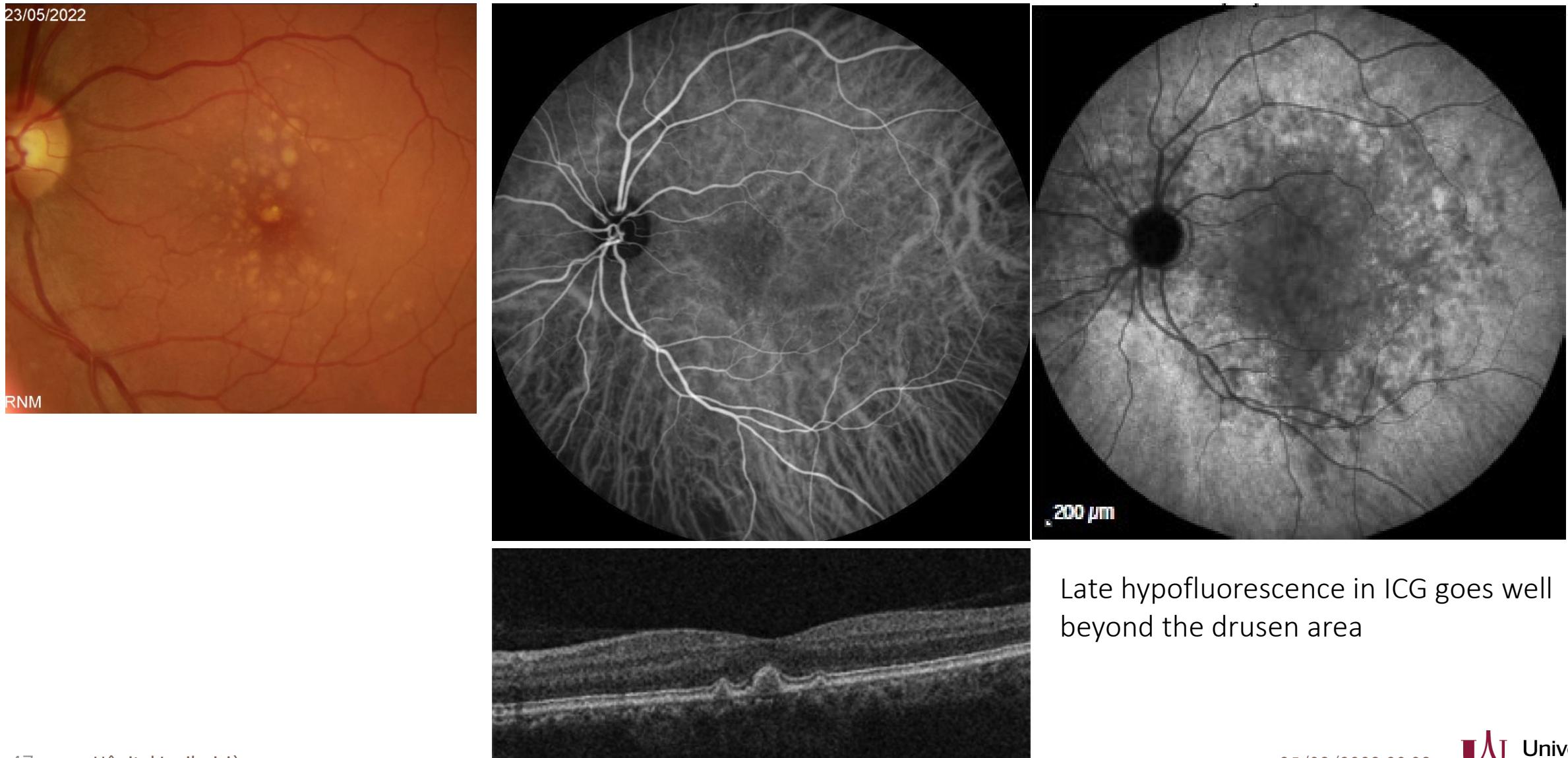
Complete Outer Retinal Atrophy



Complete RPE and Outer Retinal Atrophy



ICGA and drusen



ICGA and drusen

Retina

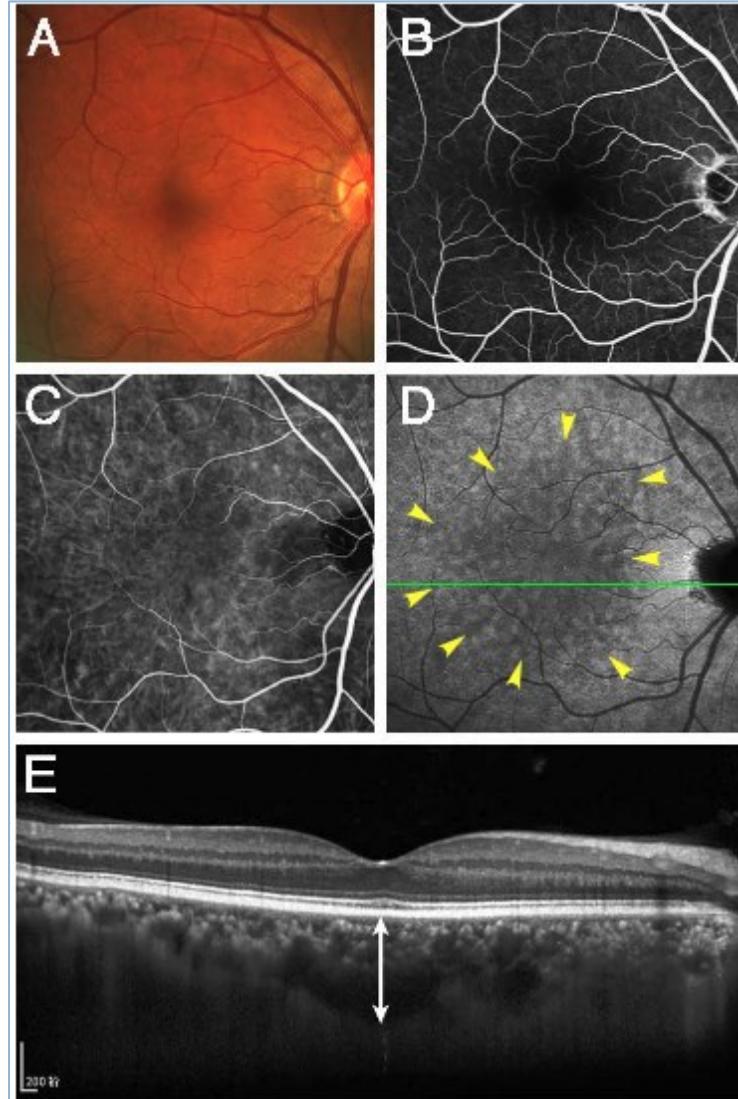
Age-Related Scattered Hypofluorescent Spots on Late-Phase Indocyanine Green Angiography as Precursor Lesions of Polypoidal Choroidal Vasculopathy

Ling Chen, Xiongze Zhang, Miaoling Li, Nanying Liao, and Feng Wen

State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China

Investigative Ophthalmology Vis Sci. 2019;60(6):2102

Age Related Scattered Hypofluorescent Spots on Late Phase IVCGA (ASHS-LIA) were mainly located in the macular region, and manifested as hypofluorescent spots on late-phase ICGA that could be scattered or confluent. No corresponding abnormalities on other multimodal imaging, including color FP, FFA, FAF, and SD-OCT were seen.



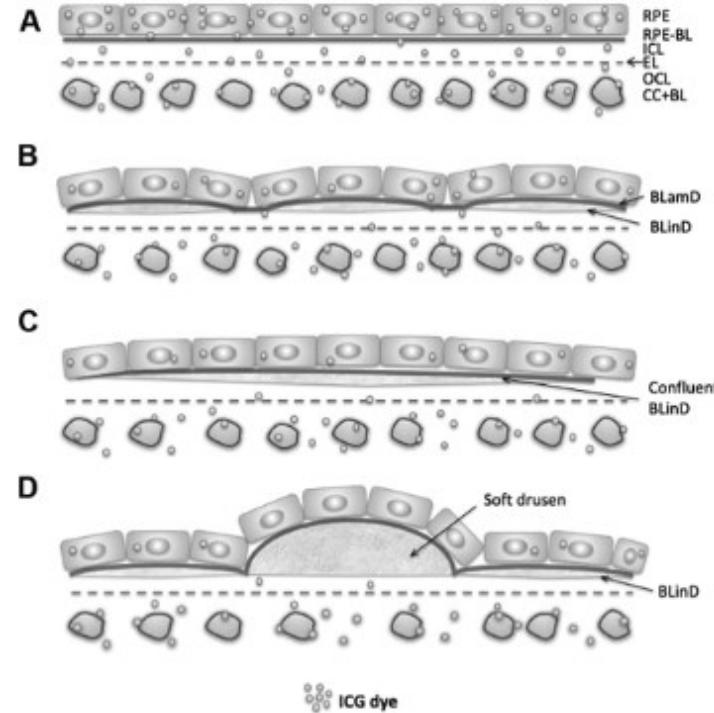
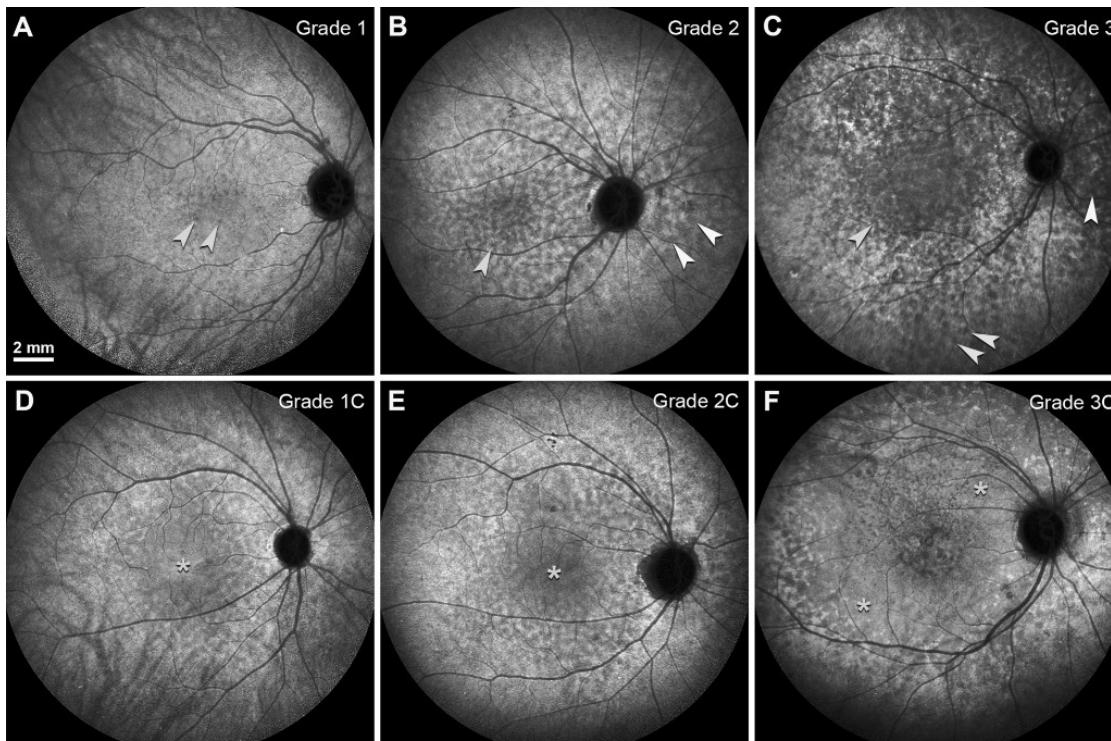
ICGA and drusen

REVIEW ARTICLE

Visualizing lipid behind the retina in aging and age-related macular degeneration, via indocyanine green angiography (ASHS-LIA)

Ling Chen¹, Peizeng Yang¹ and Christine A. Curcio²

Eye. Published online 2022:1-12. doi:10.1038/s41433-022-02016-3



ICG dye is water-soluble and binds preferentially to phospholipid over hydrophobic neutral lipid such as esterified cholesterol

Good evidence supports the hypothesis that ASHSLIA represents exclusion of a dye that does not bind the principal hydrophobic lipids in BrM and does not gain access to the RPE.

ICG et fluorescence du fond d'œil

- En résumé,
 - L'ICG pénètre activement dans les cellules de l'EPR par son pôle apical grâce à un mécanisme impliquant la pompe Na^+,K^+ -ATPase.
 - Il est moins évident de savoir comment l'EPR absorbe l'ICG par son pôle basal, qui est cependant connu pour l'internalisation des lipides et des protéines
 - La fluorescence tardive du fond d'œil dans la phase tardive de l'ICGA est principalement due à la fluorescence de l'EP
 - L'hypofluorescence uniquement tardive de l'ICGA dans diverses maladies, peut être due à défaut d'absorption de l'ICG par les cellules de l'EP altérées
 - Celà peut aider à mieux comprendre la pathogénie de ces maladies



Hôpital Lariboisière
Hôpital Saint Louis
AP-HP.Nord



HÔPITAL FONDATION
Adolphe de ROTHSCHILD
LA RÉFÉRENCE TÊTE ET COU

Merci de votre attention,

agaudric@gmail.com
alain.gaudric@aphp.fr



Service d'Ophtalmologie
Hôpital Lariboisière



